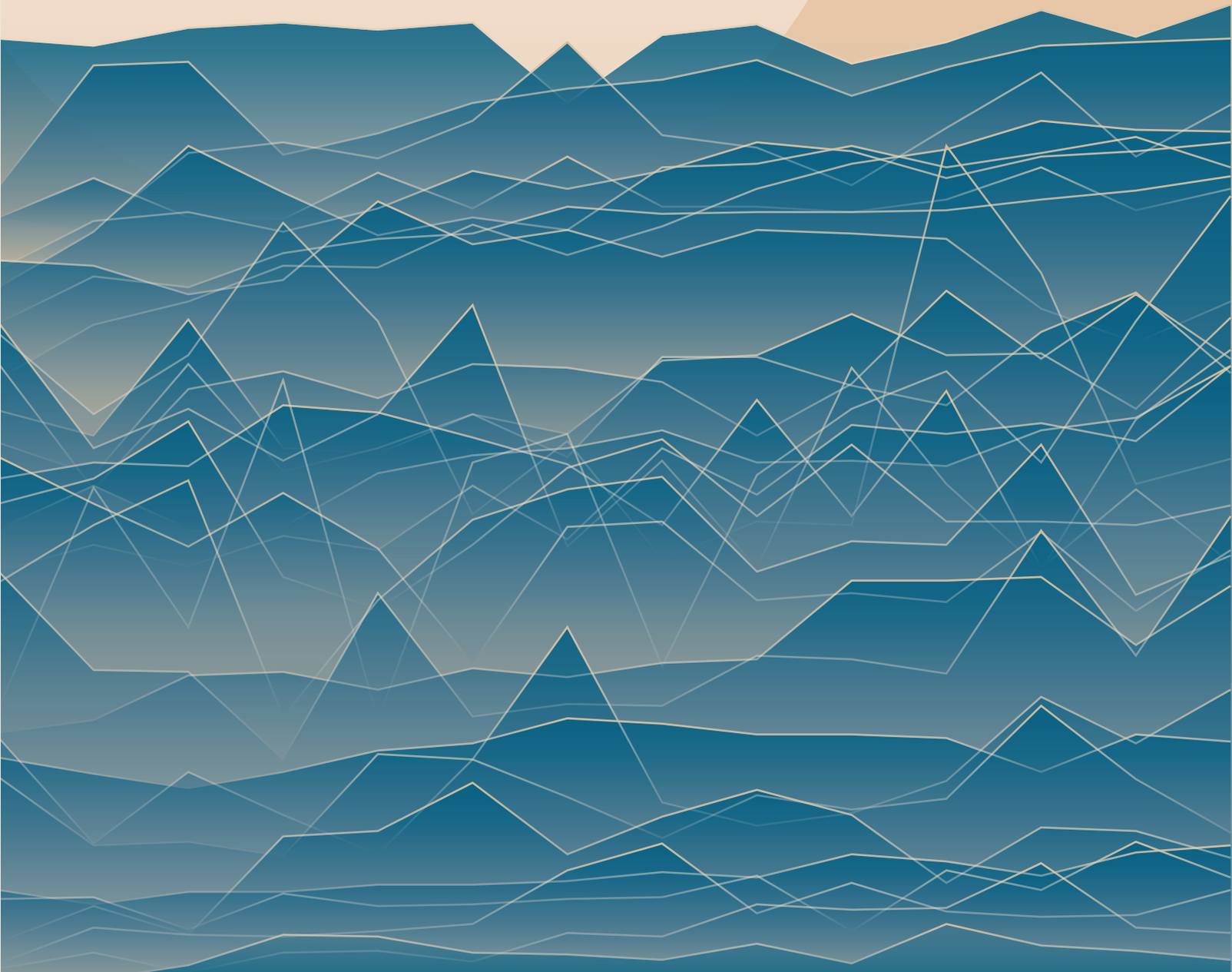
SURVIVAL of CANCER PATIENTS

DIAGNOSED IN 1997–2016 IN SLOVENIA



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SURVIVAL OF CANCER PATIENTS
DIAGNOSED IN 1997–2016 IN SLOVENIA

Cancer Registry of Republic of Slovenia
2021

CONTENTS

FOREWORD

The fourth book on the survival of cancer patients in Slovenia provides important new data and commentary on the survival of patients for all types of cancer diagnosed in Slovenia over a 20-year period between 1997 and 2016. The analysis is based on data collected in the Slovenian Cancer Registry covering the entire country, which again gives this fourth book special weight and also reminds us of the value of our population-based cancer registry, which celebrated 70 years in 2020. Historical awareness of the importance of the comprehensive, continuous and high-quality registration of cancer cases has laid the foundations for the periodicity of national survival statistics. This makes it possible to monitor the survival of cancer patients over time and assess progress in achieving the goals in controlling the cancer burden in the country.

Survival analyses carried out by epidemiologists for each type of cancer are accompanied by clinical commentary from one or more established clinical experts. These provide an insight into changes in the diagnosis and/or treatment of individual cancers and the possible reasons for the changes in survival observed during this period. This book reflects another unique feature—the daily connection between the data of the Cancer Registry and the clinical work in the hospital under the auspices of the Institute of Oncology Ljubljana from the very beginning.

If in the preface to the first book on the survival of Slovenian cancer patients in 1995, it was written that patients and doctors usually have unfavourable experiences with cancer treatment; the key findings of this publication are more encouraging. The survival of cancer patients in Slovenia is increasing over time: in the 20-year period, the five-year net survival has improved by 11 percentage points, and the five-year net survival in the last period, between 2012 and 2016, was almost 60%. However, this publication provides us with more than just survival data. It provides patients and other lay readers with a better understanding of either their own experience with cancer or cancer as a 21st century epidemic. It also enables key stakeholders in the country to use valuable data as a tool to better understand what changes are needed on a strategic level to be included in the National Cancer Control Programme to further improve cancer care in Slovenia in the future. This can also be seen from the international comparisons included in the book, showing that Slovenia still has room for improvement in the control of many types of cancer. Therefore, this publication should also be an invitation to action so that fewer people in Slovenia will get cancer, and more people with a diagnosis of cancer will live better and longer.

A sincere thank you to all the contributors to this book.

Assoc Prof Phd Irena Oblak, MD
Medical Director, Institute of Oncology

EXECUTIVE SUMMARY

Cancer is not a single disease, but several hundred different ones. These can occur in any tissue or organ of the human body. They differ in frequency, treatment and outcome, but also have different risk factors that are known to a greater or lesser extent. In Slovenia, cancer is the leading cause of death among men and the second among women. In recent years, more than 15,000 Slovenes are diagnosed with cancer annually and slightly over 6,000 die from it. There are more than 100,000 people living in Slovenia who have been diagnosed with cancer at some point in their lives. Since cancer is more common among the elderly (two-thirds of patients are older than 65 at the time of diagnosis), and the Slovenian population is ageing, it is expected that the burden of this disease will increase, even if the level of risk factors remains the same as it is today.

The continuous and systematic collection, storage and analysis of data on all cancer patients is the basis for assessing the burden of cancer and managing this major public health problem, with population-based cancer registries playing a crucial role. The Slovenian Cancer Registry (hereinafter: Cancer Registry) was established in 1950 at the Institute of Oncology Ljubljana and is one of the oldest national population-based cancer registries in the world. In Slovenia, cancer reporting has been mandatory and prescribed by law since 1950 and takes place through notification forms, which are the primary source of data. Additional sources of data for the registration of new cancer cases are death certificates sent to the Cancer Registry by the National Institute of Public Health, and data on diagnosed cancers recorded in three national screening programmes: ZORA (cervix), DORA (breast) and SVIT (colon and rectum). The Cancer Registry obtains data on the vital status of reported individuals from the Central Population Register. Detailed analyses of the spatial distribution of cancer enable the precise identification of cancer patients' addresses and regular connection with the Registry of Spatial Units of the Surveying and Mapping Authority of the Republic of Slovenia. Analysis of cancer registry data only provides a reliable assessment of the cancer burden if the data is as complete as possible and of sufficient quality. Completeness and quality are determined by international quality indicators, which the Cancer Registry consistently achieves.

Population-based cancer survival is a composite indicator that reflects the characteristics of patients as well as the organization, accessibility, quality and efficiency of the healthcare system. The current publication is the fourth extensive report of the Cancer Registry on the survival of Slovenian cancer patients.

Patient Selection and a Presentation of Results

The survival analysis included patients with permanent residence in Slovenia who were diagnosed with cancer in the years from 1997 to 2016. The entire observed period has been divided into four consecutive five-year periods. All analyses were performed using data registered in the Cancer Registry database on 1 September 2019. 234,827 cases of cancer were extracted from the database. We excluded from the analysis 1,711 cases of cancer due to death certificate only registration, 4,470 cases in which the date of registration was the same as the date of death, and 668 cases in which the person was 95 years of age or older. The vital status of patients was last checked on 31 August 2019. At the end of the observation period, the patient may be alive, dead or lost from follow up.

The results were calculated and presented in subgroups by sex and age at diagnosis, as well as the stage of cancer at diagnosis according to the simplified classification as used by population-based cancer registries (the localized, regional and distant stages of the disease). In individual sections, we show data on adult cancer patients for 26 selected primary cancer sites, as well as for all cancer sites combined. In the analyses of all cancer sites combined, non-melanoma skin cancer (C44) was excluded, as it is almost completely curable. Furthermore, due to lack of reporting, this diagnosis is also not taken into account in international comparisons when calculating the survival of all cancer sites combined. A separate chapter was prepared for cancers in children and adolescents up to and including 19 years of age with separate display for those who were diagnosed with leukaemia, lymphoma or brain tumours.

The content of each chapter is divided into two parts: epidemiology and clinical commentary. The epidemiological part presents essential data on the burden of cancer for a particular location (incidence, prevalence and mortality) and time trends. In addition to crude rates, we also show age-standardized rates. The differences between these give us an estimate of how much of the change over time can be attributed to an ageing population, and how much to other risk factors. Data on the histological subtype, the method of disease verification, the type and location of specific primary treatment, and the results of the survival analysis are also presented. We present the observed and net one-, three-, and five-year survival rates, stratified by diagnosis period, sex and stage of the disease at diagnosis, with corresponding 95% confidence intervals.

The analysis of the data carried out by the Cancer Registry is followed by a commentary from clinical experts who are involved in the specific treatment of cancer patients at the Institute of Oncology Ljubljana, the clinical divisions of the University Medical Centre Ljubljana and the Golnik University Clinic of Respiratory and Allergic Diseases. Surgeons, medical oncologists, radiotherapists and other specialists discuss changes in diagnostic and treatment methods that may have affected the survival of Slovenian patients, and point out the shortcomings that, if overcome, could further improve the survival of our patients.

Calculation of Survival and International Comparison

Survival analysis characterises a large group of statistical methods. In the present book, we consider survival exclusively as used in oncological epidemiology for the population-based data of cancer registries. In the analysis, we used a complete approach where all patients diagnosed during the observed period were included in the calculation, even if they had been followed for less than five years at the end of the study period. Patients who were followed for a shorter time only contribute to the calculation of complete survival for as long as we were actually able to follow them.

Survival time is defined as the time between the date the cancer was diagnosed and the date of death. Survival is calculated as the proportion of patients alive after defined periods, usually one, three and five years after diagnosis. The basic and at the same time the simplest measure of survival is so-called observed survival, which tells us the probability that a person is alive at a certain time after diagnosis. Among the various methods, the Kaplan-Meier method, which we used in our book, is the most common today. If we are interested in survival associated with a particular disease, while the cause of death is difficult or even impossible to determine, standard survival analysis techniques are no longer sufficient. Relative survival methods can be used in this case, which compare the survival of the observed group of patients with the survival that would be expected if they lived as long as the general population. Relative survival is thus the ratio between observed and expected survival, i.e. the survival expected in the entire population according to sex and age in the selected year. Traditional methods of calculating relative survival are subject to certain methodological shortcomings, which are largely avoided by calculating the net survival using the Pohar-Perme method, which we used in this study. Net survival is the survival that would be observed if the only cause of death was the disease we are studying, i.e. cause-specific survival. We used the relsurv software library for the R software environment for the calculation.

For 15 cancer locations, the survival of Slovenian cancer patients in an international context is also presented. We present the results of 26 European countries in the CONCORD-3 survey for the period between 2010 and 2014. International comparisons of cancer patient survival are primarily important for comparing the effectiveness of cancer control measures in the country.

Review of the Most Important Findings

1. **The survival of Slovenian cancer patients is increasing over time.** During the 20 years observed (1997–2001 and 2012–2016), the five-year net survival increased by 11 percentage points. The increase was significantly higher in men, for whom the five-year net survival increased by 17 percentage points (from 38% to 55%). In women, the five-year net survival increased by 6 percentage points (from 54% to 60%).

2. **Age and stage at diagnosis are still key when it comes to the survival of cancer patients.** The five-year net survival is lowest in those aged 75-94, though even in this age group, the five-year net survival has also improved by 7 percentage points over the past 20 years. The five-year net survival of patients with localized stage disease increased by 10 percentage points over the observed 20 years and reached 85% in the last period; the survival of patients with a distant disease has not improved.

3. **In both sexes, survival has improved significantly over the last 20 years for three common cancers:** colorectal cancer (by 14 percentage points, from 48% to 62%), melanoma of the skin (by nearly 12 percentage points, from 79% to 90%), and lung cancer (by 8 percentage points, from 10% to 18%). These results reflect earlier diagnostics and advances in systemic treatment.

4. **Progress has also been made in the two most common cancers by sex:** breast cancer in women and prostate cancer in men. The five-year net survival of breast cancer patients has increased by 10 percentage points in the last 20 years, while the five-year net survival of prostate cancer patients has increased by more than 20 percentage points. The significant improvement in prostate cancer survival is probably merely on paper since in the period under review, PSA testing in Slovenia was performed rather uncritically and resulted in the detection of prostate cancers that would have otherwise remained clinically silent for a long time in the natural course of disease, thus artificially prolonging survival due to early diagnosis.

5. The group of cancers where **no progress has been observed over time** or where survival still remains low includes pancreatic cancer, oesophageal cancer, liver, gallbladder and bile duct cancers, as well as brain tumours.

6. **In the CONCORD-3 study**, the five-year net survival of adult patients with 15 different cancer locations diagnosed between 2010 and 2014 was compared among 26 European countries. In most cases, the survival rates of Slovenian cancer patients are below the European average, which highlights the need and creates an incentive for future improvements.

7. **Less than 1% of cancer patients are children and adolescents**; they are mainly diagnosed with leukaemia, central nervous system tumours and lymphomas, and **have a better five-year survival compared to adults**. In the last 20 years (1997–2001 and 2012–2016), the five-year survival of children and adolescents with cancer has increased by 7 percentage points (from 79% to 86%).

Conclusions and Future Challenges

Population-based cancer survival is a composite indicator that reflects the characteristics of patients and the organization, accessibility, quality and efficiency of the healthcare system. This publication is the fourth comprehensive report on the survival of Slovenian cancer patients and shows the progress of Slovenian oncology and Slovenian healthcare, as well as Slovenian society as a whole over this 20 year period.

As we have determined, the survival of Slovenian cancer patients has been increasing over time, which gives us a basis and an incentive for future improvements. The National Cancer Control Programme provides us with a comprehensive set of activities in the fields of primary and secondary prevention, diagnostics, treatment and rehabilitation, as well as palliative care. Therefore, in order to reduce the cancer burden and improve the quality of life and economic sustainability, all evidence-based primary and secondary prevention programmes must be established, maintained and used, and evidence-based treatment implemented in professionally acceptable timeframes. The development of medical science, oncology and molecular biology in the last 20 years has brought many revolutionary insights in the field of oncology, which have undoubtedly had an impact and will have an even more significant impact on the survival of cancer patients in the future. To monitor the effectiveness of managing the cancer epidemic of today, the burden of cancer will need to be monitored in the future based on quality data and scientifically justified methodological approaches, while cooperation between oncological epidemiologists and clinical professionals is crucial for a comprehensive review and the preparation of proposals for improvement.

I.

BACKGROUND AND METHODOLOGY

SLOVENIAN CANCER PATIENT DATA

Cancer is not a single disease, but several hundred different ones. These can occur in any tissue or organ of the human body. They differ in frequency, treatment and outcomes, but also have different risk factors that are known to a greater or lesser extent.

Epidemiological indicators show that cancer is a major public health burden in Slovenia. Among all the causes of death, it ranks 1st in men and 2nd in women. Global health indicators also show that cancer is an epidemic of modern times. In recent years, more than 15,000 Slovenes are diagnosed with cancer annually, and slightly over 6,000 die from it. There are more than 100,000 people living in Slovenia who have been diagnosed with cancer at some point in their lives. Since cancer is more common among the elderly (only a third of patients are younger than 65 at the time of diagnosis), and as the Slovenian population is ageing, it is expected that the burden of this disease will increase, even if the level of risk factors remains the same as it is today.

These presentations of cancer burden data are intended for both the professional and lay public; however, they may have differing significance for them. Thus, with this information, individuals wonder what risk they have of getting cancer, often remembering relatives, friends and acquaintances who have been diagnosed with or died of this disease. Cancer patients are more interested in their chances of surviving the disease and how many people have been diagnosed with cancer. However, experts think about preventive measures and healthcare planning, set priorities, assess the needs for oncological care and monitor the quality and efficiency of healthcare.

The continuous and systematic collection, storage and analysis of data on all cancer patients is the basis for controlling this major public health problem. Population-based cancer registries play a key role in this. Their purpose is to collect accurate and complete cancer data that can be used to plan and evaluate the National Cancer Control Programme, specifically in the fields of primary and secondary prevention, diagnostics, treatment, rehabilitation and palliative care, in order to plan the capacities and resources needed to manage cancer (staff, medical equipment and hospital and rehabilitation facilities). They are also used for targeted clinical and epidemiological research in Slovenia and in wider international research, as well as for evaluating the effectiveness of screening programmes.

Data on new cases of cancer (incidence), survival and prevalence collected in the Slovenian Cancer Registry (hereinafter: the Cancer Registry) at the Institute of Oncology Ljubljana, together with data on mortality collected and managed by the National Institute of Public Health, are the basis for assessing the cancer burden in a country. Cancer mortality is a basic indicator of the cancer burden worldwide, since it is available for the largest number of countries. Cancer mortality depends, on the one hand, on the number of new patients (incidence) and, on the other, on their survival. Survival itself does not reflect the incidence, as it only takes into account those who already have the diagnosis, so it indirectly indicates the success of diagnostic procedures and treatment (in patients with an earlier diagnosis, the treatment is more successful). The population survival of cancer patients, as shown by cancer registries, is, therefore, a composite indicator. It reflects the characteristics of patients, as well as the organization, accessibility, quality and efficiency of the healthcare system. Clinicians usually present their results on survival analysing groups of patients with a particular disease treated in an individual hospital; population survival significantly differs from this. Population survival is affected, for example, by the disease stage at diagnosis, which depends on the time from the first signs to the time of diagnosis. This time may be reduced through better health literacy of a population, the ability of general practitioners to consider the possibility of a serious disease, through increasing the availability of diagnostic tests, and through minimising waiting times. The availability of organized screening programmes with proven benefits further increases the chances of a cure or at least better survival, as they detect precancerous lesions or early-stage disease. Once diagnosed, the success of the treatment depends on the type of cancer, the patient's characteristics (age, comorbidities and the patent's general condition) and also on the availability of multidisciplinary treatment and the qualifications of the medical team. All of these diverse factors that determine population survival must be considered by the researcher who interprets the results of population survival studies, and even more so when comparing survival between countries.

The current publication is the fourth comprehensive report of the Cancer Registry on the survival of Slovenian cancer patients. It presents the progress achieved by Slovenian oncology and Slovenian healthcare in 20 years. These achievements and the possibilities of even better results are commented on by experts from the clinical environment, who treat cancer patients daily at the Institute of Oncology Ljubljana, University Medical Centre Ljubljana and the Golnik University Clinic of Pulmonary and Allergic Diseases.

Slovenian Cancer Registry

The Slovenian Cancer Registry was established in 1950 at the Institute of Oncology Ljubljana and is one of the oldest population-based cancer registries in the world. When founding the Institute of Oncology Ljubljana in 1938, the Health Records and Statistics Service was established in a separate work unit, which, in addition to clinical research, also collected data on cancer patients. When the National Population Cancer Registry was established at the Institute of Oncology Ljubljana, the statistics service also took over all the tasks related to the mandatory reporting of cancer cases to the Cancer Registry. The Cancer Registry has been a full member of the International Association of Cancer Registries (IACR) since its founding in 1968 and from the very beginning of the European Network of Cancer Registries (ENCR). The Cancer Registry collects data, prepares statistical analyses on the cancer burden in Slovenia and conducts extensive research activities. It is also actively involved in the development and dissemination of the knowledge needed to plan and implement actions for reducing the cancer burden in the country.

In Slovenia, cancer reporting has been mandatory and prescribed by law since 1950. All healthcare institutions in Slovenia and other entities delivering healthcare activities must regularly report new cases of cancer to the Cancer Registry. All diseases that are classified in the Neoplasms section as per the 10th revision of the International Classification of Diseases and Related Health Problems for Statistical Purposes (ICD-10) must be reported. Cancer should also be reported when the diagnosis is not confirmed microscopically (histologically or cytologically) and it is first discovered upon autopsy.

Cancer notification forms are the main source of data for the Cancer Registry. Additional sources of data for the registration of new cancer cases are medical reports on the cause of death sent to the Cancer Registry by the National Institute of Public Health, and data on diagnosed cancers recorded in three national screening programmes: ZORA for the detection of precancerous and early cancerous lesions of the cervix, DORA for the early detection of breast cancer and Svit for the detection of precancerous alterations and cancer in the colon and rectum.

Vital status information (whether a person is alive, dead or lost from the population registry) is obtained from the Central Population Registry. Detailed analyses of the spatial distribution of cancer are possible with the precise identification of patients' addresses at diagnosis through regular connection with the Registry of Spatial Units of the Surveying and Mapping Authority of the Republic of Slovenia.

In the last three years, in cooperation with experts from the clinical environment, clinical cancer registries have been developed and established. They will enable a more detailed assessment of the quality of care of oncology patients. As the first of the planned clinical registries, the Clinical Registry of Cutaneous Melanoma was launched in 2017. The Clinical Registry of Lung Cancer was established in 2020, which will be followed by clinical registries for breast, prostate, colorectal and childhood cancers.

Cancer Registration and Preparation of Data for Computer Processing

The data collection unit in the Cancer Registry is the patient, and the data processing unit is a new case of cancer (an individual patient may have multiple primary cancers). Data on the patient, his or her illness and treatment are collected on a case-by-case basis. Over the years, the amount of data

collected on an individual cancer case has increased, especially with the establishment of clinical registries.

In the Cancer Registry, specially trained nurses code the data received on the notification forms in accordance with international and internal rules.

For the classification of neoplasms by primary location, the tenth revision of International Classification of Diseases and Related Health Problems for Statistical Purposes has been in use since 1997, before which we used the eighth revision. When classifying malignant diseases, it is necessary to pay attention to the classification of the morphology of neoplasms, for which we use the morphology section of the International Classification of Diseases for Oncology. We have been using its third edition since 2001 and the 2011 supplements since 2012. Each edition has some changes that need to be implemented, including an indication of which histological types are malignant and some new histological types that had not been considered separately before. For example, gastrointestinal stromal tumours (GIST) have only been classified as a special histological type since 2001. Following the modification of rules in 2001, borderline malignant ovarian tumours have been reclassified from code C56 to code D39.1, chronic myeloproliferative diseases, myelodysplastic syndromes are now considered malignant (topographic code C96.7) and polycythaemias have been reclassified under code C94.

A case is defined on the basis of the findings of any recorded examination—from the surgery report to the autopsy report, if the patient has not been previously treated. To define the stage of solid tumours in the Cancer Registry, we use a simplified classification into one of three groups: localized disease, regional (regionally extended) disease, and distant (disseminated or metastatic) disease. The simplified definition of the stages follows the TNM classification. A localized stage includes tumours marked T1 or T2. In breast, cutaneous melanoma, and thyroid cancer, T3 tumours are also included in the localized stage; in cervix, corpus uteri and sarcomas, and in ovarian, fallopian tube and trophoblastic tumours, only T1 tumours belong to the localized stage. In a localized disease, the regional lymph nodes are not affected and there are no metastases in distant organs (N0, M0). In the regional stage, the tumour is defined as T3 or T4 (except in the above-mentioned exceptions) and/or the regional lymph nodes (N1) are also affected, but there are no metastases in the distant lymph nodes and organs (M0). The group of distant (disseminated/metastatic) diseases includes cases where metastases were already in distant lymph nodes or organs (M1). The Cancer Registry also has data on the stage of the disease available according to the TNM staging or other staging scheme if it was reported on the notification form, or if there was at least enough data on it for its subsequent definition. Gynaecological tumours are also defined according to the FIGO classification, and in the case of cutaneous melanoma, their stage as per Clark and Breslow is also recorded. Malignant lymphomas are staged as per the Ann Arbor system.

Data Quality and Completeness

Analysis of the cancer registry data only allows a reliable assessment of the cancer burden if the data is as complete as possible and of sufficient quality. The completeness and quality of the data in the population cancer registries are determined by international rules, which the data of the Cancer Registry have been meeting from the very beginning.

Complete registration shows the proportion of all new cancer cases in the area covered by the registry that are included in the registry database. In general, data completeness is considered to be greater when the registry has access to the source data. Despite the long tradition and efforts of the Cancer Registry team, the number of registered cases largely depends on the diligence and accuracy of those who are obliged to report them. The completeness of the registration is also affected by the reliability and availability of diagnostic procedures. Cancer registries today mostly use two methods to detect new cases of cancer: passive and active registration. In the case of passive registration, the cancer registry receives notification forms from external sources. In active registration, cancer registry staff have access to the medical records from which they draw data for disease registration. In Slovenia, the introduction of active registration started in 2019, which means that the data presented in this report has been collected through passive registration. The exception is the data

obtained from the Institute of Oncology Ljubljana, where active registration was in place since the very establishment of the hospital registry. However, the Cancer Registry began to implement active registration in 2019 in other hospitals as well, which will contribute to the even better quality and completeness of the cancer data in the future. In Slovenia—and also in other European population-based cancer registries—there is less complete registration of non-melanoma skin cancer and other cancers that are treated only on an outpatient basis.

The main source of data in the Cancer Registry is the cancer notification forms; additional data is obtained from secondary sources. Among them, the most important is linkage to the database on causes of death, from which we get information about everyone who has died of cancer. This improves the completeness of the registration for cancers with a poor prognosis but not of less fatal ones.

The completeness of the registry data can only be measured directly through specific studies, for example by reviewing discharge diagnoses and medical records in hospitals or medical practices in a given area. We have not done such a research project in Slovenia yet. Luckily, our colleagues from the clinical environment, who follow the survival of their patients, contribute a lot to the completeness of the data. When they send us enquiries about their patients, we often find information on patients who are not yet registered in the Cancer Registry database.

Indirectly, the completeness of the registration is assessed by the ratio between mortality and incidence and by the stability of the incidence over time. This means that there are no large fluctuations in the incidence between individual years and that there are no large differences in the percentage of cases recorded by the registry after it has already completed the processing of the data for a given year. In Slovenia the mortality-to-incidence ratio is stable over time and is gradually declining due to increasingly successful treatment: from 0.53 in the first five-year period, between 1997 and 2001, to 0.42 between 2012 and 2016. The number of cases registered after the publication of the annual reports decreased from around 5% in the first five-year period, from 1997 to 2001, to around 3% between 2012 and 2016.

The traditional indicators of the quality of the cancer registry data are also the percentage of microscopically (histologically or cytologically) verified cases and the percentage of death certificate only cases. Their values in four consecutive time periods are shown in Table 1.

Period	Number of registered cases	Proportion of microscopically verified cases (%)	Proportion of cases established through other investigations (%)	Proportion of death certificate only cases (%)
1997–2001	45,390	91.6	6.7	1.7
2002–2006	54,141	92.8	6.2	1.0
2007–2011	63,984	93.8	5.9	0.4
2012–2016	71,312	94.5	5.3	0.2

TABLE 1

Incidence of cancer cases over four five-year time periods, between 1997 and 2016, according to the basis of diagnosis.

Selection of Patients

The patients with permanent residence in Slovenia who were diagnosed with cancer in the years from 1997 to 2016 were included in the survival analysis. The entire observed period is divided into four consecutive five-year periods. Patients may have one or more primary cancers. If a patient has had more than one cancer, each is included in the section dealing with the specific organ system affected by the cancer.

Data was extracted from the Slovenian Cancer Registry's database on 1st of September 2019. We are constantly updating the cancer database with the latest information—so the incidence we publish in this book may differ from the figures published by the Slovenian Cancer Registry in the annual reports. For about 4% of cancer cases, we obtain the first information with a delay of more than three years, so these cases are also not included in the regular annual reports. On the SLORA web portal, the data is updated daily and thus always reflects the current situation in the database of the Cancer Registry.

The vital status of the patients was last updated on 31st of August 2019. At the end of the observed period, the patient may be alive, dead or lost to follow-up (Table 2)—the vital status of patients is updated via a direct (available 24 hours a day, seven days a week) secure web connection to the Central Population Registry. Between 1997 and 2001, 26 persons with no follow-up information in the Central Population Registry were registered in the Cancer Registry (0.06% of 45,390 new cancer cases during this period) and only 3 persons between 2002 and 2016 (0.002% of 189,437). For persons whose vital status (alive or dead) is not known in Central Population Registry , we determined the vital status as lost to follow-up, with the date of loss being the date on which the person was last recorded in the database as still alive. The Central Population Registry also provides information on people who have moved abroad and have thus been "lost" for the Slovenian system. All persons that have not died by the end of this analysis were censored with the total survival time up to the date of loss or end of follow-up (31st of August 2019). As an event in the survival analysis, we consider the death of a person with a survival time from the date of diagnosis to the date of death.

TABLE 2

Cancer incidence over four five-year periods, between 1997 and 2016, according to the vital status of the patients as on 31st of August 2019.

Period	Number of new cases	Proportion still alive (%)	Proportion deceased (%)	Proportion lost to follow-up (%)
1997–2001	45,390	47.3	52.5	0.2
2002–2006	54,141	52.8	47.1	0.1
2007–2011	63,984	54.9	45.0	0.1
2012–2016	71,312	57.5	42.4	0.03

For this publication, we extracted 234,827 cancer cases from the Cancer Registry database (Chapter C - Neoplasms according to the ICD-10 classification). For the survival analysis data for the date of cancer diagnosis, vital status and the date of the vital status (date of death for the deceased and date of lost to follow-up for the lost) was used for each cancer case to calculate the survival time. Furthermore, for calculations and the presentation of results by subgroups, we also used the data on sex, cancer site (according to ICD-10), age at the time of diagnosis and cancer stage at the time of diagnosis according to the simplified registry definition.

In individual chapters, we discuss adult patients with 26 selected primary cancer sites and with all cancer sites combined. We excluded non-melanoma skin cancer (C44), as it is a disease that is almost completely curable and almost no one has died from it in recent decades. Furthermore, as the notification of non-melanoma skin cancer is incomplete throughout Europe and the proportion of unregistered cases varies greatly also between countries, international comparisons of the survival for all cancers combined exclude non-melanoma skin cancer. According to age at the time of diagnosis, patients were classified into three age groups: 20 to 49, 50 to 74, and 75 to 94 years. We have prepared a separate chapter for cancers in children and adolescents, which includes children and adolescents from 0 to 19 years of age who have been diagnosed with leukaemia, lymphoma, and brain tumours. All cancers combined (excluding non-melanoma skin cancer) are analysed separately for children (0-14 years) and adolescents (15-19 years).

We excluded 1,711 cancer cases from the survival analysis, which were only registered in the Cancer Registry on the basis of a medical report on the causes of death, as we do not know the date of the diagnosis. We additionally excluded 2,759 cases of cancer in which the date of diagnosis is the same as the date of death, which makes a zero survival time—most of them are diagnosed during an autopsy.

In addition, we excluded 668 cases of cancer in which the person was 95 years of age or older at the time of the diagnosis, as high variability in survival estimates for this age group is expected. From the population tables, we already know that the life expectancy is short for this age group (or in other words, the population survival of this age group is not expected to be 5 years or more). Therefore, it is not possible to realistically estimate the five- or multi-year net survival of the elderly, and survival estimates are often unreliable even for a shorter observational period. Furthermore, there is usually a small number of people in this age group.

TABLE 3

Number of cancer cases (excluding non-melanoma skin cancer) excluded from the survival analysis.

Period	Number of registered cases	Diagnosis on the same day as the person died	The age at diagnosis is 95 years or older	Proportion of excluded cases (%)
1997–2001	39,712	1,383	93	3.7
2002–2006	46,079	1,120	141	2.7
2007–2011	53,569	956	225	2.2
2012–2016	57,994	1,011	209	2.1

Calculation of Survival

The term survival analysis includes a large group of statistical methods used in various methodological areas. What they have in common is that the outcome we are interested in is the survival time i.e. the time between two events (though the observed event can be any decided on by the researcher, and not necessarily the death of the person). In this report, we consider survival exclusively as used in oncological epidemiology for the population-based data of cancer registries. The survival time is defined as between the date of the cancer diagnosis and the date of death or date of censoring. The calculated survival is interpreted as the proportion of patients who are still alive after a certain time from the diagnosis.

The reason why a special methodology has to be used for survival analyses instead of conventional methods for quantitative data analysis is the presence of censoring, i.e. the fact that not all individuals can be monitored until the final event (death in the case of population cancer registries). Nevertheless, censored cases should also be included in the survival analysis. There are several reasons for censoring: there are often some patients who are still alive at the end of the study, and sometimes

a patient is lost-to-follow-up, for example due to moving abroad. In any case, due to censored observations, a special approach is needed when estimating the survival rate.

There are several methods for calculating survival. The basic and at the same time the simplest measure of survival is the so-called observed survival, which tells us the probability that a person is alive after a specific time after diagnosis. Among the various methods available to calculate the observed survival, the Kaplan-Meier method is the most commonly used today, it provides a high level of accuracy and the calculation is easy.

In clinical trials, we are usually interested in deaths due to a specific disease; all deaths due to other causes are considered censored in the analysis (cause-specific survival). Such an approach would also be of interest for research at a population level, but in practice, it turns out that the number of patients included is generally too large for manually verifying the exact cause of death for each one. The causes of death collected by the National Institute of Public Health in Slovenia are often not sufficiently precise for such particular purposes. Therefore, and also due to the incomparability of the observed survival between different populations (for example between countries), instead of the observed survival, other survival measures are used, for the calculation of which data on the cause of death is not needed.

If we are interested in survival associated with a particular disease but the cause of death is difficult or even impossible to determine, standard survival analysis techniques are no longer appropriate. Instead, we use relative or net survival measures, which compare the survival of the observed group of patients with the survival that would be expected if they lived the same as the general population (the comparison takes into account the demographic structure of both patients and the population stratified by sex and age). Relative survival is thus the ratio between observed and expected survival. Expected survival is calculated based on data on overall mortality, which is routinely published in the form of life tables by sex, age and calendar year for each country as part of the demographic statistics. Relative survival is interpreted as the observed survival of patients compared to the survival of the general population with the same demographic structure. For example, a relative five-year survival of 0.30 tells us that the patient survival after five years is 30% of the survival in a comparable underlying population.

Classical methods of relative survival are subject to certain methodological shortcomings, which are largely avoided by calculating the net survival. Net survival is the survival that would be observed if the only cause of death was the disease we are studying, i.e. cause-specific survival. A net survival of 30% over five years tells us that in a hypothetical case where patients would die from cancer alone, 70% of those patients would die within up to five years of diagnosis. Net survival allows comparisons with the population at the individual level and thus offers additional insight into the data: classical methods of relative survival only give a good insight into the survival of the observed group. In addition, with net survival, we can also answer the question of how long someone lived relative to the general population, or whether one person lived relatively longer than another. The net survival of a group of patients is calculated as the average of the individual survival curves. The most commonly used method of net survival is the Pohar-Perme method.

In practice, the relative and net survivals of cancer patients are less than 100%. In rare cases, when the relative survival equals 100%, it can be concluded that the survival of a group of cancer patients is equal to the survival of the general population and therefore the disease itself did not shorten the lifespan. Theoretically, the calculated relative survival can also exceed 100%, meaning that observed patients have better survival than the general population. This could happen if patients adopt healthier living habits or if their comorbidities are under better surveillance and treatment than in the general population. Sometimes, however, the reason is methodological and results from a small number of cases not evenly distributed among age groups.

There are several approaches to calculating survival. In the cohort method, we follow a group of patients for a certain period, usually five years. Each person included in the analysis must, therefore, be able to survive for five years. Survival is calculated as the proportion of patients alive after the specified time, usually one, three and five years after diagnosis. In the complete method, we also include in the calculation patients who were followed for less than the specified time and only

contribute to the calculation of complete survival for as long as we were able to follow them. Thus, patients diagnosed with the disease three years before the end of the study contribute to one- and three-year complete survival, but when calculating the five-year survival, the survival time is censored after three years. A special form of complete survival is the period survival method, where only those patients who were diagnosed in the last year of the analysed period are included in the calculation of one-year survival; only those patients who were diagnosed two years ago are included in the calculation of the two-year survival; and so on.

In this report, we used the complete method to calculate survival. The observed survival was calculated using the Kaplan-Meier method, and for the calculation of the net survival, the Pohar-Perme method was implemented. For the calculation, we used the relsurv software library (rs.surv function) for the R software environment. We used the Slovenian annual complete life tables. Just a word of caution: on the SLORA web portal, the survival analysis shows the observed survival calculated using the Kaplan-Meier method and the relative survival calculated using the Hakulinen method. In the previous comprehensive report on the Survival of Slovenian Cancer Patients in 1991-2005 and in the annual reports of the Slovenian Cancer Registry until 2013, relative survival according to the Ederer II method was used. In the annual reports since 2014, we have been using net survival calculated using the Pohar-Perme method.

INTERNATIONAL COMPARISONS OF CANCER SURVIVAL – THE CONCORD PROGRAMME

In 15 Figures, we also show the survival of Slovenian cancer patients in the international context. International comparisons of cancer patient survival are important primarily because they show all the countries under comparison how successful they are in controlling cancer. In many countries, those comparisons have already been used to improve the organization of healthcare, as poor outcomes in survival compared with other countries have opened up many issues—not only professional concerns, but also political priorities.

All the participating countries know that such international comparisons of survival have their limitations due to differences between the countries. Such as: the registration of all cancer patients and follow-ups for their vital status are not equally complete and high-quality in all countries, and the definitions of some cancers in patient registration are not completely uniform. Some registries cover entire countries and some only individual regions.

The short title of the world's largest study of cancer patient survival is the CONCORD programme. CONCORD is a global scientific collaboration programme run by the Cancer Survival Group at the London School of Hygiene and Tropical Medicine. It is designed to monitor global trends in the survival of cancer patients worldwide. The CONCORD programme includes 40 national and international agencies, including the World Health Organisation Regional Office for Europe, the Organisation for Economic Co-operation and Development (OECD), and the World Bank. The CONCORD Steering Committee includes scientists and cancer patients from 13 countries with expertise in biostatistics, epidemiology, cancer registration and public health. The CONCORD programme involves 600 researchers from more than 300 institutions in 71 countries and territories. It is designed to shape national and global policy on cancer control.

The first CONCORD study was published in 2008. It brought together data from 101 cancer registries in 31 countries and covered 1.9 million patients diagnosed with colon, rectal, breast or prostate cancer between 1990 and 1994. It revealed very large international differences in five-year survival at the end of the 20th century. In 2015, the CONCORD-2 study enabled the global monitoring of cancer survival trends for the first time. It examined trends in the five-year survival of patients diagnosed with cancer over a 15-year period, from 1995 to 2009. It included data on more than 25 million cancer patients collected from 279 cancer registries; in 40 out of 67 countries, the registries covered 100 percent of the country's population. The study included patients with ten common

cancers and covered a total of two-thirds (63%) of all cancer diagnoses worldwide in high- and low-income countries.

The CONCORD-3 study covered five additional years of cancer data (2010-2014) just three years after the publication of the CONCORD-2 study. CONCORD-3 is a systematic analysis of more than 37.5 million patients diagnosed with cancer between 2000 and 2014 in more than 4,700 datasets using a strict protocol, standardized quality control, and centralized analysis using state-of-the-art procedures. In order to control for the very wide international variation in the risk that cancer patients can also die from causes other than cancer, the CONCORD-3 study produced more than 8,000 life tables of all-cause mortality by year of age (0–99 years), covering each combination of country or geographical area, individual calendar year (2000–2014), sex, and—where known for cancer patients—race or ethnicity. To allow a fair comparison of cancer survival estimates by country and cancer, the estimates were age-standardized to the International Cancer Survival Standard weights.

In 2014, two-thirds of the world's population lived in the 71 countries and territories participating in the CONCORD programme. CONCORD-3 included data from 322 population-based cancer registries; 47 of these registries covered 100 percent of the population. The analysis used data on 18 common cancers, which together account for 75 percent of all cancers diagnosed worldwide, including melanoma of the skin and cancers of the oesophagus, stomach, colon, rectum, liver, pancreas, lung, breast, cervix, ovary and prostate in adults, as well as brain tumours, leukaemia and lymphomas in both adults and children. Cancer patients were excluded from survival analyses if diagnosed with an in situ tumour. The outcome data was stratified by time period: from 2000 to 2004, from 2005 to 2009 and from 2010 to 2014. The authors estimated the net survival up to five years after cancer diagnosis taking into account the 'baseline mortality' (other causes of death). This criterion is 'recognized by doctors as an indicator of the effectiveness of cancer treatment'.

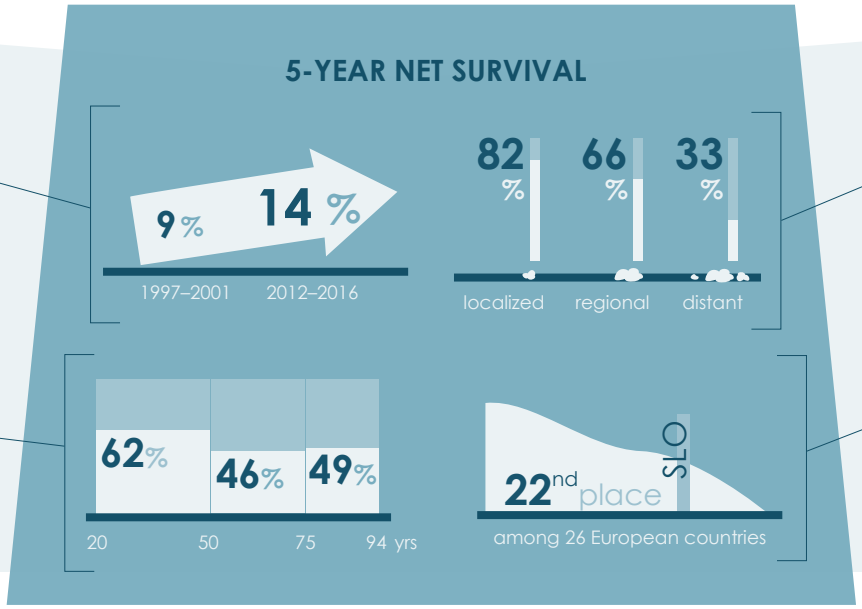
Since 2017, the OECD has included CONCORD survival estimates for 48 countries in its biennial publications on health indicators Health at a Glance. Survival estimates from the CONCORD programme have thus become the standard for international comparisons of cancer survival. This is formal recognition by the international community of the global coverage, methodological rigour and international comparability of the CONCORD survival estimates. These estimates have become key to assessing the performance of healthcare systems in all OECD member countries.

Although the CONCORD-3 study uses data from the Slovenian Cancer Registry, and the net survival is also calculated using the Pohar-Perme estimator using population-specific life tables, the results presented in this report and the results from CONCORD-3 should not be directly compared. CONCORD-3 takes into account different time periods, and to obtain more relevant comparisons between countries, net survival was also standardized by age.

PRESENTATION OF RESULTS

Each chapter in this report discusses one of the cancers in adults according to the organ of origin. Followed by all cancer sites combined excluding non-melanoma skin cancer in adults, and finally, cancers in children and adolescents are presented.

Each chapter begins with a graphical display (infographics) of the key results from the chapter. The trend in the five-year net survival for the first and last five-year period under review (1997–2001 and 2012–2016) is shown. This is followed by a presentation of the five-year net survival in the 2012–2016 period by stage and/or age and sex, and where available, also a presentation of Slovenia's ranking in the five-year net survival for the individual cancer for the period 2010–2014 from the international CONCORD-3 study, which includes 26 European countries.



The trend of the five-year survival between 1997–2001 and 2012–2016.
(example: p. 68, Gallbladder)

The five-year net survival in the period 2012–2016 by age groups.
(example: p. 26, Lip, oral cavity and pharynx)

The five-year net survival in the period 2012–2016 by stage.
(example: p. 128, Ovary)

Slovenia's ranking in the international comparison of age-standardized five-year net survival for the period 2010–2014 (CONCORD-3 study).
(example: p. 38, Oesophagus)

The content of each chapter is divided into two parts: epidemiology and clinical commentary. The epidemiological part begins with an indication of the average number of new cases and deaths by sex in the last included five-year period (2012–2016). Figure 1 shows the most basic indicators of the disease burden, incidence and mortality rates of cancer in both sexes combined and their time trends over 20 years, between 1997 and 2016. Both crude and age-standardized rates are presented. We used the direct method for standardisation, and the age structure of the population of Slovenia in 1997 as the standard. The difference between the crude and age-standardized incidence rates can give us an estimate of how much of the change can be attributed to the ageing of the Slovenian population, and how much to other risk factors. Changes in mortality rates reflect changes in the incidence and efficacy of treatment. The average annual percentage changes were estimated using mathematical models of segmental linear regression. For modelling, we used the statistical program Joinpoint (version 4.1.1), which uses consecutive points in time to fit one or more regression lines. The regression coefficient of each of the lines represents the average annual change for the specific period represented by the line (or segment).

We further present prevalence data, i.e. the number of patients alive as at 31 December 2016 who had ever been diagnosed with a specific cancer, separately according to the time interval since the diagnosis. This indirectly indicates whether patients are still being treated in relation to cancer (as part of primary treatment, rehabilitation or surveillance) or most likely do not have any more appointments in relation to the specific cancer.

The incidence and mortality rates and prevalence data refer to all cancer patients of all ages, including those diagnosed on the day of death. As described in the previous section, all the survival analyses were limited to patients who were not diagnosed on the day of death; the analysis of the net survival also takes into account the age limit of up to 95 years. Thus, the chapters describing cancer in adults include patients aged 20 to 94 years, and the chapter on cancer in children and adolescents includes patients aged 0 to 19 years at diagnosis. The presentation of the incidence and mortality trends and prevalence is followed by a description of the number of patients included and excluded from the survival analysis.

Where appropriate, the percentages of patients according to the more specific site within each organ and the proportion of microscopically confirmed cases and the most common histological type of cancer are presented.

The sex, age of patients at diagnosis and stage of the disease in four five-year periods (1997–2001, 2002–2006, 2007–2011 and 2012–2016) are shown in Table 1. For each cancer site, we also show the percentage of patients who received specific primary treatment, what kind of primary treatment and in which of the Slovenian hospitals.

The net survival by period of diagnosis for four five-year periods (1997–2001, 2002–2006, 2007–2011, and 2012–2016) is shown in Figure 2. Table 3, on the other hand, shows the one-, three-, and five-year observed and net survival rates, divided by the period of diagnosis and sex, with corresponding 95% confidence intervals. Figure 3 shows the five-year net survival by age groups and Figure 4 by stage. In both figures, the net survival of all patients combined is presented for comparison. The results from the survival analysis are also given in the text, where the exact values are given.

At the end of the epidemiological part, if data is available, we show the five-year net survival of Slovenian patients with 95% confidence intervals, compared to patients from 26 European countries included in the international CONCORD-3 study. Figure 5 shows the data for the three observed periods (2000–2004, 2005–2009 and 2010–2014). The ranking of countries is shown according to the data from the last observation period. In the international study, they sometimes used slightly different groups of diagnoses than are presented in our analysis in the rest of the chapter. In such cases, the included diagnoses are clearly defined in the title or in the footnote of the figure.

The analysis of the data carried out by the Cancer Registry is followed by a commentary from clinical experts who are involved in the specific treatment of cancer patients every day at the Institute of Oncology Ljubljana, the clinical divisions of the University Medical Centre Ljubljana and the Golnik University Clinic of Respiratory and Allergic Diseases. Surgeons, medical oncologists, radiotherapists and other specialists discuss changes in diagnostic and treatment methods that may have affected the survival of Slovenian patients, and point out shortcomings that, if overcome, could further improve the survival of our patients.

References

Allemani C, Matsuda T, Di Carlo V, et al. Global surveillance of trends in cancer survival 2000–14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. Lancet 2018; 391(10125): 1023–75.

Allemani C, Weir HK, Carreira H, et al. Global surveillance of cancer survival 1995–2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2). Lancet 2015; 385(9972): 977–1010 [published correction appears in Lancet 2015; 385(9972): 946].

Brenner H, Gefeller O. An alternative approach to monitoring cancer patient survival. Cancer 1996; 78: 2004–10.

Coleman MP, Quaresma M, Berrino F, et al. Cancer survival in five continents: A worldwide population-based study. Lancet Oncology 2008; 9: 730–56.

Ederer F, Axtell LM, Cutler SJ. The relative survival rate: a statistical methodology. Natl Cancer Inst Monogr 1961; 6: 101–21.

National Cancer Control Programme 2017–2021. Ljubljana: Ministry of Health, Republic of Slovenia; 2020. Available from: http://www.dpor.si/

EUROCARE: Survival of cancer patients in Europe. Italy: Istituto Nazionale Tumori di Milano, Istituto Superiore di Sanita; 2020. Available from: http://www.eurocare.it/

Cancer Registry for Slovenia. Incidence of cancer in Slovenia (1983–2008). Ljubljana: Institute of Oncology, Cancer Registry; 1986–2005.

Institute of Public Health. International Classification of Diseases and Related Health Problems for Statistical Purposes. 10th revision (International Statistical Classification of Diseases and Related Health Problems). Ljubljana: Institute of Public Health of Republic of Slovenia; 1995.

Kaplan EL, Meier P. Non-parametric estimation from incomplete observations. J Am Stat Assoc 1958; 53: 457–81.

Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for Joinpoint regression with applications to cancer rates. Stat Med 2000; 19: 335-51 [published correction appears in Stat Med 2001; 20: 655].

London School of Hygiene & Tropical Medicine. Cancer Survival Group, CONCORD Programme.

London: London School of Hygiene & Tropical Medicine; 2020. Available from: https://csg.lshtm.ac.uk/research/themes/concord-programme/

Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB, eds. Cancer incidence in five continents. Vol 8. Lyon: International Agency for Research on Cancer; 2002.

Pohar M, Stare J. Relative survival analysis in R. Comput Methods Programs Biomed 2006; 81: 272–8.

Pohar Perme M, Stare J. Individual relative survival. Infor Med Slov 2007; 12(1): 15–23.

Pohar Perme M, Esteve J, Rachet B. Analysing population-based cancer survival – settling the controversies. BMC Cancer 2016; 16: 933.

Pohar Perme M, Stare J, Esteve J. On estimation in relative survival. Biometrics 2012; 68: 113–20.

Pompe-Kirn V, Zakotnik B, Volk N, et al. Preživetje bolnikov z rakom v Sloveniji 1963–1990 (Cancer Patients' Survival in Slovenia 1963–1990). Ljubljana: Institute of Oncology, Cancer Registry for Slovenia; 1995.

Pompe-Kirn V, Zakotnik B, Zadnik V. Preživetje bolnikov z rakom v Sloveniji 1983–1997 (Cancer Patients' Survival in Slovenia 1983–1997). Ljubljana: Institute of Oncology, Cancer Registry for Slovenia; 2003.

Primic-Žakelj M, Pompe-Kirn V, Škrlec F, et al. Can we rely on cancer mortality data? Checking the validity of cervical cancer mortality data for Slovenia. Radiol Oncol 2001; 35: 243–7.

Primic-Žakelj M, Zadnik V, Žagar T, et all. Preživetje bolnikov z rakom, zbolelih v letih 1991-2005 v Sloveniji (Survival of cancer patients, diagnosed in 1991–2005 in Slovenia). Ljubljana: Institute of Oncology, Cancer Registry for Slovenia; 2009.

R Development Core Team. A language and environment for statistical computing. Vienna: R Foundation for Statistical Computing; 2005. Available from: https://www.R-project.org.

World Health Organisation. International Classification of Diseases for Oncology. Geneva: World Health Organisation; 2000.

Zadnik V, Primic-Žakelj M, Lokar K, et al. Cancer burden in Slovenia with the time trends analysis. Radiol Oncol 2017; 51(1): 47–55.

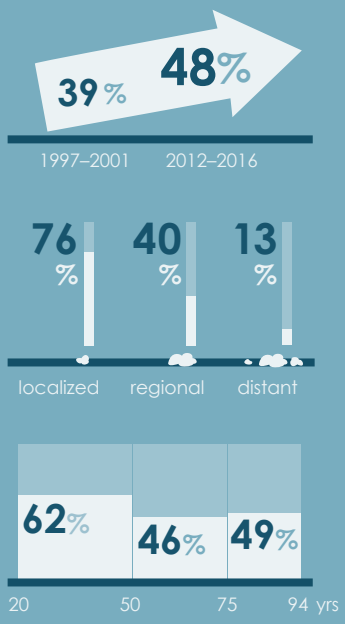
Žagar T. Lifetables for Slovenia 1982-2004. Rostock: Max Planck; 2005. Available from: https://www.mortality.org/cgi-bin/hmd/country.php?cntr=SVN&level=1.

II.

SURVIVAL BY CANCER SITE

C00–C14

LIP, ORAL CAVITY AND PHARYNX

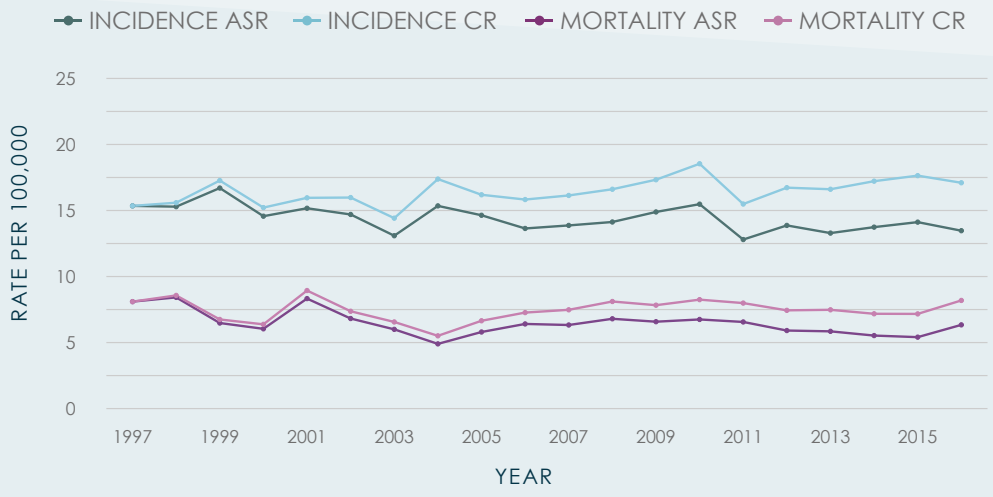


EPIDEMIOLOGY

In the last five-year period (2012–2016), 351 people per year on average were diagnosed with oral and pharyngeal cancer in Slovenia, 274 men and 77 women, and 155 people died, 128 men and 27 women. As shown in Figure 1, the incidence rates of oral and pharyngeal cancer did not change significantly but fluctuated considerably throughout the observed period. Between 2007 and 2016, the crude incidence rate of oral and pharyngeal cancer in women increased statistically significantly by 2.8% per year, while in men and in both genders together, it did not change in a statistically significant way. Head and neck cancer is closely related to smoking. Although it affects men more frequently than women, the incidence of this cancer is increasing faster in women than in men, which has also been observed in Slovenia for other smoking-related cancers. The mortality rates of oral and pharyngeal cancer also did not change significantly. From 2007 to 2016, the crude mortality rate of oral and pharyngeal cancer decreased by 0.8% per year in men and increased by 0.9% per year in women.

FIGURE 1

The crude (CR) and age-standardized (ASR) incidence and mortality rates of oral and pharyngeal cancer in Slovenia in 1997–2016.



At the end of 2016, there were 2,391 people living in Slovenia who had been diagnosed with oral and pharyngeal cancer at some point in their lives. Of those, the diagnosis had been established less than one year ago in 309 people, one to four years ago in 763 people, and over ten years ago in 735 people.

The survival analysis included 6,592 cases of patients aged 20 to 94 years; 54 cases (1%) were excluded because they were diagnosed on the day of death or because they did not fulfil the age inclusion criteria.

In the observed periods, in most cases (11–20%), cancer occurred in the oropharynx (C10), tonsils (C09), other and unspecified parts of the tongue (C02) and the floor of mouth (C04). In 6-12%, cancer occurred in the hypopharynx (C13), the lip (C00), the palate (C05), and other and unspecified parts of the mouth (C06). In less than 5% of cases, cancer occurred in the nasopharynx (C11), the gum (C03), other and unspecified major salivary glands (C08), and other and ill-defined sites in lip, oral cavity and pharynx (C14).

	Sex		Age			Stage			Total
	Men	Women	20–49 yrs	50–74 yrs	75–94 yrs	Localized	Regional	Distant	
1997–2001	1320	248	359	1073	136	440	1087	27	1568
1997–2001 %	84.2	15.8	22.9	68.4	8.7	28.1	69.3	1.7	
2002–2006	1260	318	277	1102	199	482	1035	45	1578
2002–2006 %	79.9	20.2	17.6	69.8	12.6	30.5	65.6	2.9	
2007–2011	1354	345	253	1219	227	496	1142	55	1699
2007–2011 %	79.7	20.3	14.9	71.8	13.4	29.2	67.2	3.2	
2012–2016	1366	381	230	1272	245	466	1209	66	1747
2012–2016 %	78.2	21.8	13.2	72.8	14.0	26.7	69.2	3.8	

TABLE 1

Number and proportion of patients with oral and pharyngeal cancer by sex, ages, stage and period of diagnosis in Slovenia in 1997–2016.

Less than 1% of patients in each period did not have their disease confirmed microscopically. In all periods, squamous cell carcinoma was the most common among the microscopically confirmed cases, occurring in more than 90% of cases in the last period.

In all periods, more men than women were diagnosed with oral and pharyngeal cancer, of which the largest proportion was aged 50 to 74 years. The disease was most commonly diagnosed in the distant stage (Table 1).

FIGURE 2

Net survival of patients with oral and pharyngeal cancer by period of diagnosis in Slovenia in 1997–2016.

Regarding the specific primary treatment of oral and pharyngeal cancer, between 1997 and 2016, the largest proportion of patients (30%) were treated with surgery and radiotherapy; 21% and 39% of them, respectively, received radiochemotherapy in the last two observed periods. 27% of patients were treated with radiotherapy alone and 18% or 41% of them received radiochemotherapy in the last two observed periods. 22% of patients were treated with surgery alone. Systemic treatment (neoadjuvant or adjuvant) was administered to 15% of patients, most often in combination with radiotherapy (11%). Throughout the entire observed period, six percent of patients did not receive specific primary treatment; the proportion of these persons did not change significantly during the observed five-year periods.

TABLE 2

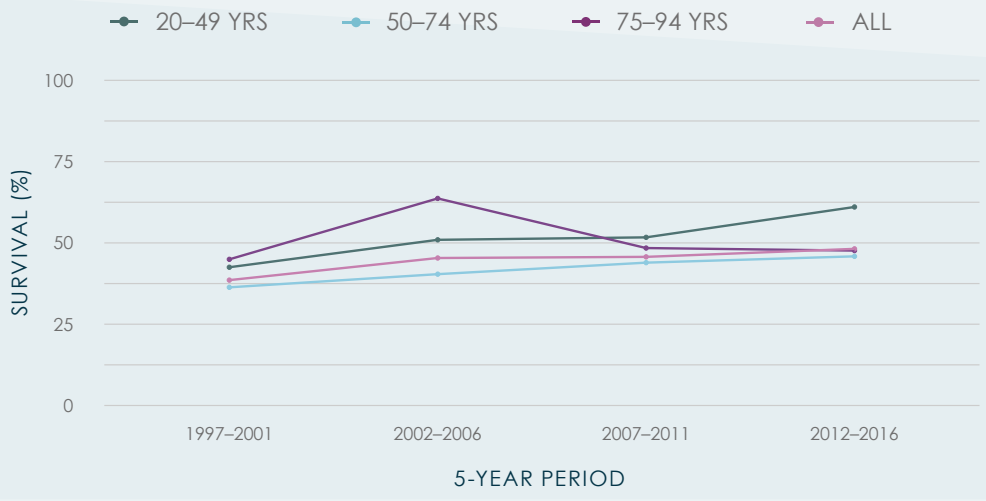
One-, three- and five-year observed and net survival (with a 95% confidence interval – CI) of patients with oral and pharyngeal cancer by sex and period of diagnosis in Slovenia in 1997–2016.

Survival / Period			1997–2001	(95% CI)	2002–2006	(95% CI)	2007–2011	(95% CI)	2012–2016	(95% CI)
Observed	1-year	all	65.8	63.5–68.2	72.7	70.6–75.0	73.4	71.3–75.5	73.6	71.6–75.7
		men	62.3	59.7–65.0	70.1	67.6–72.7	71.8	69.5–74.3	70.9	68.6–73.4
		women	84.7	80.3–89.3	83.0	79.0–87.3	79.4	75.3–83.8	83.2	79.5–87.0
	3-year	all	43.9	41.5–46.4	48.5	46.1–51.0	50.1	47.8–52.6	52.3	50.0–54.7
		men	39.2	36.7–42.0	44.3	41.6–47.1	47.1	44.5–49.8	48.0	45.4–50.7
		women	68.6	63.0–74.6	65.1	60.1–70.6	62.0	57.1–67.4	67.7	63.2–72.6
	5-year	all	33.9	31.7–36.3	38.6	36.3–41.1	40.9	38.6–43.3	43.3	40.9–45.9
		men	30.0	27.6–32.6	34.3	31.7–37.0	37.5	35.0–40.2	39.2	36.5–42.0
		women	54.8	49.0–61.4	56.0	50.8–61.7	54.2	49.2–59.7	58.5	53.3–64.2
Net	1-year	all	67.4	65.0–69.8	74.6	72.4–76.9	75.0	72.9–77.2	75.1	73.0–77.2
		men	63.8	61.2–66.5	71.8	69.2–74.4	73.4	71.0–75.9	72.3	69.9–74.8
		women	86.6	82.1–91.3	85.8	81.7–90.2	81.2	76.9–85.7	84.9	81.1–88.8
	3-year	all	47.4	44.8–50.1	52.6	50.0–55.4	53.4	50.9–56.1	55.6	53.1–58.2
		men	42.3	39.6–45.3	47.7	44.8–50.8	50.3	47.5–53.2	51.0	48.2–53.9
		women	74.2	68.2–80.8	71.5	65.6–77.9	65.7	60.3–71.5	72.3	67.3–77.6
	5-year	all	38.6	35.9–41.4	45.4	42.6–48.3	45.7	43.1–48.5	48.3	45.5–51.2
		men	34.3	31.6–37.3	39.3	36.4–42.5	42.2	39.3–45.2	43.6	40.6–46.8
		women	61.1	53.8–69.4	69.1	62.2–76.7	59.6	53.7–66.0	65.2	58.5–72.8

Throughout the observed period, oral and pharyngeal carcinoma surgeries were performed in at least 10 hospitals, most of them at the University Medical Centre Ljubljana (64%) and University Medical Centre Maribor (31%), with less than 2% in other hospitals. In the last five-year period, patients only received systemic treatment and radiotherapy at the Institute of Oncology Ljubljana.

FIGURE 3

Five-year net survival of patients with oral and pharyngeal cancer by age group in Slovenia in 1997–2016.



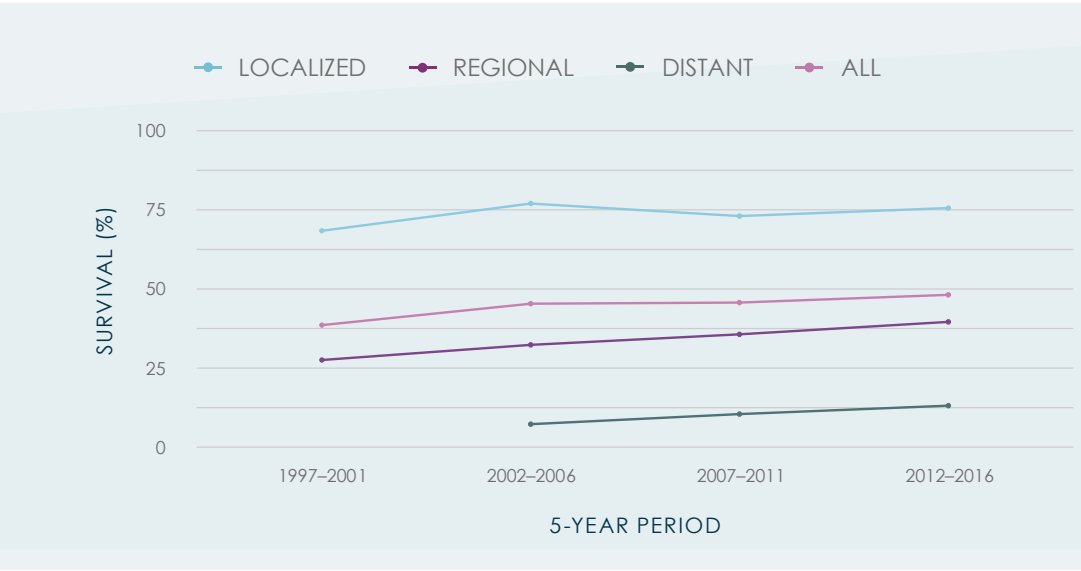


FIGURE 4

Five-year net survival of patients with oral and pharyngeal cancer by stage in Slovenia in 1997–2016.

The survival of patients with oral and pharyngeal cancer has gradually increased in the observed periods (Figure 2, Table 2). In the 20 years under review, the five-year net survival increased by slightly less than 10 percentage points. Regarding the five-year net survival of patients with oral and pharyngeal cancer, women have a much better survival rate than men throughout the observed period; the difference varies between 17 and 30 percentage points (Table 2).

In Slovenia, compared to other selected cancers, oral and pharyngeal cancer ranks 14th in men and 10th in women by five-year net survival.

Figure 3 shows the impact of age on the survival of patients with oral and pharyngeal cancer. The five-year net survival was lowest in patients aged 50 to 74 years. In the 20 years under review, five-year net survival increased by slightly less than 10 percentage points. The survival of persons aged 20 to 49 was better in the last two periods compared to other age groups and improved by 19 percentage points between the 2012–2016 period compared to the 1997–2001 period.

The importance of the stage at diagnosis is shown in Figure 4. The five-year net survival of patients with the localized stage of the disease has recently reached 76%. The five-year net survival of patients with the regional stage approaches 40%, whereas in patients with the distant stage at diagnosis, it is just over 13%. The temporal trend of the five-year net survival of patients with oral and pharyngeal cancer between 1997 and 2016 is improving for all stages of disease.

CLINICAL COMMENTARY

Primož Strojan, Cvetka Grašič Kuhar, Aleksandar Aničin

In the observed 20-year period, the number of patients with oral and pharyngeal cancer in the Slovenian population gradually increased, but only in women; no changes in incidence were observed in men. It seems that women in Slovenia adopted smoking and drinking habits later than men and also began to abandon them later, or that awareness-raising and anti-smoking legislation have been less effective in women. However, a comparison of age-standardized incidence rates over time also shows a clear trend of their decline. The same, but to a lesser extent, applies to age-standardized mortality. In Slovenia, we did not detect an increased incidence of oropharyngeal cancer associated with human papillomavirus (HPV) in the analysed period. In many countries, it is already a major aetiological factor for the development of this cancer, more important than smoking and alcohol, and significantly contributes to increasing its incidence. In the youngest age group (20–49 years), where we expect the highest incidence of HPV-related oropharyngeal cancer, the incidence decreased by almost 10%, while the proportion of patients in both older age groups increased by about 5%.

The proportion of microscopically confirmed cases remains stably high at more than 99%. Although the diagnostic treatment of patients with oral and pharyngeal cancers takes place mainly at the secondary level and in both university clinical centres, most patients start the specific primary treatment at the Institute of Oncology Ljubljana (42%) followed by University Medical Centres Ljubljana (39%) and Maribor (16%). The share of other Slovenian hospitals is, as expected, negligible and declining; the Murska Sobota General Hospital stands out as a smaller hospital with an increasing number of treatments initiated. This could indicate the inadequacy of the diagnostic procedure performed there and, in the absence of a multidisciplinary consultation board in this hospital, may constitute dangerous clinical practice. The non-negligible 6% share of patients who did not receive any specific treatment reflects the aetiological association of oral and pharyngeal cancer with excessive drinking and smoking habits and related defects of other organs that impair the patients' performance and thus the possibility of introducing aggressive oncological treatments. The distribution by stage did not change significantly: at the time of diagnosis, only slightly less than one third of the patients had a localized disease and two thirds had regional metastases. Due to the more consistent use of modern diagnostic imaging methods, especially computed tomography, and recently also positron emission tomography (PET-CT), the share of patients with distant metastases has increased or doubled, but still remains small (below 4%).

Surgery was indicated as the first-line treatment of choice, either alone or in combination with other forms of treatment, in more than half of patients, while slightly less than 70% of all patients with these cancers received radiotherapy. This means 5–15% less than as per international recommendations. A small proportion of patients (1%) who received systemic treatment alone matched the proportion of patients who already had systemic metastases at the time of diagnosis.

Survival increases from period to period, in particular the 5- and 10-year survival rates when the likelihood of recurrence is already very low or nil. This means that as a result of advances in surgical and radiation techniques (the introduction of intensity-modulated radiotherapy after 2007), fewer and fewer people die from late side effects of the treatment. Improvement in survival over time is seen for all stages of the disease, both genders and all age groups. The increase in survival rates is more pronounced in men and especially in younger patients aged 20 to 49 years. In younger patients and in women, survival is also more favourable than in the elderly or in men, which is expected given the organism's performance status (better in the young) and the attitude towards disease and treatment (more positive among women).

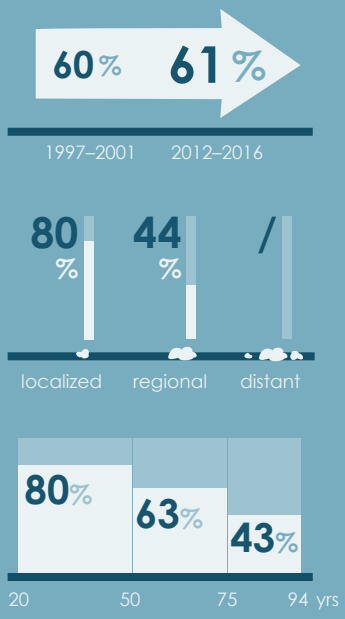
References

Borras JM, Barton M, Grau C, et al. The impact of cancer incidence and stage on optimal utilization of radiotherapy: Methodology of a population based analysis by the ESTRO–HERO project. Radiother Oncol 2015; 116: 45–50.

Strojan P, Zadnik V, Šifrer R, et al. Incidence trends in head and neck squamous cell carcinoma in Slovenia, 1983–2009: role of human papillomavirus infection. Eur Arch Otorhinolaryngol 2015; 272: 3805–14.

C32

LARYNX



EPIDEMIOLOGY

In the last five-year period (2012–2016), 99 people per year on average were diagnosed with laryngeal cancer in Slovenia, 86 men and 13 women, and 56 people died, 48 men and 8 women. As shown in Figure 1, the incidence and mortality rates of laryngeal cancer gradually decreased throughout the observed period, despite occasional fluctuations. Between 2007 and 2016, the crude incidence rate of laryngeal cancer decreased by 1.6% per year; in men it decreased by 2%, while in women it increased by 1.5% per year. The crude mortality rate of laryngeal cancer decreased by 1.4% per year; it decreased by 2.4% in men, and it increased by 4.8% per year in women. The time trends are not statistically significant, but they follow the pattern observed for smoking cancers, reflecting the changing smoking habits of men and women in Slovenia.

At the end of 2016, there were 997 people living in Slovenia who had been diagnosed with laryngeal cancer at some point in their lives. Of those, the diagnosis had been established less than one year ago

FIGURE 1

The crude (CR) and age-standardized (ASR) incidence and mortality rates of laryngeal cancer in Slovenia in 1997–2016.

in 100 people, one to four years ago in 250 people, and over ten years ago in 381 people.

The survival analysis included 2,115 cases of patients aged 20 to 94 years; 37 cases (2%) were excluded because they were diagnosed on the day of death or because they did not fulfil the age inclusion criteria.

Over the observed periods, most cases of laryngeal cancer occurred in the glottis (C32.0), 43–56%, and supraglottis (C32.1), 29–41%. The proportion of glottis tumours has been increasing over time at the expense of the proportion of supraglottic tumours. In 5–7% of patients, the disease occurred as an overlapping lesion of the larynx (C32.8), in about 2% it occurred in the subglottis (C32.2) and in less than 1% in the laryngeal cartilage (C32.3). In 5–12% of cases, the site of laryngeal cancer was unspecified (C32.9).

	Sex		Age			Stage			Total
	Men	Women	20–49 yrs	50–74 yrs	75–94 yrs	Localized	Regional	Distant	
1997–2001	519	53	90	428	54	314	249	6	572
1997–2001 %	90.7	9.3	15.7	74.8	9.4	54.9	43.5	1.1	
2002–2006	467	56	80	374	69	274	243	4	523
2002–2006 %	89.3	10.7	15.3	71.5	13.2	52.4	46.5	0.8	
2007–2011	489	52	46	423	72	312	222	3	541
2007–2011 %	90.4	9.6	8.5	78.2	13.3	57.7	41.0	0.6	
2012–2016	415	64	25	375	79	235	236	7	479
2012–2016 %	86.6	13.4	5.2	78.3	16.5	49.1	49.3	1.5	

TABLE 1

Number and proportion of patients with laryngeal cancer by sex, age, stage and period of diagnosis in Slovenia in 1997–2016.

In total, only ten patients did not have their disease confirmed microscopically. In all periods, the most common histological type among all the microscopically confirmed cases was squamous cell carcinoma, occurring in 95 % of cases in the last five-year period.

Throughout the observed period, 8.4 times more men than women were diagnosed with laryngeal cancer; the majority of patients were aged 50 to 74 years. The disease was most commonly diagnosed in the localized stage (Table 1). In the last five-year period (2012–2016), a decrease in the proportion of cancers diagnosed in the localized stage is noticeable compared to previous periods, which means that the proportions of cancers diagnosed in the localized and regional stages are roughly equal.

Regarding the specific primary treatment of laryngeal cancer between 1997 and 2016, 47% of patients received radiotherapy alone, 6% and 9% of them, respectively, received radiochemotherapy in the

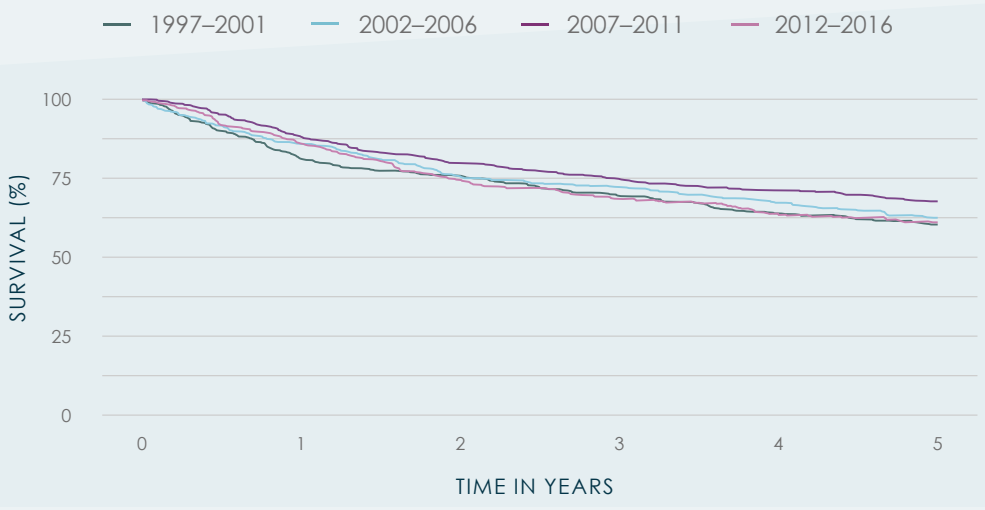


FIGURE 2

Net survival of patients with laryngeal cancer by period of diagnosis in Slovenia in 1997–2016.

last two observed periods. 28% of patients were treated with surgery as well as radiotherapy (9% of them received radiochemotherapy), while 13% were treated with surgery alone. Systemic treatment (neoadjuvant or adjuvant) was given to 7% of patients, most often in combination with radiotherapy (4%). Across the entire observed period, 5% of patients did not receive specific primary treatment; the proportion of these persons did not change significantly during the observed five-year periods.

TABLE 2

One-, three-, and five-year observed and net survival (with a 95% confidence interval-CI) of patients with laryngeal cancer by sex and period of diagnosis in Slovenia in 1997–2016.

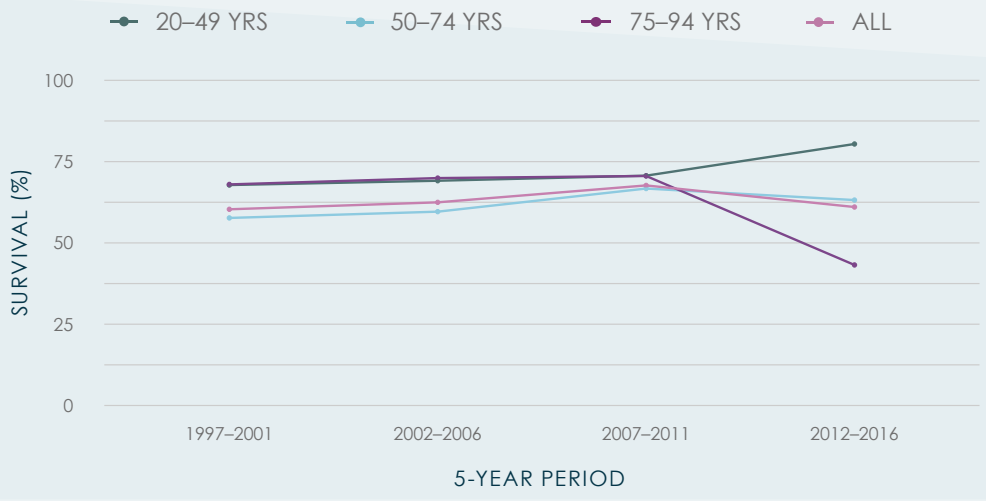
Survival / Period			1997–2001	(95% CI)	2002–2006	(95% CI)	2007–2011	(95% CI)	2012–2016	(95% CI)
Observed	1-year	all	79.0	75.7–82.4	83.8	80.6–87.0	86.0	83.1–88.9	84.1	80.9–87.5
		men	78.7	75.3–82.4	83.7	80.4–87.1	85.5	82.4–88.7	84.3	80.9–87.9
		women	81.1	71.3–92.4	83.9	74.8–94.1	90.4	82.7–98.8	82.8	74.1–92.6
	3-year	all	63.5	59.7–67.6	66.0	62.0–70.2	69.5	65.7–73.5	63.8	59.7–68.3
		men	62.9	58.9–67.2	66.2	62.0–70.6	68.3	64.3–72.6	64.5	60.1–69.3
		women	69.8	58.5–83.3	64.3	52.9–78.1	80.8	70.7–92.2	59.3	48.3–72.6
	5-year	all	51.9	48.0–56.2	53.5	49.4–58.0	59.7	55.7–64.0	53.9	49.4–58.8
		men	50.9	46.8–55.4	53.5	49.2–58.3	58.5	54.3–63.0	54.5	49.6–59.9
		women	62.3	50.5–76.8	53.6	42.0–68.4	71.2	59.9–84.6	48.3	36.8–63.4
Net	1-year	all	81.1	77.7–84.7	86.0	82.8–89.3	88.1	85.1–91.1	86.0	82.7–89.4
		men	81.0	77.4–84.7	86.1	82.7–89.6	87.7	84.5–91.0	86.3	82.8–90.0
		women	82.4	72.4–93.8	84.6	75.5–94.8	91.7	84.1–100.1	83.9	75.0–93.7
	3-year	all	69.3	65.1–73.8	72.2	67.9–76.8	74.8	70.7–79.1	68.5	64.0–73.3
		men	68.9	64.5–73.7	72.9	68.3–77.7	73.8	69.5–78.4	69.5	64.7–74.7
		women	73.2	61.3–87.5	66.6	54.9–80.9	83.7	73.2–95.7	62.0	50.6–75.8
	5-year	all	60.3	55.5–65.4	62.4	57.4–67.8	67.6	63.0–72.6	60.8	55.5–66.6
		men	59.4	54.4–64.9	63.1	57.7–68.9	66.7	61.7–71.9	62.1	56.3–68.4
		women	67.9	55.2–83.5	56.1	43.9–71.8	76.6	64.5–91.0	51.5	38.6–68.5

Most laryngeal cancer surgeries are performed at the University Medical Centre Ljubljana (70% in the last period) and at the University Medical Centre Maribor (29% in the last period). As part of their primary treatment, in the last five-year period, patients received systemic treatment at the Institute of Oncology Ljubljana (92%) and the University Medical Centre Ljubljana (8%).

The net survival of patients with laryngeal cancer does not change significantly according to the year of diagnosis (Figure 2, Table 2). Between 2007 and 2011, the five-year net survival improved by around 5 percentage points compared to the previous period, while between 2012 and 2016, it returned

FIGURE 3

Five-year net survival of patients with laryngeal cancer by age group in Slovenia in 1997–2016.



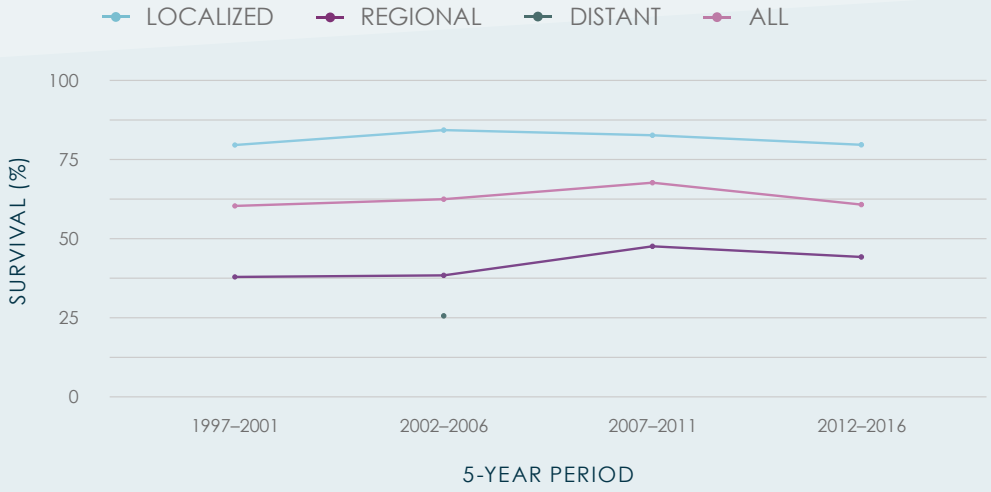


FIGURE 4

Five-year net survival of patients with laryngeal cancer by stage in Slovenia in 1997–2016.

to the previous level. Throughout the observed period, there were no major differences between the sexes in the five-year net survival of patients with laryngeal cancer (Table 2).

In Slovenia, compared to other selected cancers, laryngeal cancer ranks 10th in men and 13th in women by five-year net survival.

Figure 3 shows the impact of age on the survival of patients with laryngeal cancer. The five-year net survival in the first three observed periods is lowest in people aged 50 to 74 and ranges from 58 to 67%. Survival is similar in the observed periods in the younger and older age groups, 67 to 71%. In the last period (2012–2016), there has been a major change in the survival rate in all age groups. It was most pronounced in people aged 75–94 years, but these changes are not statistically significant and are most likely due to the small number of patients.

The importance of the stage at diagnosis is shown in Figure 4. The five-year net survival of patients with the localized stage of the disease is similar in all periods and ranges from 79 to 84%. The five-year net survival rate of patients with the regional stage is much lower compared to patients with the localized stage and ranges from 38 to 48% over the entire observed period. In patients with the distant stage of the disease at diagnosis, the net survival could not be calculated for all periods due to the small number of cases.

CLINICAL COMMENTARY

Primož Strojan, Cvetka Grašič Kuhar, Aleksandar Aničin

The crude and age-standardised incidence of laryngeal cancer decreased steadily during the observed period. The reason is a significantly lower number of newly diagnosed cases of this cancer in men (by 104 cases or 25%), while in women it even increased slightly (by 11 cases or 17%), which is in line with the pattern of changes in the smoking habits of Slovenian men and women. The proportion of the youngest (20–49 years) among all laryngeal cancer patients decreased by as much as 10 percentage points, while for those aged 50 to 74 and the elderly (75–94 years), it increased by 4 and 7 percentage points, which is most likely a reflection of the ageing Slovenian population. The ratio of men to women decreased from a baseline of 10 to 1 to 6.5 to 1.

The proportion of microscopically confirmed cases remains high, close to 100%. The number of patients with the localised stage of the disease decreased continually throughout the observed period, while the number of patients with regional lymph node involvement increased (in both cases by 5 percentage points) and was comparable for both groups in the last observed period (49%). These

changes reflect the better accessibility and thus more consistent use of modern diagnostic tests. About one percent of patients already had distant metastases at diagnosis: this proportion did not change significantly.

Most patients (more than half) started their treatment at the Institute of Oncology Ljubljana, with a more than 10% drop in the specific primary treatments in this institution in the last observed period. The reason is to be found in the introduction of new surgical approaches for the treatment of early-stage glottis cancers (laser surgery), which have become established since 2010. As a result, the proportion of patients who received primary treatment in both clinical centres, where the surgical part of the treatment of head and neck cancer is performed, has increased.

The largest proportion of patients is still treated with radiotherapy alone, although this is steadily declining (1997–2001: 50%; 2012–2016: 41%). In contrast, the number of patients treated with surgery followed by postoperative radiotherapy is increasing (1997–2001: 26%; 2012–2016: 32%), as well as patients treated with surgery alone (1997–2001: 12%; 2012–2016: 19%), which can be attributed to the above-mentioned new surgical approaches. In the last two five-year observed periods, around 10 % of patients received radiotherapy and systemic treatment, a combination of treatment that allows the conservation of the larynx in two-thirds of patients. Only one patient (0.2%) received systemic treatment as palliative treatment, which corresponds to the small number of patients who already had distant metastases at the time of diagnosis (up to 1.5%). Over 5% of patients did not receive specific oncological treatment. The reason for foregoing aggressive oncological treatment in those patients could be significant impairment of organs due to unhealthy habits, especially smoking, which worsens the general condition of patients.

Patient survival remained stable in all the observed periods. Only an improvement in 10-year survival is noticeable, when the risk of disease recurrence is nil. The reason for this is lower treatment-related late toxicity and tissue damage, mainly due to technological advances in surgery and radiotherapy and the more successful treatment of secondary malignancies.

References

Baird BJ, Sung CK, Beadle BM, et al. Treatment of early–stage laryngeal cancer: A comparison of treatment options. Oral Oncol 2018; 87: 8–16.

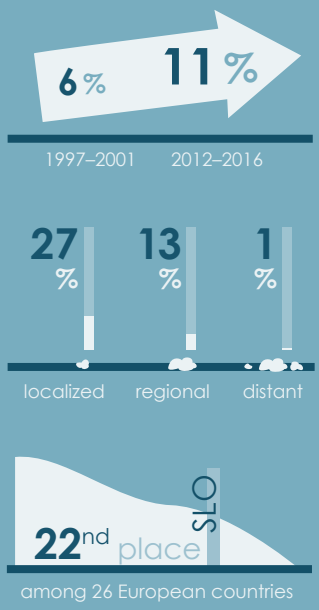
Li M, Zhang T, Tan B, et al. Role of postoperative adjuvant radiotherapy for locally advanced laryngeal cancer: a meta–analysis. Acta Otolaryngol 2019; 139: 172–7.

Spector ME, Rosko AJ, Swiecicki PL, et al. From VA Larynx to the future of chemoselection: Defining the role of induction chemotherapy in larynx cancer. Oral Oncol 2018; 86: 200–05.

Sanabria A, Chaves ALF, Kowalski LP, et al. Organ preservation with chemoradiation in advanced laryngeal cancer: The problem of generalizing results from randomized controlled trials. Auris Nasus Larynx 2017; 44: 18–25.

C15

OESOPHAGUS



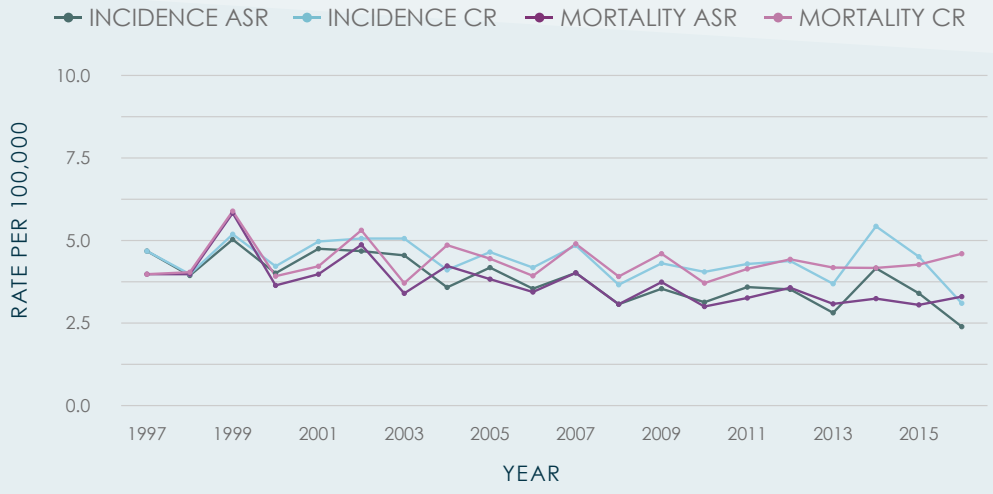
EPIDEMIOLOGY

In the last five-year period (2012–2016), 87 people per year on average were diagnosed with oesophageal cancer in Slovenia, 72 men and 15 women, and 89 people died, 72 men and 17 women. As shown in Figure 1, the incidence rates of oesophageal cancer gradually decreased throughout the observed period, despite repeated fluctuations. In the 2007–2016 period, the crude incidence rate of oesophageal cancer decreased by 1% per year—by 1.1% in men and by 0.3% in women. The reduction in the crude incidence rate is not statistically significant. The mortality rates of oesophageal cancer did not change significantly. From 2007 to 2016, the crude mortality rate of oesophageal cancer decreased by 0.4% per year in men and increased by 0.6% per year in women.

At the end of 2016, there were 155 people living in Slovenia who had been diagnosed with oesophageal cancer at some point in their lives. Of those, the diagnosis had been established less than one year ago in 42 people, one to four years ago in 55 people, and over ten years ago in 35 people.

FIGURE 1

The crude (CR) and age-standardized (ASR) incidence and mortality rates of oesophageal cancer in Slovenia in 1997–2016.



The survival analysis included 1,729 cases of patients aged 20 to 94 years; 54 cases (3%) were excluded because they were diagnosed on the day of death or because they did not fulfil the age inclusion criteria.

In the observed periods, in 14–42% of cases, the site of the cancer was unspecified (C15.9), though the proportion of unspecified cases of oesophageal cancer decreased threefold in the last period (2012–2016) compared to the 1997–2001 period. Among cases with specified site, most cases, 21–35%, occurred in the lower third of the oesophagus (C15.5), followed by the middle third of the oesophagus (C15.4), where 17–24% of cases occurred, and the upper third of the oesophagus (C15.3) with 10–16% of cases. In 5% or less, the oesophageal cancer occurred in the cervical (C15.0), thoracic (C15.1) and abdominal (C15.2) parts of the oesophagus or in the form of an overlapping lesion (C15.8).

Depending on the specific observation period, between 5–10% of patients did not have microscopically confirmed disease; this proportion falls with increasing age. Among the microscopically confirmed cases, squamous cell carcinoma was the most common histological type, occurring in 73% of cases in the last five-year period. The second most common type in all periods was adenocarcinoma; in the last period, it occurred in 23% of cases. In 2% of cases, the histological type was not specified.

	Sex		Age			Stage			Total
	Males	Females	20–49 yrs	50–74 yrs	75–94 yrs	Localized	Regional	Distant	
1997–2001	361	78	47	329	63	145	156	65	439
1997–2001 %	82.2	17.8	10.7	74.9	14.4	33.0	35.5	14.8	
2002–2006	362	81	43	309	91	83	172	126	443
2002–2006 %	81.7	18.3	9.7	69.8	20.5	18.7	38.8	28.4	
2007–2011	340	80	32	279	109	70	194	127	420
2007–2011 %	81.0	19.1	7.6	66.4	26.0	16.7	46.2	30.2	
2012–2016	351	76	26	307	94	67	205	126	427
2012–2016 %	82.2	17.8	6.1	71.9	22.0	15.7	48.0	29.5	

TABLE 1

Number and proportion of patients with oesophageal cancer by sex, age, stage and period of diagnosis in Slovenia in 1997–2016.

In all the observed periods, four times more men than women were diagnosed with oesophageal cancer; the majority of patients were aged 50 to 74 years. The disease was most commonly diagnosed in the regional stage (Table 1). Over the years, there has been a decline in the number of cancers diagnosed in the localized stage and an increase in cancers diagnosed in the regional and distant stages.

Regarding the specific primary treatment of oesophageal cancer between 1997 and 2016, 20% of patients received radiotherapy alone, 15% were treated with radiotherapy and systemic treatment, and 13%

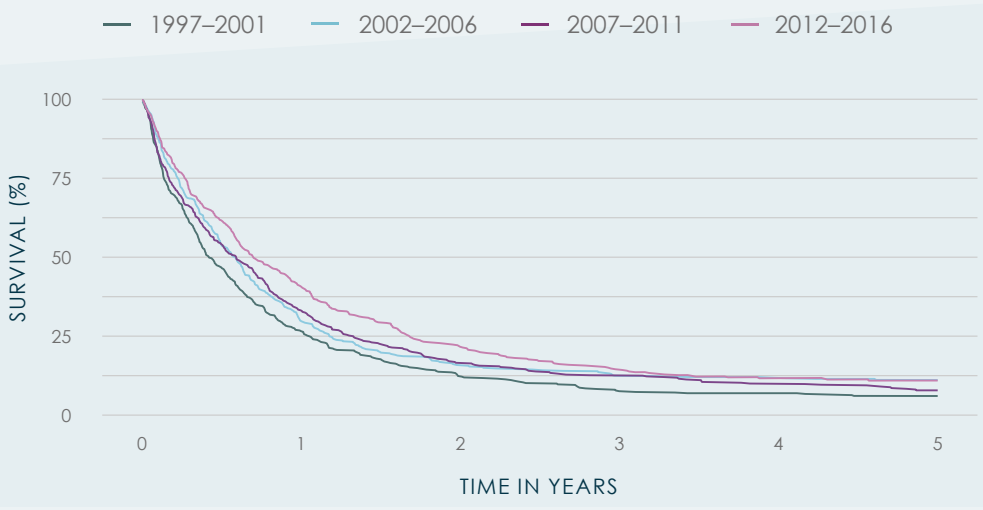


FIGURE 2

Net survival of patients with oesophageal cancer by period of diagnosis in Slovenia in 1997–2016.

were treated with surgery alone. Systemic treatment was given to 26% of patients, most often in combination with radiotherapy. Across the entire observed period, a total of 40% of patients did not receive specific primary treatment; the proportion of patients who did not receive specific primary treatment did not decrease over the years.

TABLE 2

One-, three- and five-year observed and net survival (with a 95% confidence interval–CI) of patients with oesophageal cancer by sex and period of diagnosis in Slovenia in 1997–2016.

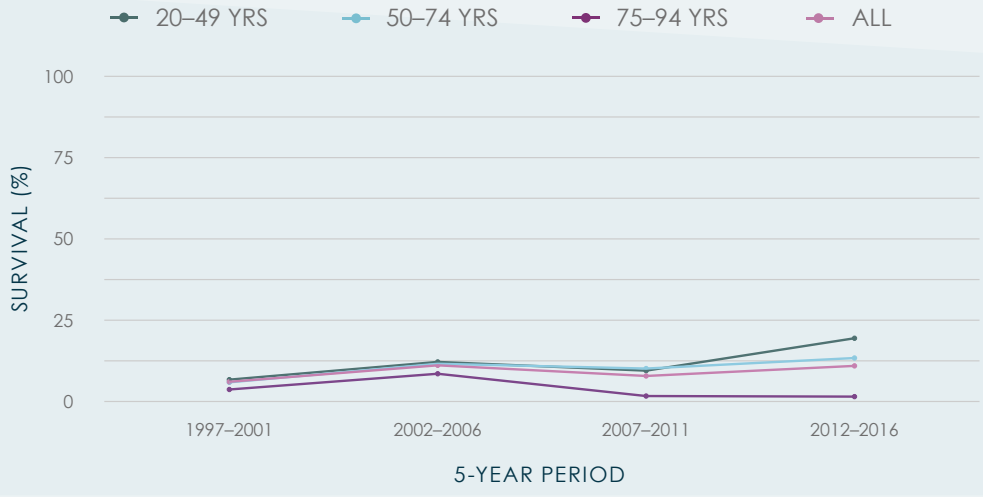
Survival / Period			1997–2001	(95% CI)	2002–2006	(95% CI)	2007–2011	(95% CI)	2012–2016	(95% CI)
Observed	1-year	all	25.6	21.8–30.0	29.0	25.1–33.6	32.4	28.2–37.2	39.8	35.4–44.7
		men	25.3	21.2–30.2	29.1	24.8–34.2	33.5	28.9–38.9	40.2	35.4–45.6
		women	26.9	18.7–38.8	28.4	20.1–40.1	27.5	19.3–39.3	38.2	28.7–50.8
	3-year	all	6.9	4.9–9.7	11.3	8.7–14.7	11.9	9.2–15.4	13.8	10.9–17.5
		men	7.0	4.8–10.1	10.5	7.8–14.2	10.6	7.8–14.4	13.9	10.7–18.1
		women	6.4	2.8–15.0	14.8	8.8–25.0	17.5	10.9–28.2	13.2	7.4–23.4
	5-year	all	4.8	3.2–7.3	9.1	6.7–12.2	7.1	5.1–10.1	10.5	7.9–14.0
		men	4.5	2.8–7.2	8.0	5.7–11.4	5.9	3.9–9.0	9.9	7.2–13.8
		women	6.4	2.8–15.0	13.6	7.8–23.5	12.5	7.0–22.3	13.2	7.4–23.4
Net	1-year	all	26.4	22.5–31.0	29.9	25.9–34.6	33.3	29.0–38.2	40.8	36.3–45.8
		men	26.0	21.8–31.0	30.2	25.7–35.4	34.5	29.7–40.0	41.2	36.3–46.8
		women	28.2	19.7–40.3	29.0	20.5–40.9	28.1	19.7–40.1	39.0	29.4–51.7
	3-year	all	7.6	5.4–10.7	12.5	9.6–16.2	12.7	9.8–16.4	14.5	11.4–18.5
		men	7.5	5.1–10.9	11.8	8.7–15.9	11.3	8.3–15.4	14.7	11.3–19.1
		women	8.2	3.7–18.3	15.7	9.4–26.3	18.1	11.2–29.2	13.7	7.7–24.2
	5-year	all	6.1	4.1–9.1	11.1	8.3–14.9	7.9	5.5–11.2	11.2	8.3–15.1
		men	5.1	3.2–8.1	10.3	7.3–14.6	6.6	4.3–10.1	10.5	7.5–14.9
		women	8.2	3.7–18.3	14.6	8.4–25.6	13.2	7.3–23.8	14.2	8.0–25.1

Throughout the observed period, oesophageal cancer surgery was performed in two hospitals: in the last five-year period, 81% of surgical procedures were performed at the University Medical Centre Ljubljana and 17% at the University Medical Centre Maribor. In the last five-year period, as part of their primary treatment, patients received systemic treatment at the Institute of Oncology Ljubljana (92%), the University Medical Centre Maribor (6%), and the University Medical Centre Ljubljana (3%).

The net survival of patients with oesophageal cancer is low and does not change significantly depending on the year of diagnosis (Figure 2, Table 2). In the 20 years under review, the five-year net survival improved by 5 percentage points. Over the entire observed period, the five-year net survival of patients with oesophageal cancer in women is slightly less than 5% higher on average compared to the survival in men (Table 2).

FIGURE 3

Five-year net survival of patients with oesophageal cancer by age group in Slovenia in 1997–2016.



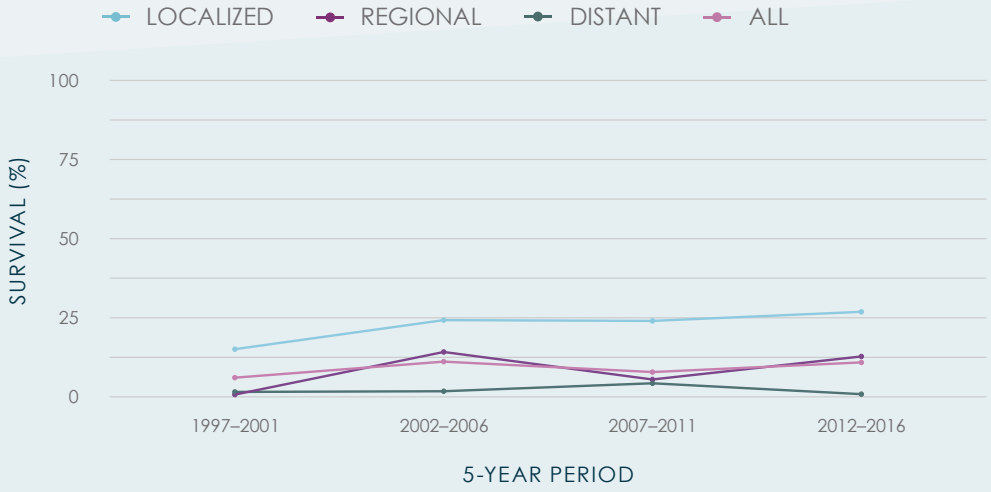


FIGURE 4

Five-year net survival of patients with oesophageal cancer by stage in Slovenia in 1997–2016.

In Slovenia, compared to other selected cancers, oesophageal cancer ranks 21st in men and 21st in women by five-year net survival.

Figure 3 shows the impact of age on the survival of patients with oesophageal cancer. The five-year

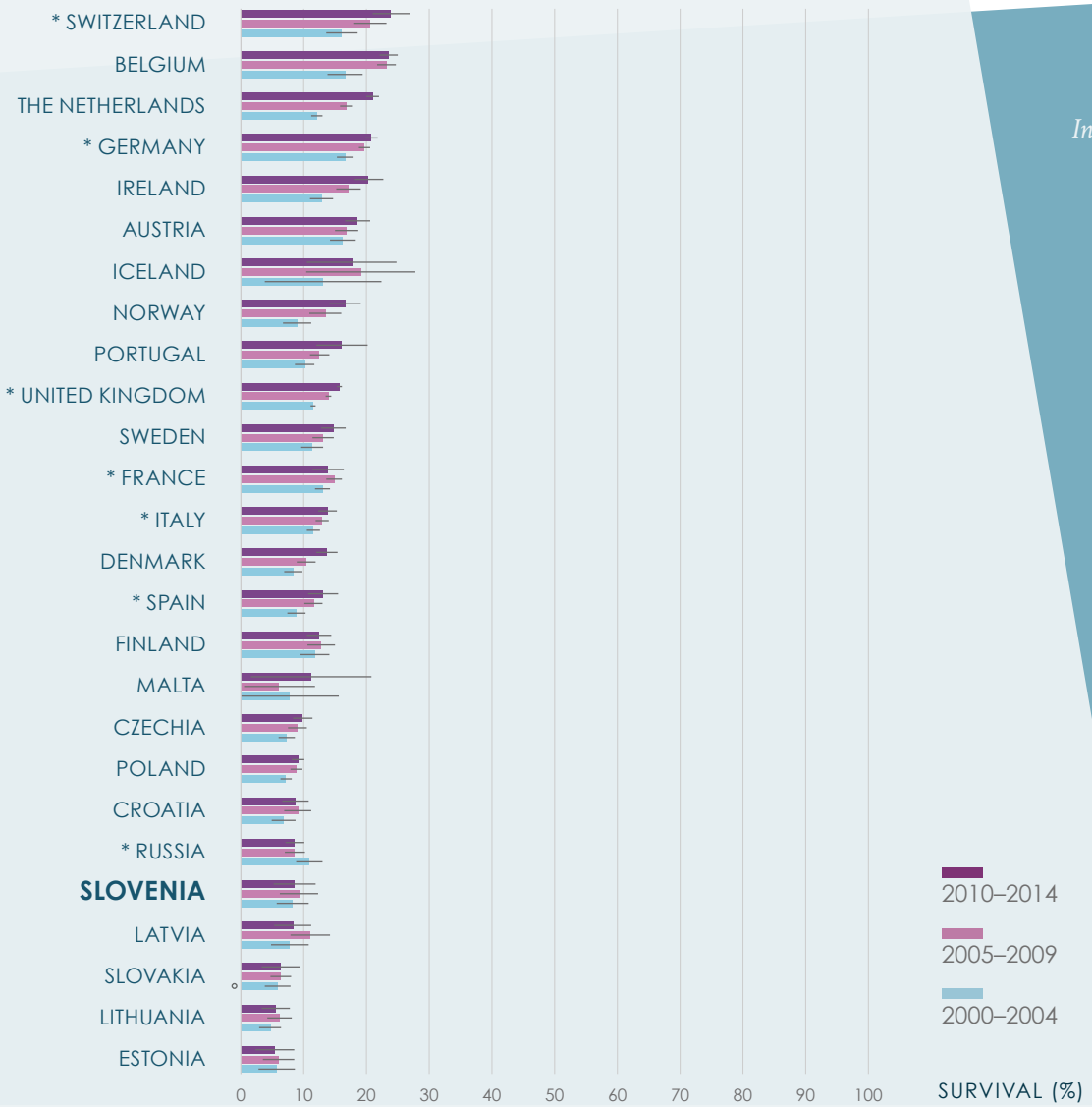


FIGURE 5

International comparison of age-standardized five-year net survival for oesophageal cancer (with 95% confidence intervals) in patients diagnosed during 2000–2004, 2005–2009 and 2010–2014 (CONCORD-3).

** Data doesn't cover a 100% of the country's population.*

° Survival estimate is less reliable.

net survival is lowest in patients aged 75–94, and declines over time. The survival of people aged 20 to 49 and 50 to 74 at diagnosis is similar in the first three observed periods in both age groups (6–12%). In the last observed period (2012–2016), the survival of people aged 20 to 49 improved and increased to 19%, while the survival of people aged 50 to 74 was only slightly higher than in previous periods (14%).

The importance of the stage at diagnosis is shown in Figure 4. The five-year net survival of patients with the localized stage of the disease is similar in all periods and is around 25%. The five-year net survival of patients with the regional stage is much lower compared to patients with a localized stage and ranges from 1 to 14% over the entire observed period. In patients with a distant stage of the disease at diagnosis, however, the five-year net survival is on average only about 2%.

The results of the world-wide CONCORD-3 study of patients diagnosed with cancer during the 15 years 2000–2014 in 71 countries and territories show that the five-year net survival of Slovenian patients with oesophageal cancer in the 2010–2014 period deteriorated compared to the previous period, but the difference was not statistically significant (Figure 5). For patients diagnosed during the most recent period (2010–2014), Slovenia ranked 22nd among the 26 participating European countries.

CLINICAL COMMENTARY

Mirko Omejc

The survival of patients with oesophageal cancer in the observed period (1997–2016) remains low. The slight trend of improved survival can be attributed to better survival in patients younger than 50 years and in patients with localized stage cancer. These were treated with surgery. Early diagnosis is still critical, but unfortunately there have been no breakthroughs in this area. In the last part of the observed period, compared to previous periods, even fewer patients in the localized stage and more patients in the regional stage were registered. Fewer cases of cancer in the localized stage at diagnosis points, on the one hand, to the highly malignant nature of oesophageal cancer and, on the other hand, more precise diagnostics during the last period. However, modern diagnostics are still not optimal since the most suitable tests for determining the stage of the disease—computed tomography (CT) of the chest and upper abdomen and endoscopic ultrasound examination—are unreliable in almost half the cases. The localized stages of oesophageal cancer are rare, particularly because oesophageal cancer metastasizes to the lymph nodes in 30% of cases already in stage T1 and 60% in stage T2. Lymph node metastases are possible even in the clinical stage of N0. Most often, tumours are already in the T2 stage at the time of diagnosis. Fewer cases of cancer in the localized stage are reflected in a smaller number of resections. Lower postoperative mortality and better intensive postoperative care also contribute to the improved survival of patients with localized cancer who have undergone surgery. Surgery remains the first-line treatment of choice. Radical resection can only be done occasionally, as the oesophagus and regional lymph nodes are difficult to access. The protocols for multimodal treatment with radiotherapy, chemotherapy and surgery changed slightly during the observed period. Given the poor prognosis of patients with a regional stage of the disease, it is appropriate to consider the feasibility of surgery, because these patients are mostly elderly with many comorbidities and poor physical performance.

Vaneja Velenik

Despite advances in diagnostics and treatment, oesophageal cancer remains an aggressive disease with a high rate of local and systemic recurrence and mortality. Patient survival has increased only slightly in the last observed periods. In addition to the disease stage, the histological cancer type (squamous cell carcinoma, adenocarcinoma) and the site of origin should be considered when assessing the survival trend. Histological types differ in the incidence, course, treatment and outcome of the disease. Squamous cell carcinoma is still the predominant type in Slovenia, while in the Western world the incidence of oesophageal adenocarcinoma is rising sharply in all age groups, the fastest among all types of cancer, and in some countries, it is already more frequent than squamous cell carcinoma.

According to the last two TNM classifications (with minor modifications in the eighth version), oesophageal cancer also includes cancer of the gastroesophageal junction, which is sometimes classified and treated as gastric cancer. This makes the comparison of survival between oncology centres unreliable.

In the last two observed periods, patients were irradiated with a three-dimensional technique, while before that, simpler techniques were used. For the last three years, we have been using more precise procedures, intensity-modulated radiotherapy and volumetric modulated arc therapy. These new approaches also contribute to lower cardiac mortality and mortality from other causes in patients over the age of 65.

In addition, this year, instead of 5-fluorouracil and cisplatin, we introduced the more effective and less toxic chemotherapeutics carboplatin and paclitaxel as radiosensitizers into the preoperative radiochemotherapy regimen. The lower acute toxicity of preoperative or radical treatment allows more patients to complete it and the more effective multimodal treatment contributes to a greater reduction in the stage of the disease, which may be followed by less demanding or minimal surgery with minor postoperative complications. In a matched analysis based on three randomized trials comparing perioperative chemotherapy (FLOT study: 5-fluorouracil, folic acid, oxaliplatin, docetaxel) and preoperative radiochemotherapy with carboplatin and paclitaxel (CROSS study), there were statistically significantly more radical resections in favour of the CROSS scheme, in both histological types. Therefore, the use of more toxic perioperative chemotherapy for locally advanced oesophageal and gastroesophageal junction cancer is quite incomprehensible.

Janja Ocvirk

The incidence of oesophageal cancer in all four five-year periods is similar in both sexes and is much higher in men than women. Unfortunately, the prognosis of the outcome of the disease is still very poor in Slovenia and around the world. Survival has increased slightly over the last five years, mainly because more patients received some kind of specific primary treatment. More patients also received systemic treatment. Cytostatics other than in the previous observation period were introduced as part of systemic treatment. The proportion of patients who received multimodal treatment as part of their primary treatment, including all three methods of specific treatment, i.e. radiotherapy, chemotherapy and surgery, is also increasing.

In the last five years, almost all patients have been treated in only three institutions: the Institute of Oncology Ljubljana, the University Medical Centre Ljubljana, and the University Medical Centre Maribor, which provide multimodal treatment for these patients together with the presentation of patients to multidisciplinary teams, which also leads to improved treatment outcomes.

References

Brierley JD, Gospodarowicz MK, Wittekind C, eds. TNM classification of malignant tumors. 8th ed. Chichester, West Sussex: Wiley–Blackwell; 2017.

Chang HK, Young TK, Sang–Hoon J, et al. Lymphadenectomy extent is closely related to long–term survival in esophageal cancer. Eur J Cardiothorac Surg 2007; 31: 154–60.

Favi F, Bollschweiler E, Berlth F, et al. Neoadjuvant chemotherapy or chemoradiation for patients with advanced adenocarcinoma of the oesophagus? A propensity score–matched study. Eur J Surg Oncol 2017; 43(8): 1572–80.

Graham AJ, Shrive FM, Ghali WA, et al. Defining the optimal treatment of locally advanced esophageal cancer: A systematic review and decision analysis. Ann Thorac Surg 2007; 83: 1257–64.

Lin SH, Zhang N, Godby J, et al. Radiation modality use and cardiopulmonary mortality risk in elderly

patients with esophageal cancer. Cancer 2016; 122(6): 917–28.

Satoshi Y, Kawahara K, Maekawa T, et al. Minimally invasive esophagectomy for stage I and II esophageal cancer. Ann Thorac Surg 2005; 80: 2070–5.

Zacherl J. The current evidence in support of multimodal treatment of locally advanced, potentially resectable esophageal cancer. Dig Dis 2014; 32: 171–5.

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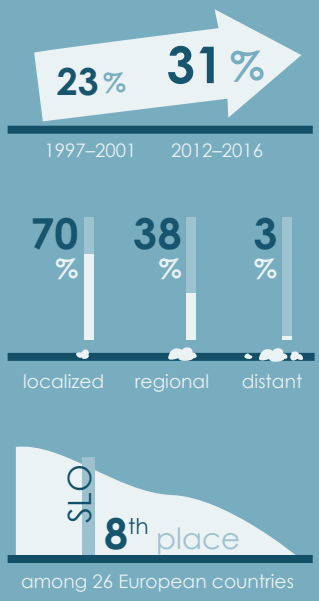
STOMACH



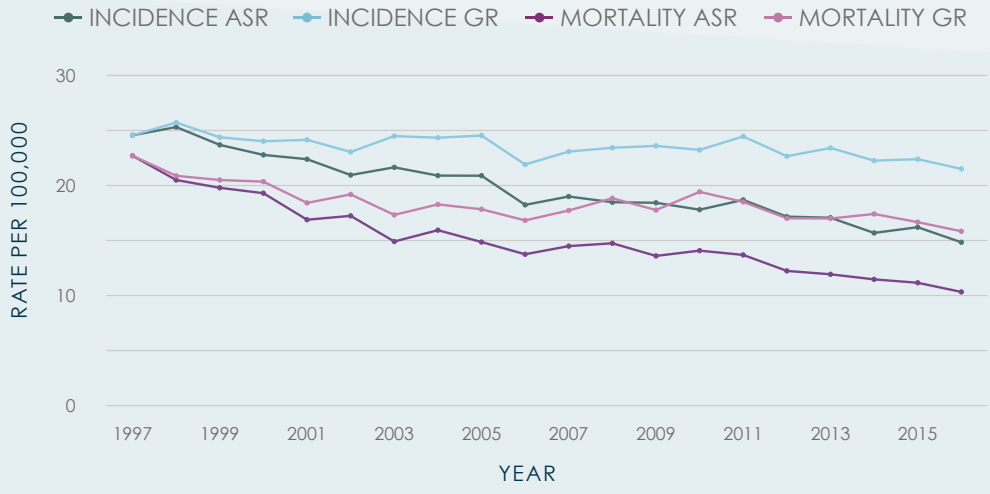
EPIDEMIOLOGY

In the last five-year period (2012–2016), 462 people per year on average were diagnosed with gastric cancer in Slovenia, 292 men and 170 women, and 346 people died, 208 men and 138 women. As shown in Figure 1, the incidence rates of gastric cancer gradually decreased throughout the observed period. Between 2007 and 2016, the crude incidence rate of gastric cancer decreased by 0.8% per year; in men it decreased by 0.4% and in women by 1.6% per year. The decline is statistically significant in women and in both sexes combined. Gastric cancer mortality rates are also declining. Between 2007 and 2016, the crude mortality rate of gastric cancer decreased by 1.5% per year; by 1.4% in men and by 1.7% per year in women. The decline is statistically significant in both sexes combined.

At the end of 2016, there were 2,044 people living in Slovenia who had been diagnosed with gastric cancer at some point in their lives. Of these, the diagnosis had been established less than one year ago in 294 people, one to four years ago in 591 people, and over ten years ago in 723 people.

FIGURE 1

The crude (CR) and age-standardized (ASR) incidence and mortality rates of gastric cancer in Slovenia in 1997–2016.



The survival analysis included 9,154 cases of patients aged 20 to 94 years; 362 cases (4%) were excluded because they were diagnosed on the day of death or because they did not fulfil the age inclusion criteria.

Over the observed periods, in 26–44% of cases, the site of the cancer was unspecified (C16.9), though the proportion of unspecified cases of gastric cancer decreased by 18 percentage points in the last period (2012–2016) compared to the 1997–2001 period. Among cases with specified locations, most cases (18–23%) occurred in the pyloric antrum (C16.3), followed by the cardia (C16.0) and the body of the stomach (C16.2), where the disease occurred in 11–17% of cases. An overlapping lesion of the stomach (C16.8) was present in 8–11%, while the lesser curvature of the stomach (C16.5) was affected in 5–9% of cases. In less than 2%, the disease occurred in the fundus of the stomach (C16.1), the pylorus (C16.4) and the greater curvature of the stomach (C16.6).

	Sex		Age			Stage			Total
	Males	Females	20–49 yrs	50–74 yrs	75–94 yrs	Localized	Regional	Distant	
1997–2001	1404	889	207	1428	658	491	867	720	2293
	% 61.2	38.8	9.0	62.3	28.7	21.4	37.8	31.4	
2002–2006	1399	876	198	1289	788	469	873	738	2275
	% 61.5	38.5	8.7	56.7	34.6	20.6	38.4	32.4	
2007–2011	1425	911	187	1207	942	469	895	852	2336
	% 61.0	39.0	8.0	51.7	40.3	20.1	38.3	36.5	
2012–2016	1423	827	142	1189	919	444	966	786	2250
	% 63.2	36.8	6.3	52.8	40.8	19.7	42.9	34.9	

TABLE 1

Number and proportion of patients with gastric cancer by sex, age, stage and period of diagnosis in Slovenia in 1997–2016.

Depending on the specific observation period, up to 6% of patients did not have their disease confirmed microscopically. In all periods, the most common histological type among all microscopically confirmed cases was adenocarcinoma, which occurred in 92% of cases in the last period. In 2% of the cases, the histological type was not precisely specified.

Throughout the observed period, more men than women were diagnosed with gastric cancer; the majority of patients were aged 50 to 74 years. The disease was most commonly diagnosed in the regional stage (Table 1). Over the years, there has been a slight decline in the number of cancers diagnosed in the localized stage and an increase in cancers diagnosed in the regional and distant stages.

FIGURE 2

Net survival of patients with gastric cancer by period of diagnosis in Slovenia in 1997–2016.

Regarding the specific primary treatment of gastric cancer between 1997 and 2016, 37% of patients were treated with surgery alone, while 9% were treated with surgery, radiotherapy and systemic treatment. Systemic treatment was given to 21% of patients throughout the period, most often in combination with surgery and radiotherapy. Throughout the observed period, 40% of patients did not receive specific primary treatment. The proportion of people who did not receive specific primary treatment decreased slightly over the five-year periods observed.

TABLE 2

One-, three- and five-year observed and net survival (with a 95% confidence interval–CI) of patients with gastric cancer by sex and period of diagnosis in Slovenia in 1997–2016.

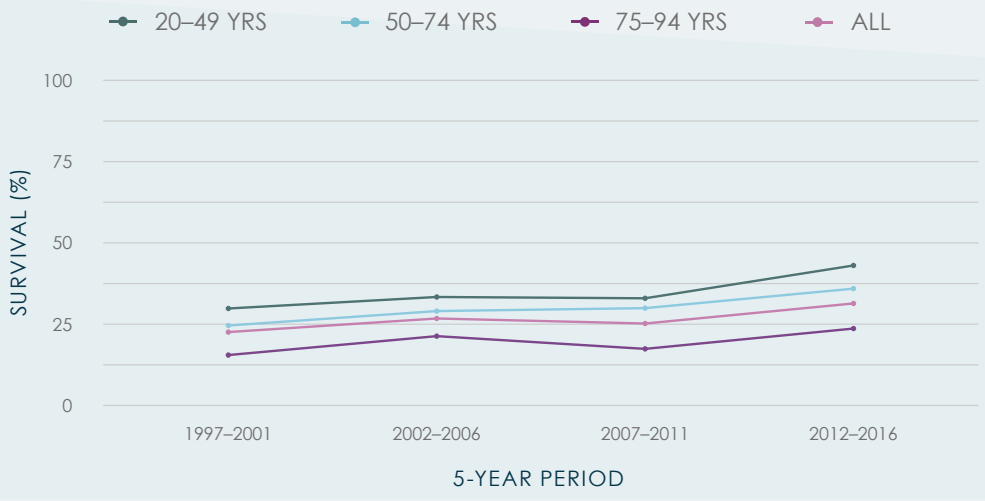
Survival / Period			1997–2001	(95% CI)	2002–2006	(95% CI)	2007–2011	(95% CI)	2012–2016	(95% CI)
Observed	1-year	all	38.3	36.3–40.3	43.7	41.7–45.8	44.1	42.2–46.2	49.7	47.7–51.8
		men	37.4	35.0–40.0	43.4	40.9–46.1	44.0	41.5–46.7	51.1	48.6–53.8
		women	39.6	36.5–42.9	44.1	40.9–47.5	44.2	41.1–47.6	47.2	44.0–50.8
	3-year	all	22.2	20.5–23.9	26.6	24.8–28.4	25.8	24.1–27.7	31.3	29.5–33.3
		men	20.1	18.1–22.3	25.3	23.1–27.7	24.8	22.7–27.1	31.2	28.8–33.7
		women	25.4	22.7–28.5	28.5	25.7–31.7	27.4	24.7–30.5	31.6	28.6–35.0
	5-year	all	18.8	17.2–20.4	21.9	20.3–23.7	21.4	19.8–23.2	26.3	24.4–28.2
		men	16.6	14.8–18.7	20.2	18.2–22.5	20.2	18.3–22.4	26.2	23.9–28.7
		women	22.2	19.6–25.1	24.5	21.9–27.6	23.3	20.7–26.2	26.3	23.4–29.6
Net	1-year	all	39.7	37.7–41.8	45.4	43.3–47.5	45.7	43.6–47.8	51.3	49.2–53.5
		men	39.0	36.5–41.8	45.2	42.6–48.0	45.8	43.1–48.5	52.9	50.2–55.6
		women	40.7	37.6–44.2	45.6	42.3–49.1	45.6	42.3–49.0	48.6	45.2–52.2
	3-year	all	24.6	22.7–26.6	29.7	27.7–31.9	28.5	26.6–30.6	34.4	32.3–36.6
		men	22.7	20.5–25.3	28.5	26.0–31.2	27.7	25.3–30.4	34.6	32.0–37.4
		women	27.4	24.5–30.8	31.6	28.4–35.2	29.8	26.7–33.1	34.1	30.8–37.8
	5-year	all	22.6	20.7–24.7	26.8	24.7–29.0	25.3	23.3–27.4	31.3	29.1–33.7
		men	20.7	18.4–23.4	24.8	22.2–27.6	24.4	21.9–27.1	31.6	28.8–34.7
		women	25.4	22.4–28.9	30.0	26.6–33.8	26.5	23.5–30.0	30.7	27.3–34.7

In all periods, gastric cancer surgery was performed in at least 10 hospitals. In the last five-year period, most surgical procedures were performed at the University Medical Centre Ljubljana (45%) and University Medical Centre Maribor (34%), and less than 5% in other hospitals. As part of their primary treatment, in the last five-year period most patients received systemic treatment at the Institute of Oncology Ljubljana (71%), followed by the University Medical Centre Maribor (15%), and the University Medical Centre Ljubljana (12%).

The net survival of patients with gastric cancer has been gradually improving with an increasing year of diagnosis (Figure 1, Table 2). In the 20 years under review, the five-year net survival increased by

FIGURE 3

Five-year net survival of patients with gastric cancer by age group in Slovenia in 1997–2016.



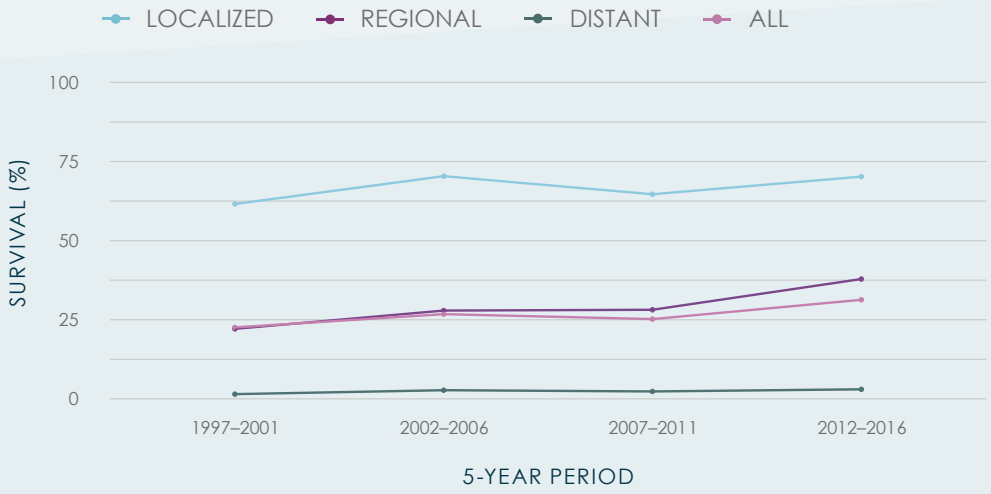


FIGURE 4

Five-year net survival of patients with gastric cancer by stage in Slovenia in 1997–2016.

9 percentage points. Throughout the observed period, there were no major differences between the sexes in the five-year net survival of patients with laryngeal cancer (Table 2).

In Slovenia, compared to other selected cancers, gastric cancer ranks 16th in men and 18th in women by five-year net survival.

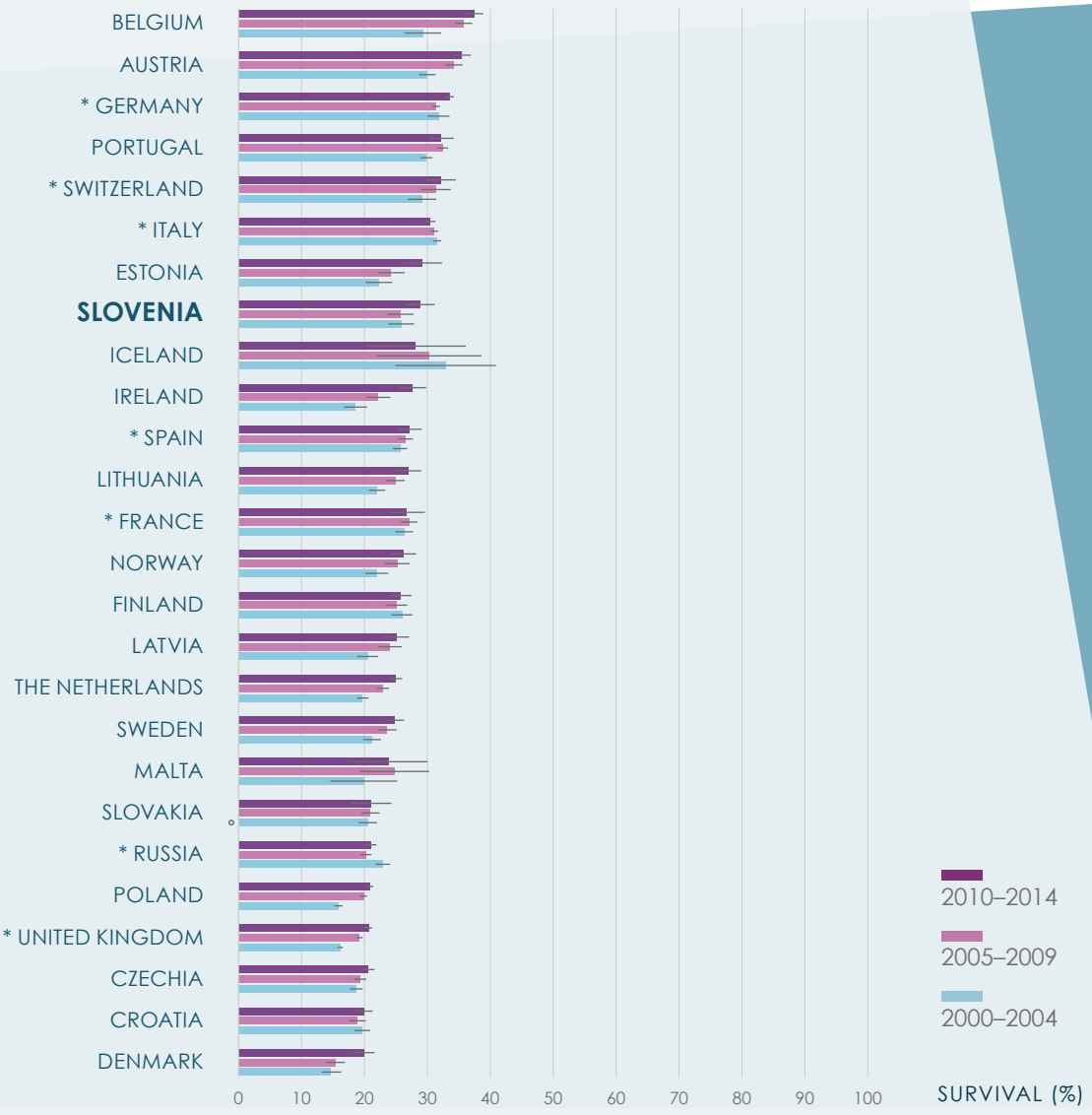


FIGURE 5

International comparison of age-standardized five-year net survival for gastric cancer (with 95% confidence intervals) in patients diagnosed during 2000–2004, 2005–2009 and 2010–2014 (CONCORD–3).

** Data doesn't cover a 100% of the country's population.*

° Survival estimate is less reliable.

Figure 3 shows the impact of age on the survival of patients with gastric cancer. In all the observed periods, the five-year net survival was highest in patients aged 20 to 49 years at diagnosis and lowest in patients aged 75–94 years. In the last observed period (2012–2016), compared to the first period, survival improved in all age groups: by 13 percentage points in the 20–49 age group, 11 percentage points in the 50–74 age group, and 8 percentage points in the 75–94 age group.

The importance of the stage at diagnosis is shown in Figure 4. In the last period, the five-year net survival of patients with the localized stage of the disease reached almost 70%. The five-year net survival of patients with the regional stage was 38% in the last observed period, and only 3% in patients with the distant stage of the disease at diagnosis. The five-year net survival of patients with gastric cancer improved overall between 1997 and 2016, most notably in patients with the regional stage of the disease.

The results of the world-wide CONCORD-3 study of patients diagnosed with cancer during the 15 years 2000–2014 in 71 countries and territories show that the five-year net survival of Slovenian patients with gastric cancer has been improving (Figure 5). For patients diagnosed during the most recent period (2010–2014), Slovenia ranked 8th among the 26 participating European countries.

CLINICAL COMMENTARY

Mirko Omejc

The development and state of the surgical treatment of gastric cancer in Slovenia in the years 1983–1997 was described in the 2003 monograph Survival of Cancer Patients in Slovenia. At that time, it was considered that the increased professional efforts in the field of gastric cancer after 1980 (professional meetings, national surveys, multidisciplinary teams, workshops and symposia, publications) would only be reflected in improved survival at the national level in the long term. In the 1997–2016 period, which has now been analysed with respect to five-year survival, surgeons in Slovenia adhered to doctrinal principles for the treatment of patients with gastric cancer developed in the early 1990s. At the same time, the treatment of gastric cancer became largely centralized in two main centres in Slovenia. Resection, radical and/or palliative, was the first-line treatment of choice, regardless of the patient's age. The type of surgery—distal subtotal resection or total gastrectomy with the systematic lymphadenectomy of all lymph nodes of the 1st and 2nd group (D2 lymphadenectomy)—depends on the cancer site in the stomach (by thirds) and on the histological type according to Lauren. During the observed period, D2 lymphadenectomy was an integral part of radical surgery regardless of the T category. Neoadjuvant chemotherapy and/or radiotherapy in advanced stage (T3, T4) became accepted methods of treatment, as did adjuvant oncological treatment. After 2000, gastric cancer treatment practices in Slovenia began to change gradually in terms of individualized surgery (mucosectomy for T1N0 tumours, D1 lymphadenectomy alone for T1Nx tumours) and neoadjuvant radiochemotherapy for tumours with categories above T2bNxMx. Initially, individual cases became more numerous over time. The results of surveys conducted in the surgical departments of Slovenian hospitals show that postoperative patient mortality had gradually decreased; in 1994 it was 6% and in 2004 4%. Since then, it has stayed below 5% despite the fact that more and more elderly patients with comorbidities are being treated with surgery. The progress stemming from the joint efforts of surgeons, particularly those from Ljubljana and Maribor, has only become evident at the national level in the period under study in this report. The five-year survival of patients with gastric cancer in Slovenia has been gradually increasing and is already above the European average.

An indication that in the future, further improvements can be expected are the improved results of clinical analyses from the two main institutions in Slovenia, the University Medical Centre Ljubljana and the University Medical Centre Maribor, which are deeply involved in gastric cancer surgery and where resectability is higher, postoperative mortality is lower, the proportion of multimodally treated patients is higher, and the five-year survival is higher than in many Western European centres.

Vaneja Velenik

The poor survival of patients with gastric cancer in Slovenia in the first observed periods was largely a result of the high proportion of cases in an advanced stage of the disease at diagnosis, the insufficient resection of mainly regional lymph nodes (less than D2 lymphadenectomy), and a high percentage of patients who did not receive specific treatment. Advances in surgical technique, reduction in postoperative complications and good postoperative care have enabled more and more patients to receive surgical treatment in old age, the proportion of which is growing in our country. Postoperative chemoradiotherapy became the standard of care worldwide after 2001, when the results of a randomized study were published showing the statistically better survival of patients treated with combination of therapies compared to those who were treated with surgery alone. As many as 90% of the patients in the study underwent a D2 lymphadenectomy, so the study could not demonstrate better locoregional control after postoperative chemoradiotherapy in patients who received appropriate surgical treatment. Subsequent studies of patients with D2 and D3 lymphadenectomy did not confirm the benefits of postoperative chemoradiotherapy, except in a subset of patients with the histologically confirmed involvement of regional lymph nodes. The randomized ARTIST II study is expected to definitively elucidate the role of postoperative chemoradiotherapy.

Better knowledge of tumour biology, as well as a high proportion of patients with the rapid and most often systemic recurrence of the disease and thus awareness that there is a high likelihood of micrometastases being present at diagnosis, has, as with most gastrointestinal tumours, changed our view regarding treatment with a tendency to include various preoperative approaches. Perioperative chemotherapy in combination with epirubicin, 5-fluorouracil and cisplatin (the MAGIC study from 2006) improved survival by 13% compared to surgery alone. The taxane scheme (the FLOT4 study), now recommended by all guidelines, later proved to be even more effective and less toxic. In addition to many advantages, this type of treatment also has some negative aspects: possible non-response to therapy, time lag before surgery, and high toxicity in the postoperative part of treatment and thus poor patient compliance. Furthermore, the first study included as many as 25% of patients with lower oesophageal and gastroesophageal junction cancer, while the second included 56%. These tumours respond better to systemic treatment than those localized in the body of the stomach; therefore, the site of tumour origin should also be considered when evaluating treatment success.

We can expect that the survival of our patients with gastric cancer will further improve due to the introduction of preoperative treatment with effective chemotherapy. Despite the improvement in survival, both around the world and in Slovenia, we still see a high proportion of disease recurrence. Therefore, research is underway on radiotherapy as part of preoperative treatment. Radiotherapy improves the resectability of tumours, does not increase the number of postoperative complications, and is well-tolerated by patients. In a meta-analysis of treatment outcomes with preoperative chemotherapy and/or chemoradiotherapy, adding chemoradiotherapy is associated with an even better disease outcome. Although the greater efficacy of postoperative chemoradiotherapy has been demonstrated compared to postoperative chemotherapy in gastroesophageal junction adenocarcinomas (the POET study), the advantage of one or the other modality in the preoperative treatment of these tumours is not yet clear.

Janja Ocvirk

The incidence of gastric cancer in all four five-year periods is similar in both sexes and is almost twice as high in men compared to women. Unfortunately, the prognosis of the disease in the advanced, distant stage is still very poor. Survival has improved slightly over the last five years, mainly because more patients have received some type of specific primary treatment for stomach cancer. In the last five years, perioperative chemotherapy treatment for the localized and regional stages of gastric cancers has become fully established, contributing to better survival. The proportion of patients who, as part of their primary treatment, receive multimodal treatment including all three treatment modalities, i.e. radiotherapy, chemotherapy and surgery, is also increasing, especially in locally advanced disease localized in the upper part of the stomach or at the gastroesophageal junction.

The higher numbers of patients diagnosed with a regional compared to a localized stage of the disease is the result of better diagnostic procedures (CT, MRI, PET-CT) that have become part of routine use in the last period. Patients with a highly advanced disease more often received systemic treatment, and second-line therapies were introduced, as well as second-line biological drugs.

Over the last five years, survival has improved in all groups regardless of disease stage, as well as age.

References

Al–Batran SE, Hofheinz RD, Pauligk C, et al. Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastro–oesophageal junction adenocarcinoma (FLOT4–AIO) results from the phase 2 part of a multicentre, open–label, randomised phase 2/3 trial. Lancet Oncol 2016; 17(12): 1697–708.

Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006; 355: 11–20.

Juvan R, Omejc M, Jelenc F, et al. Rezultati operacijskega zdravljenja raka želodca v obdobju 1993–2002 (Results of the operative treatment of gastric cancer in period 1993–2002). In: Juvan, R, Jelenc, F, Omejc M, Repše S, eds. Kirurgija želodca: standardi in novosti. Zbornik simpozija (Gastric surgery: standards & novelties: proceedings of the symposium), Ljubljana. Ljubljana: University Medical Centre, Division of Surgery; 2005. p. 210–6.

Kumagai K, Rouvelas I, Tsai JA, et al. Survival benefit and additional value of preoperative chemoradiotherapy in resectable gastric and gastro–oesophageal junction cancer: a direct and adjusted indirect comparison meta–analysis. Eur J Surg Oncol 2015; 41(3): 282–94.

Lešničar H. Preživetje bolnikov z rakom (Survival of cancer patients). Onkologija 2003: 2(7); 63–7.

Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 2001; 345: 725–30.

Omejc M, Juvan R, Jelenc F, et al. Spreminjanje pogledov na rak želodca v Sloveniji (Changing views on gastric cancer in Slovenia). Gastroenterolog 2005; 9: 91–7.

Omejc M, Repše S. Rak želodca v Sloveniji 2004 (Gastric cancer in Slovenia 2004). In: Omejc M, Repše S, eds. Kirurgija želodca: standardi in novosti. Zbornik simpozija (Gastric surgery: standards & novelties: proceedings of the symposium), Ljubljana. Ljubljana: University Medical Center, Division of Surgery; 2005. p. 128–33.

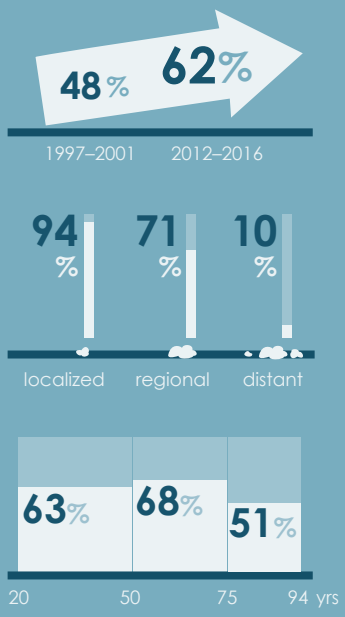
Omejc M. Kirurgija raka želodca (Gastric cancer surgery). Onkologija 2014; 18: 23–5.

Omejc M. Limfadenektomija in multivisceralne resekcije pri napredovalem raku želodca (The importance of lymphadenectomy and the role of multivisceral resection in advanced gastric cancer). In: Omejc M, Repše S, eds. Kirurgija želodca: zbornik Simpozija kirurgije prebavil (Gastric surgery: proceedings of the Digestive Surgery Symposium), Ljubljana. Ljubljana: University Medical Center, Division of Surgery; 2019. p. 76–82.

Potrč S, Horvat M, Ivanez A, et al. Kaj smo se naučili pri kirurškem zdravljenju adenokarcinoma želodca: primerjava dveh obdobij (What did we learn in surgical treatment of gastric adenocarcinoma: comparison of two periods). In: Omejc M, Repse S. Kirurgija želodca: zbornik Simpozija kirurgije prebavil (Gastric surgery: proceedings of the Digestive Surgery Symposium), Ljubljana. Ljubljana: University Medical Centre, Division of Surgery; 2005. p. 197–209.

C18–C20

COLON AND RECTUM

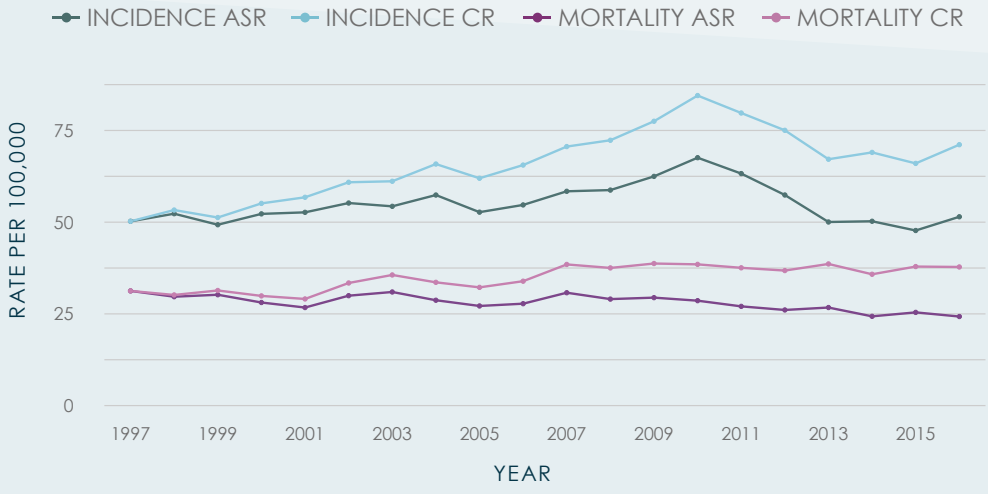


EPIDEMIOLOGY

In the last five-year period (2012–2016), 1,436 people per year on average were diagnosed with colorectal cancer in Slovenia, of these 854 men and 582 women, and 770 people died, of these 439 men and 331 women. The incidence rates of colorectal cancer (Figure 1) increased until 2010, but then the curve turned downwards, which can be attributed to the introduction of the national screening and early detection programme for colorectal cancer—the Svit Programme. Until the introduction of the programme, between 2007 and 2010, the crude incidence rate of colorectal cancer in both sexes increased by 5.1% per year, and after its introduction between 2010 and 2016, it decreased in a statistically significant way by 3.4% per year. The mortality rates of colorectal cancer did not change significantly from 2007 to 2016, but there is a declining trend. The crude mortality rate of colorectal cancer is declining by 0.3% per year in both sexes; in men by 0.1% and in women by 0.6% per year. The decline is not statistically significant.

FIGURE 1

The crude (CR) and age-standardized (ASR) incidence and mortality rates of colorectal cancer in Slovenia in 1997–2016.



At the end of 2016, there were 11,571 people living in Slovenia who had been diagnosed with colorectal cancer at some point in their lives. Of those, the diagnosis had been established less than one year ago in 1,237 people, one to four years ago in 3,418 people, and over ten years ago in 3,560 people.

The survival analysis included 25,975 cases of patients aged 20 to 94 years; 629 cases (2%) were excluded because they were diagnosed on the day of death or because they did not fulfil the age inclusion criteria.

Throughout the observed period, 54–60% of cases occurred in the colon (C18), 9% in the rectosigmoid junction (C19), and 31–37% in the rectum (C20). In all the observed periods, in 1–2 % of cases, the site was unspecified (C18.9). Among colon cancer cases with a specified site, most cases, 22–24%, occurred in the sigmoid colon (C18.7), followed by the caecum (C18.0) with 8–10% and the ascending colon (C18.2) with 7–10%. In less than 5% of cases, the disease occurred elsewhere in the colon (C18.1, C18.3, C18.4, C18.5, C18.6, C18.8)

	Sex		Age			Stage			Total
	Men	Women	20–49 yrs	50–74 yrs	75–94 yrs	Localized	Regional	Distant	
1997–2001	2837	2267	386	3392	1326	746	2937	1184	5104
	% 55.6	44.4	7.6	66.5	26.0	14.6	57.5	23.2	
2002–2006	3487	2663	377	3843	1930	860	3669	1402	6150
	% 56.7	43.3	6.1	62.5	31.4	14.0	59.7	22.8	
2007–2011	4527	3168	412	4864	2419	1349	4512	1678	7695
	% 58.8	41.2	5.4	63.2	31.4	17.5	58.6	21.8	
2012–2016	4186	2840	397	4064	2565	1492	3866	1587	7026
	% 59.6	40.4	5.7	57.8	36.5	21.2	55.0	22.6	

TABLE 1

Number and proportion of patients with colorectal cancer by sex, age, stage and period of diagnosis in Slovenia in 1997–2016.

Depending on the individual observed period, 2–5% of patients did not have their disease confirmed microscopically. In all periods, adenocarcinoma was the most common histological type of microscopically confirmed cases. In the last period, it occurred in more than 98% of cases. In 1% of cases, the histological type was not defined.

In all periods, more men than women were diagnosed with colorectal cancer: the majority of patients were aged 50 to 74 years. The disease was most commonly diagnosed in the regional stage (Table 1). In the last five-year period (2012–2016), an increase in cancers diagnosed in the localized stage was noted, which may to a substantial extent be attributed to the effect of the Svit programme.

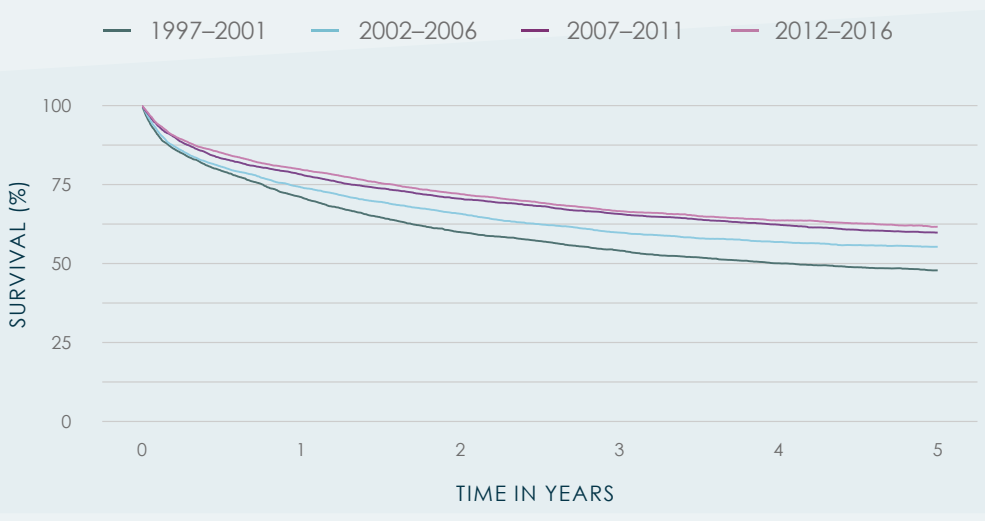


FIGURE 2

Net survival of patients with colorectal cancer by period of diagnosis in Slovenia in 1997–2016.

TABLE 2

One-, three- and five-year observed and net survival (with a 95% confidence interval-CI) of patients with colorectal cancer by sex and period of diagnosis in Slovenia in 1997–2016.

Survival / Period			1997–2001	(95% CI)	2002–2006	(95% CI)	2007–2011	(95% CI)	2012–2016	(95% CI)
Observed	1-year	all	68.5	67.3–69.8	71.3	70.2–72.5	75.6	74.7–76.6	77.2	76.2–78.2
		men	68.1	66.4–69.8	71.3	69.9–72.9	75.8	74.6–77.1	79.1	77.9–80.3
		women	69.1	67.2–71.0	71.3	69.6–73.1	75.4	73.9–76.9	74.4	72.8–76.0
	3-year	all	48.5	47.2–49.9	52.9	51.7–54.2	59.6	58.6–60.8	60.4	59.3–61.6
		men	47.1	45.3–49.0	53.2	51.6–54.9	59.1	57.6–60.5	61.6	60.1–63.1
		women	50.3	48.3–52.4	52.5	50.7–54.5	60.5	58.8–62.2	58.7	56.9–60.5
	5-year	all	39.3	38.0–40.7	44.5	43.3–45.8	50.7	49.6–51.8	51.8	50.6–53.0
		men	37.5	35.8–39.4	44.3	42.7–46.0	49.5	48.0–51.0	52.2	50.6–53.8
		women	41.5	39.6–43.6	44.8	43.0–46.8	52.3	50.6–54.1	51.2	49.4–53.2
Net	1-year	all	71.0	69.7–72.4	74.1	72.9–75.3	78.2	77.2–79.2	79.7	78.7–80.8
		men	71.0	69.2–72.8	74.4	72.9–76.0	78.7	77.4–80.0	81.9	80.6–83.2
		women	71.1	69.2–73.1	73.7	71.9–75.5	77.6	76.0–79.1	76.5	74.9–78.2
	3-year	all	54.1	52.6–55.7	59.8	58.4–61.3	65.7	64.5–67.0	66.6	65.3–67.9
		men	53.4	51.3–55.6	61.0	59.1–63.0	65.8	64.2–67.4	68.6	66.9–70.3
		women	55.0	52.7–57.3	58.1	56.0–60.3	65.7	63.8–67.6	63.7	61.7–65.8
	5-year	all	47.8	46.2–49.6	55.3	53.7–57.0	59.8	58.4–61.2	61.7	60.2–63.3
		men	47.1	44.9–49.5	56.2	54.1–58.5	59.3	57.4–61.1	63.1	61.1–65.2
		women	48.7	46.3–51.2	54.0	51.6–56.5	60.6	58.5–62.8	59.7	57.4–62.1

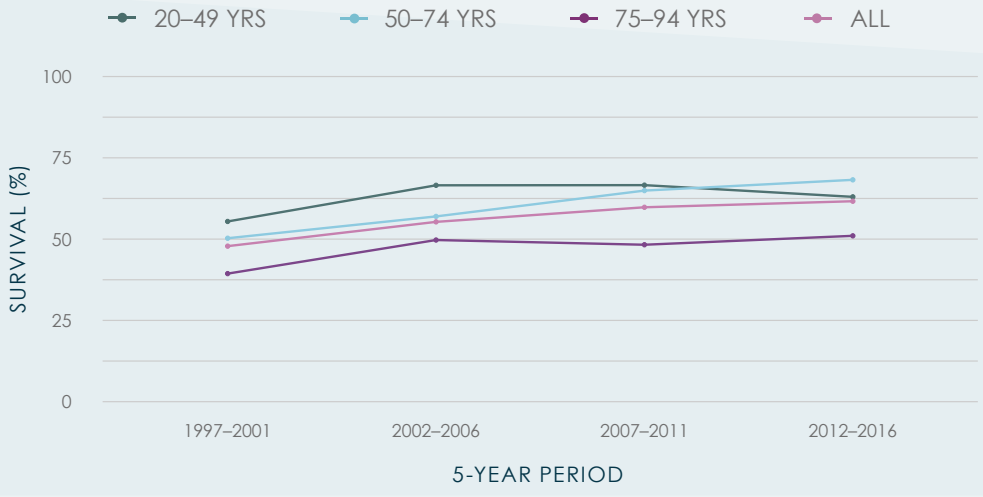
Regarding the specific primary treatment of colon cancer in the 1997–2016 period, over 62% of patients were treated with surgery alone, and over 22% received systemic therapy in addition to surgery. Throughout the entire observed period, 13% of patients did not receive specific primary treatment; the proportion of patients who did not receive specific primary treatment decreased during the observed five-year periods (1997–2001: 17%; 2012–2016: 12%).

In the 1997–2016 period, 41% of patients with rectal cancer were treated with surgery alone, and 22% were treated with a combination of surgery, radiotherapy and systemic treatment. Systemic treatment in any form was given to 35% of patients with rectal cancer, mostly in combination with other treatments. Throughout the observed period, 14% of patients did not receive specific primary treatment; the proportion of patients who did not receive specific primary treatment decreased during the observed five-year periods (1997–2001: 17%; 2012–2016: 13%).

In all periods, colorectal cancer surgeries were performed in at least 13 medical institutions. In the last five-year period, most of them were performed at the University Medical Centre Ljubljana (30%), the University Medical Centre Maribor (15%), the Institute of Oncology Ljubljana (11%), Jesenice General Hospital (8%), Celje General Hospital (7%), and Izola General Hospital, Murska Sobota General Hospital, and Novo Mesto General Hospital (5% each). As part of their primary treatment, in

FIGURE 3

Five-year net survival of patients with colorectal cancer by age group in Slovenia in 1997–2016.



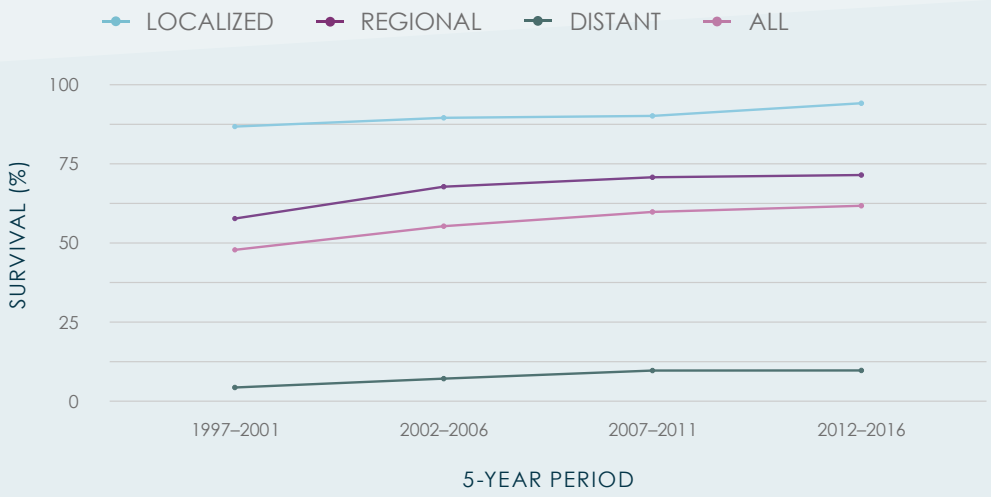


FIGURE 4

Five-year net survival of patients with colorectal cancer by stage in Slovenia in 1997–2016.

the last five-year period, patients received systemic treatment at the Institute of Oncology Ljubljana (over 87%), at the University Medical Centre Maribor (6%), Slovenj Gradec General Hospital (2%), Celje General Hospital, Nova Gorica General Hospital, and the University Medical Centre Ljubljana (1–2%), and in individual cases also in other hospitals.

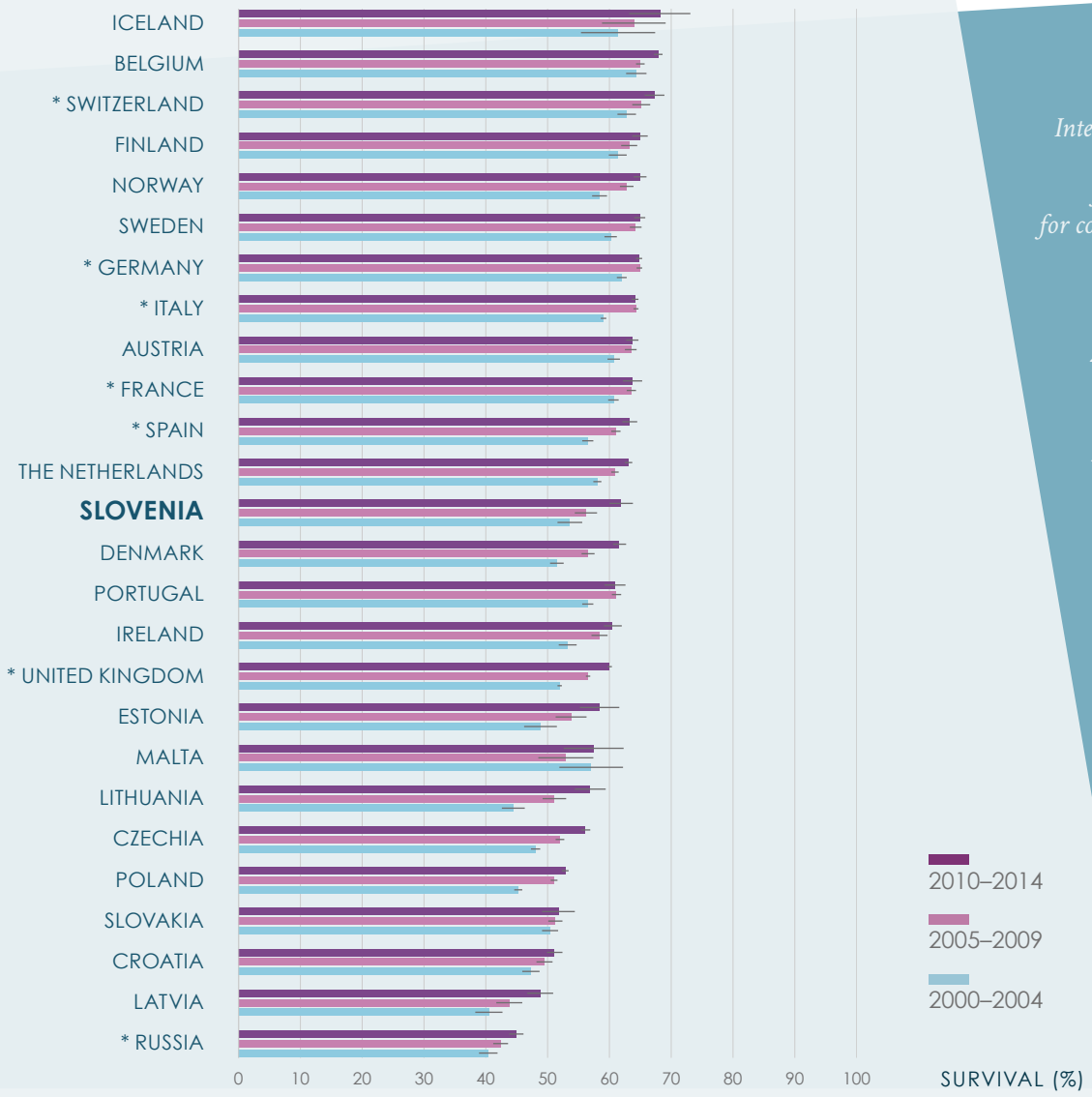


FIGURE 5

International comparison of age-standardized five-year net survival for colon cancer (C18–C19) (with 95% confidence intervals) in patients diagnosed during 2000–2004, 2005–2009 and 2010–2014 (CONCORD-3).

** Data doesn't cover a 100% of the country's population.*

The net survival of patients with colorectal cancer has been gradually increasing with respect to the year of diagnosis (Figure 2, Table 2). During the observed 20 years, the five-year net survival increased by almost 14 percentage points. In the first three observed five-year periods, patients with colon cancer achieved slightly better survival than those with rectal cancer, while in the last period, the survival of patients with colon and rectal cancer is roughly the same. During the entire observed period, for colorectal cancer, no major differences between the sexes in the five-year net survival were observed (Table 2).

In Slovenia, compared to other selected cancers, colorectal cancer ranks 9th in men and 9th in women by five-year net survival.

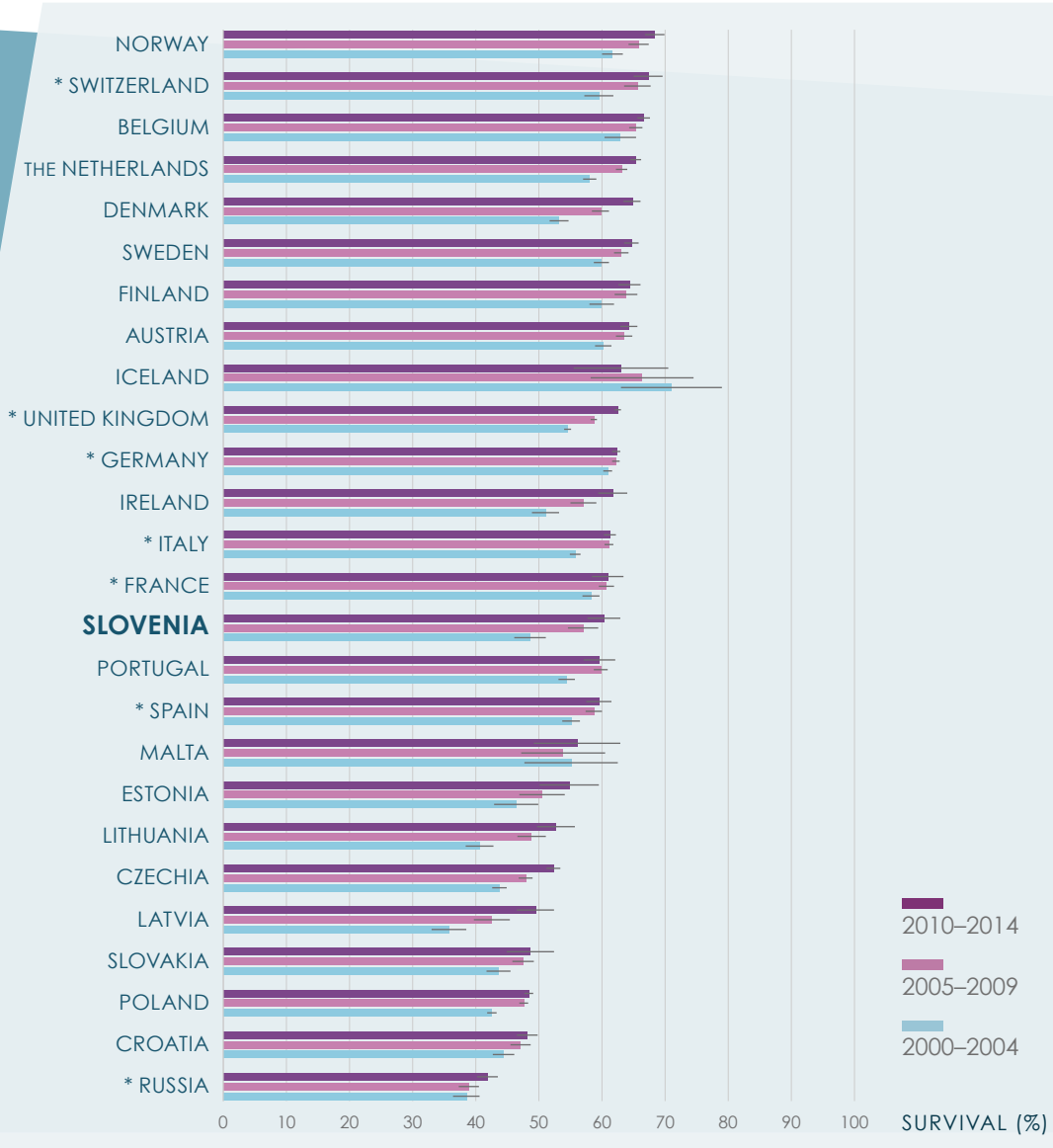
Figure 3 shows the impact of age on the survival of patients with colorectal cancer. Namely, net survival is lowest in persons aged 75–94, whereas survival in patients aged 50 to 74 at diagnosis has reached the net survival of patients younger than 50 years in the 2007–2011 period. In the last five-year period (2012–2016), the net survival of patients younger than 50 years at diagnosis (63%) are below the net survival of patients aged 50 to 74 years (68%) (Figure 3). This is due to the Svit screening programme, which includes men and women between the ages of 50 and 74. No differences in survival by age groups were observed between patients with colon cancer and rectal cancer.

The importance of the stage at diagnosis is shown in Figure 4. The five-year net survival of patients with the localized stage of the disease has surpassed 94% in the last period. The five-year net survival of patients with the regional stage has approached 71%, whereas in patients with the distant stage of

FIGURE 6

International comparison of age-standardized five-year net survival for rectum cancer (C20) (with 95% confidence intervals) in patients diagnosed during 2000–2004, 2005–2009 and 2010–2014 (CONCORD-3).

** Data doesn't cover a 100% of the country's population.*



the disease at diagnosis, it is slightly below 10%. The temporal trend of the five-year net survival of patients with colorectal cancer in the 1997–2016 period shows improvement in all stages. No differences in survival by stage were observed between patients with colon cancer and rectal cancer.

The results of the world-wide CONCORD-3 study of patients diagnosed with cancer during the 15 years 2000–2014 in 71 countries and territories show that the five-year net survival of Slovenian patients with colon and rectal cancer has been improving (Figure 5, Figure 6). For patients diagnosed during the most recent period (2010–2014), Slovenia ranked 13th for colon cancer and 15th for rectal cancer among the 26 participating European countries.

CLINICAL COMMENTARY

Mirko Omejc

The improvement in the survival of patients with colon cancer is likely a consequence of earlier cancer detection (increasing proportion of low-stage tumours with better survival), while advancements in treatment may also be a factor. During the period analysed using five-year survival rates, surgeons in Slovenia followed the clinical guidelines for the treatment of patients with colon cancer, which were developed and published in the early 1990s. The standard resection of the affected intestinal section, combined with radicular vessel ligation and lymphadenectomy, was the surgical standard. Postoperative oncological treatment in the regional stage of the disease was routine practice. In the observed 1997–2016 period, tumours were increasingly diagnosed at an earlier stage. The survival of patients in the 50–74 age group, in particular, who make up almost two-thirds of patients, improved in this period. These were mostly patients who participated in the Svit screening programme and had the disease detected in an early stage.

Survival analysis of colon cancer patients in the observed 1997–2016 period showed an increased proportion of patients with the localized stage of the disease and a reduced proportion of patients with regional and distant stages of the disease. In the last two five-year periods especially, there was an increase in the proportion of patients who received additional oncological treatment, as well as undergoing surgery. However, the survival curves did not exhibit any significant improvement, particularly regarding patients with a regional disease and patients younger than 50. In Slovenia, as in other countries, there is still no answer to the question of what impact unsupervised and uncontrolled minimally invasive surgical methods in the treatment of regional stage colon cancer has on survival.

In contrast to localized cancer where we see clear improvements in survival, the survival of patients with distant stage cancer has remained low despite advancements in surgical and oncological treatments, which only further emphasises the need to redouble efforts to detect cancers in the earlier stages. With the data showing five-year survival rates of patients with the localized stage of the disease exceeding 90% since 1997 and standing at almost 95% in the last period, it is likely that this trend could continue and the national survival rates will improve even further if even more cases of the disease are discovered in the localized stage thanks to the Svit screening programme.

The survival of patients with rectal cancer in Slovenia improved throughout the observed 1997–2016 period in all stages—the localized, regional and distant stages—and across all age groups. The main reasons for this improvement in survival are the earlier detection of cancer, the centralization and improvement of surgical treatment, as well as a multidisciplinary approach to treatment. There has been an increase in the proportion of patients diagnosed with earlier stage cancers (localized stage rectal cancer), largely as a result of the screening programme for the early detection of colorectal cancer (Svit).

During the period analysed using five-year survival rates, surgeons in Slovenia followed the clinical guidelines for the treatment of patients with rectal cancer that were developed and published in the early 1990s. Rectal cancer surgery requires specific expertise and experience, and thus depends on the individual surgeon, as well as on the technical capabilities of the healthcare facility providing treatment for rectal cancer (an adequate MRI scan). Standard resection of the rectum with the partial (upper third of the rectum) or total excision of the mesorectum (middle, lower third of the rectum with radical vessel

ligature, lymphadenectomy, and the preservation of nerve structures in the lesser pelvis was the surgical standard. Preoperative and postoperative oncological treatment for the regional stage of the disease was routine practice. Improved survival over the observed period has also been a consequence of the increasing use of neoadjuvant and systemic therapy. The role of minimally invasive surgical methods in the treatment of regional stage rectal cancer has not yet been definitively defined and in the observed period, such approaches have probably not significantly affected patient survival.

Vaneja Velenik

The high incidence and mortality from colorectal cancer has been and remains a major public health problem. According to the data from the cohort analysis of survival in the four observed periods, the survival of patients with this disease is increasing and is almost 20 percentage points better for patients with rectal cancer in the last observed period compared to the first. In part, this can be attributed to the higher proportion of patients detected in the early disease stages as a result of the successful Svit screening programme. With the more precise planning of radiotherapy using magnetic resonance for all patients, state-of-the-art irradiation techniques and a regime of higher daily doses in a shorter time (hypofractionation), we have achieved very good results with neoadjuvant treatment; in 25% of cases, we have seen a complete response. Patients thus have a better prognosis, and the proportion of radical resections is also higher. In 2016, we introduced complete neoadjuvant treatment (i.e. full radiotherapy and systemic therapy is preoperative) of patients with the highest risk of local and/or systemic recurrence. Due to the lower acute toxicity of this approach, the proportion of patients who complete the entire treatment is higher than those who receive postoperative chemotherapy after preoperative radiochemotherapy and surgery. The results of the treatment are even better and the proportion with a complete response is even higher, despite very advanced tumours. Therefore, we expect that the five-year survival will be even higher in the next observed period.

The survival of patients with the distant stage of rectal cancer at diagnosis is also increasing and is better than the survival of patients with colon cancer of the same stage. The strong connection and coordination of all disciplines within a multidisciplinary team, the centralization of complex systemic and radiation treatment, and the scheduling of different radiation regimens at the most appropriate time for the patient certainly contribute to this.

The growing proportion of patients who were 75–94 years of age at diagnosis is not a cause for concern, as their improvement in survival has been the steepest compared to other age groups. This indicates that specific oncological treatments have been appropriately and successfully adapted to accommodate older people's health conditions and comorbidities.

The fragmented delivery of oncological surgery, which is performed in almost all Slovenian healthcare centres with surgical facilities, remains unchanged. From the analysis, we can see that the primary specific treatment of colorectal cancer is carried out in at least 13 different institutions. In some institutions, where non-surgical treatments are not provided, records show that in five years, barely a few dozen oncological operations were performed. Since there are several physicians at each institution that perform colon and rectal cancer surgery, the number of surgical procedures per individual is unacceptably low. In Slovenia, the fact that the surgeon's experience is of key importance for patient outcomes has been neglected for at least 20 years.

Janja Ocvirk

The incidence of colon cancer increased in the first three five-year periods, but decreased in the last, as a result of the Svit screening programme and probably also greater awareness. The Svit screening programme, which has been in operation for 10 years, first covered the age group from 50 to 69 years and later from 50 to 74 years. A clear decline in the incidence of colon cancer is seen in the last observed five-year period for this age group. Unfortunately, we still observe increasing incidence in the age groups not covered by the programme, i.e. in the group of 20 to 49 years and over 75 years, with the largest increase seen in the latter. The incidence of rectal cancer increased in the first three five-year periods from 2,347 to 3,271, and in the last, it fell back to 2,811 as a result of the Svit screening programme and probably also

greater awareness. The incidence of rectal cancer is higher in men than in women in all periods.

The Svit screening programme and greater awareness of the disease have led to an increase in the proportion of patients with early-stage cancer, i.e. the localized disease and a decrease in regional stage cancer, while the proportion of patients with distant metastases remains approximately the same across all periods for both colon and rectal cancer.

The survival of patients with colorectal cancer has been increasing in all periods since 1997; these increases have been seen for all patients with the localized and regional stages. Better diagnostics, improved and standardized surgical techniques, as well as additional systemic treatment and radiotherapy, are important factors for increasing the survival of patients with colorectal cancer of all these groups. In patients with regional colon cancer, the increase in survival is also attributed to adjuvant chemotherapy, as the proportion of patients who received it in addition to surgical treatment has increased significantly. While for patients with rectal cancer, the increase in survival is partially attributed to additional preoperative radiotherapy, either alone or in combination with chemotherapy, depending on the local stage of the disease, as well as the period of treatment.

The survival of patients with colon cancer has been increasing in the 50 to 74 age group, largely due to the detection of a higher proportion of patients at an early stage, and in the 75–94 age group due to additional systemic treatment. However, survival has been declining in the 20 to 49 age group, where cancers are mostly detected at an advanced stage. The survival of patients with rectal cancer is increasing in the 50 to 74 age group, both due to the detection of a higher proportion of patients at an early stage and due to multimodal treatment, it has also increased in the 75–94 years group due to additional treatment, which this group received to a greater extent than before in the last two periods, while it has improved the least in the 20 to 49 age group.

References

Archampong D, Borowski D, Wille–Jørgensen P, et al. Workload and surgeon's specialty for outcome after colorectal cancer surgery. Cochrane Database Syst Rev 2012; (3): CD005391.

But Hadžić J, Velenik V. Preoperative intensity–modulated chemoradiation therapy with simultaneous integrated boost in rectal cancer: 2–year follow–up results of phase II study. Radiol Oncol 2018; 52(1): 23–29.

Etzioni DA, Young–Fadok TM, Cima RR, et al. Patient survival after surgical treatment of rectal cancer: impact of surgeon and hospital characteristics. Cancer 2014; 120(16): 2472–81.

Grosek J, Velenik V, Edhemović I, Omejc M. The influence of the distal resection margin length on local recurrence and long– term survival in patients with rectal cancer after chemoradiotherapy and sphincter–preserving rectal resection. Radiol Oncol 2017; 51: 169–77.

Lučovnik M, Omejc M. Resection margins in rectal cancer. Eur Surg 2006; 38 (Suppl 209): 38–94.

Omejc M, Štor Z, Juvan R, Jelenc F, Repše S. Colorectal cancer in Slovenia at the turn of the century. Eur Surg 2004; 36: 356–9.

Omejc M. Kirurško zdravljenje raka debelega črevesa. Onkologija 2013; 17: 111–13.

Omejc M. Surgeon as a prognostic factor in rectal cancer. Proktologia 2006; 1: 31–32.

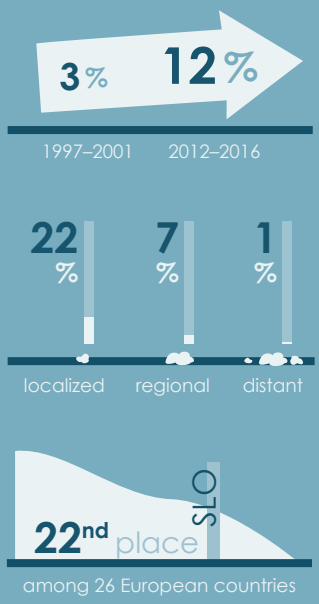
Omejc M. TME – kirurški standard pri raku danke (TME – Surgical standard in rectal cancer). In: Repše S, Štor Z, eds. Kirurgija raka debelega črevesa in danke: standardi in novosti: zbornik simpozija (Colorectal cancer surgery: standards & novelties: proceedings of the symposium), Ljubljana. Ljubljana: University Medical Center, Division of Surgery; 2006. p. 104–09.

Repše S, Jelenc F, Štor Z, et al. Kirurgija raka debelega črevesa in danke v Sloveniji v obdobju 1995 do 2005 (Surgical treatment of the colorectal canter in Slovenia in the period from 1995 to 2005). In: Repše S, Štor Z, eds. Kirurgija raka debelega črevesa in danke: standardi in novosti: zbornik simpozija. (Colorectal cancer surgery: standards & novelties: proceedings of the symposium), Ljubljana. Ljubljana: University Medical Center, Division of Surgery,; 2006. p. 3–13.

National Institute of Public Health. National screening and early detection programme for colorectal cancer – the Svit Programme. Ljubljana: National Institute of Public Health of Republic of Slovenia, 2021. Available from: www.program-svit.si

C22.0

LIVER (HEPATOCELLULAR CARCINOMA)



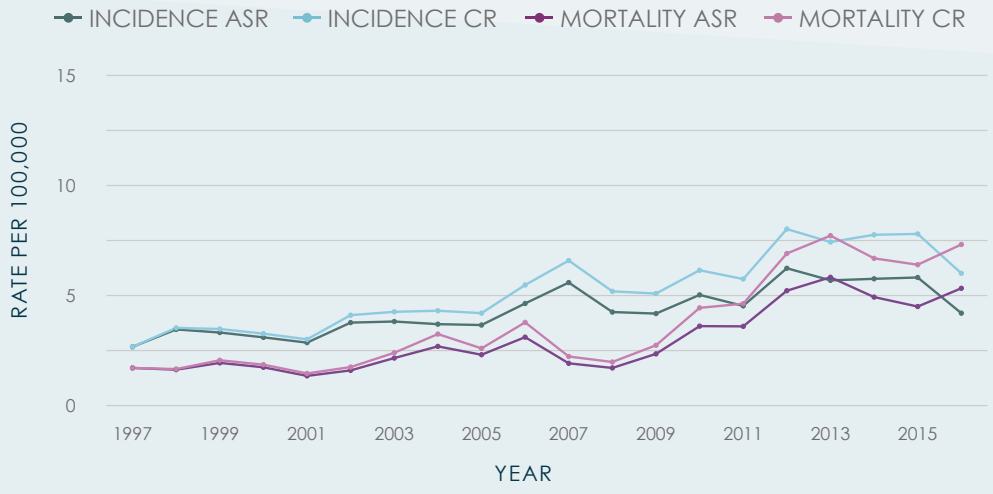
EPIDEMIOLOGY

In the last five-year period (2012–2016), 153 people per year on average were diagnosed with hepatocellular carcinoma in Slovenia, 122 men and 31 women, and 144 people died, 116 men and 28 women. As shown in Figure 1, the incidence rates of hepatocellular carcinoma gradually increased. Between 2007 and 2016, the crude incidence rate for hepatocellular carcinoma in both sexes combined and in men increased by 3.1% per year, while in women it increased by 4.1%. The upward trend in crude incidence rates is not statistically significant. The mortality rates of hepatocellular carcinoma are also rising. Between 2007 and 2016, the crude mortality rate of hepatocellular carcinoma increased by 16.8% per year in both sexes combined, by 17% in men and by 16.5% in women. The trend of increasing crude mortality rates is statistically significant.

At the end of 2016, there were 272 people in Slovenia who had been diagnosed with hepatocellular carcinoma at some point in their lives. Of those, the diagnosis had been established less than one year ago in 90 people, one to four years ago in 127 people, and over ten years ago in 29 people.

FIGURE 1

The crude (CR) and age-standardized (ASR) incidence and mortality rates of hepatocellular carcinoma in Slovenia in 1997–2016.



The survival analysis included 1,949 cases of patients aged 20 to 94 years; 164 cases (8%) were excluded because they were diagnosed on the day of death or because they did not fulfil the age inclusion criteria.

Due to the increasing use of the elevated tumour marker alpha-fetoprotein to confirm the diagnosis, the proportion of microscopically confirmed cases decreased over time; between 1997 and 2001, 83% of cases were microscopically confirmed, while between 2012 and 2016, this proportion fell to only 46%.

	Sex		Age			Stage			Total
	Men	Women	20–49 yrs	50–74 yrs	75–94 yrs	Localized	Regional	Distant	
1997–2001	212	64	22	215	39	153	46	50	276
1997–2001 %	76.8	23.2	8.0	77.9	14.1	55.4	16.7	18.1	
2002–2006	322	93	29	286	100	206	63	76	415
2002–2006 %	77.6	22.4	7.0	68.9	24.1	49.6	15.2	18.3	
2007–2011	423	115	13	382	143	280	95	109	538
2007–2011 %	78.6	21.4	2.4	71.0	26.6	52.0	17.7	20.3	
2012–2016	577	143	12	467	241	315	206	164	720
2012–2016 %	80.1	19.9	1.7	64.9	33.5	43.8	28.6	22.8	

TABLE 1

Number and proportion of patients with hepatocellular carcinoma by sex, age, stage and period of diagnosis in Slovenia in 1997–2016.

Throughout the observed period, 3.5 times more men than women were diagnosed with hepatocellular carcinoma; the majority of patients were aged 50 to 74 years. The disease was most commonly diagnosed at a localized stage (Table 1). In the last five-year period (2012–2016), an increase in the proportion of cancers diagnosed at higher stages was noticeable compared to previous periods.

Regarding the specific primary treatment of hepatocellular carcinoma between 1997 and 2016, 17% of patients received systemic treatment alone and 11% were treated with surgery alone. Across the entire covered period, 67% of patients did not receive specific primary treatment. The proportion of persons who did not receive specific primary treatment decreased during the observed five-year periods (1997–2001: 72%; 2012–2016: 61%).

In all periods, hepatocellular carcinoma surgery was performed in two hospitals: at the University Medical Centre Ljubljana (68% in the last period) and the University Medical Centre Maribor (30%). As part of their primary treatment, in the last five-year period, more than 76% of patients received systemic treatment at the University Medical Centre Ljubljana. To a lesser extent, they received systemic treatment at the University Medical Centre Maribor (16%), the Institute of Oncology Ljubljana (4%), and the Celje General Hospital (2%).

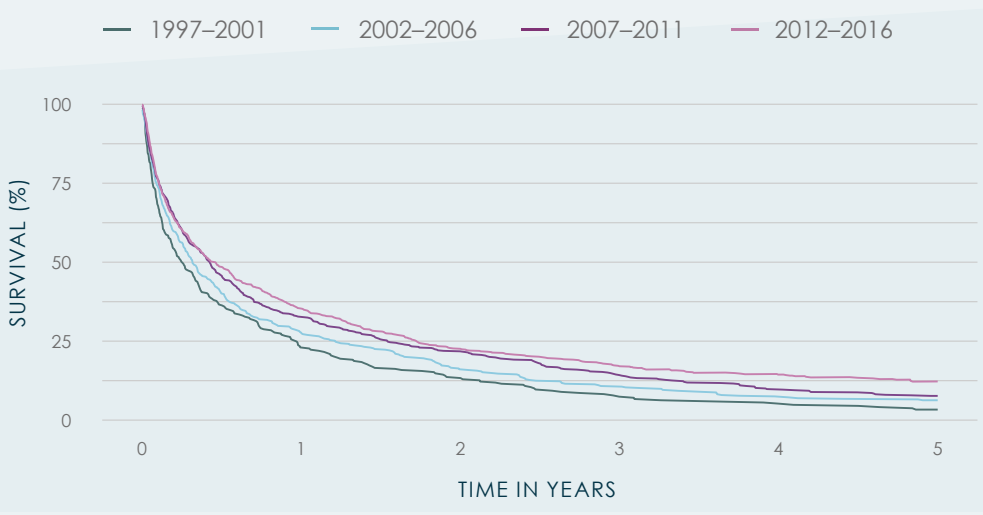


FIGURE 2

Net survival of patients with hepatocellular carcinoma by period of diagnosis in Slovenia in 1997–2016.

The net survival of patients with hepatocellular carcinoma has been gradually increasing according to the year of diagnosis (Figure 2, Table 2). In the 20 years under review, the five-year net survival improved by 9 percentage points. During the first three observed periods, there were no major differences between the sexes in the net five-year survival of patients with hepatocellular carcinoma, whereas in the last period (2012–2016), male survival was slightly more than 3 percentage points better than female survival (Table 2).

TABLE 2

One-, three-, and five-year observed and net survival (with a 95% confidence interval–CI) of patients with hepatocellular carcinoma by sex and period of diagnosis in Slovenia in 1997–2016.

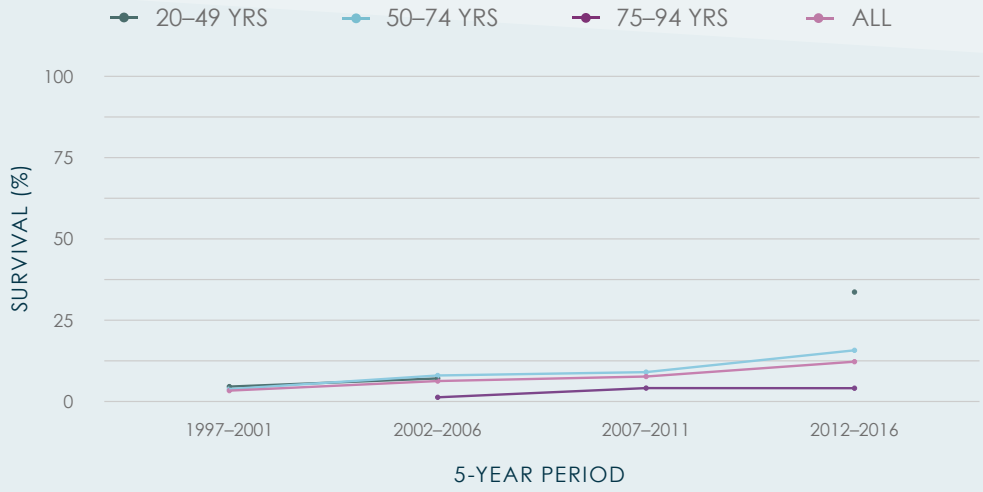
Survival / Period			1997–2001	(95% CI)	2002–2006	(95% CI)	2007–2011	(95% CI)	2012–2016	(95% CI)
Observed	1-year	all	22.1	17.7–27.6	26.9	22.9–31.5	31.8	28.1–36.0	34.4	31.1–38.1
		men	21.7	16.8–28.0	28.7	24.1–34.1	33.3	29.1–38.1	34.5	30.8–38.6
		women	23.4	15.1–36.5	20.7	13.9–30.9	26.1	19.2–35.5	34.3	27.3–43.0
	3-year	all	6.5	4.2–10.2	9.9	7.4–13.3	13.2	10.6–16.4	16.0	13.6–19.0
		men	6.1	3.6–10.4	10.0	7.2–13.9	14.0	11.0–17.7	16.4	13.6–19.7
		women	7.8	3.4–18.1	9.8	5.3–18.2	10.4	6.1–17.8	14.5	9.7–21.6
	5-year	all	2.5	1.2–5.3	5.6	3.8–8.3	6.7	4.9–9.2	10.6	8.4–13.4
		men	2.4	1.0–5.6	5.6	3.6–8.8	6.9	4.8–9.7	11.0	8.5–14.1
		women	3.1	0.8–12.2	5.4	2.3–12.8	6.1	3.0–12.5	8.4	4.3–16.5
Net	1-year	all	22.7	18.3–28.4	27.7	23.6–32.5	32.8	29.0–37.1	35.4	32.0–39.2
		men	22.4	17.4–28.9	29.6	24.9–35.2	34.5	30.1–39.4	35.5	31.7–39.7
		women	23.8	15.4–36.7	21.0	14.2–31.2	26.5	19.6–36.0	35.1	28.0–43.9
	3-year	all	7.1	4.6–11.0	10.8	8.1–14.4	14.3	11.5–17.8	17.2	14.5–20.4
		men	6.7	4.0–11.3	11.0	7.9–15.2	15.2	12.0–19.3	17.7	14.7–21.3
		women	8.2	3.7–18.1	10.1	5.5–18.6	11.0	6.5–18.6	15.2	10.1–22.7
	5-year	all	3.0	1.5–6.0	6.3	4.2–9.4	7.7	5.6–10.5	11.8	9.3–15.0
		men	2.9	1.3–6.4	6.4	4.1–10.1	8.0	5.6–11.3	12.3	9.5–15.9
		women	3.4	1.0–11.6	5.9	2.6–13.2	6.6	3.2–13.3	9.1	4.8–17.1

In Slovenia, compared to other selected cancers, hepatocellular carcinoma ranks 20th in men and 23rd in women by five-year net survival.

Figure 3 shows the impact of age on the survival of patients with hepatocellular carcinoma. Five-year net survival is lowest in patients aged 75–94. The survival of people aged 20 to 49 and 50 to 74 at diagnosis did not differ significantly during the first three observation periods, though in the last period (2012–2016), the net survival of those under 50 has improved significantly and is almost 19 percentage points higher than the survival of people aged 50 to 74 years.

FIGURE 3

Five-year net survival of patients with hepatocellular carcinoma by age group in Slovenia in 1997–2016.



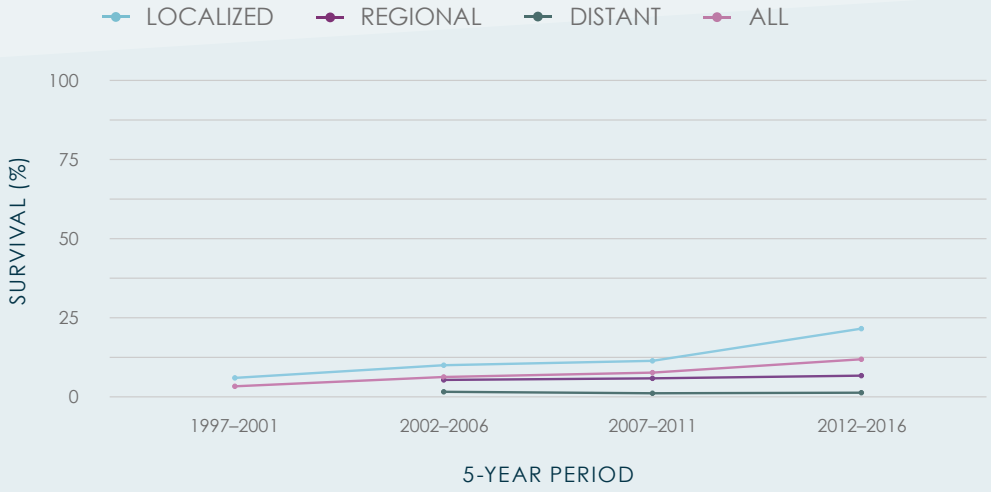


FIGURE 4

Five-year net survival of patients with hepatocellular carcinoma by stage in Slovenia in 1997–2016.

The importance of stage at diagnosis is shown in Figure 4. The five-year net survival of patients with the localized stage of the disease was almost 22% in the last period and has improved by slightly more than 16 percentage points compared to the period between 1997 and 2001. The five-year net survival of patients with the regional stage is 20%, whereas patients with the distant stage of the disease

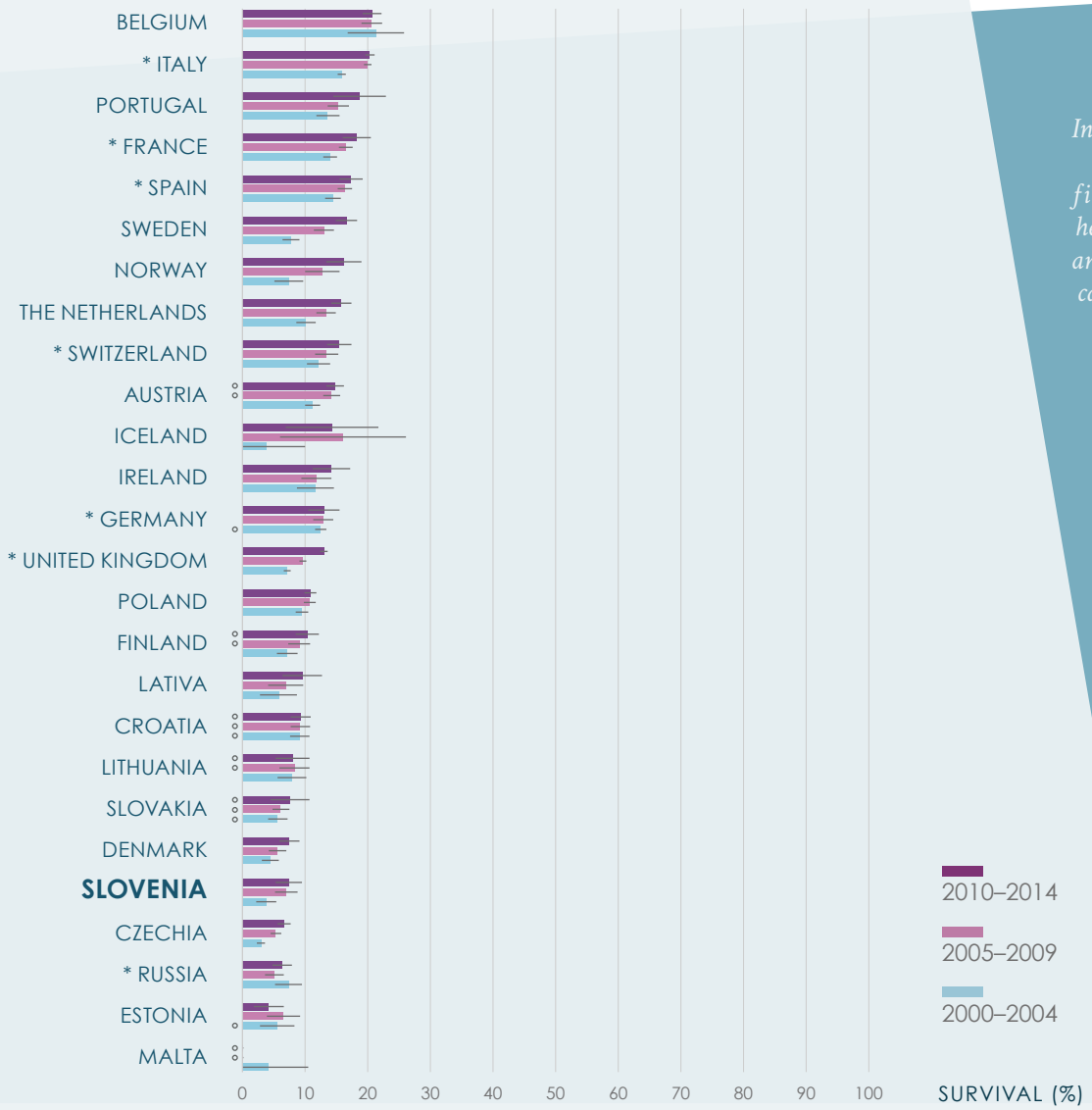


FIGURE 5

International comparison of the age-standardized five-year net survival for hepatocellular carcinoma and intrahepatic bile duct carcinoma (C22.0–C22.1) (with 95% confidence intervals) in patients during 2000–2004, 2005–2009 and 2010–2014 (CONCORD–3).

** Data doesn't cover a 100% of the country's population.*

° Survival estimate is less reliable.

at diagnosis rarely survive five years. The time trend in the five-year net survival of patients with hepatocellular carcinoma in the period 1997–2016 shows a gradual improvement for all stages, most notably for the localized stage of the disease.

The results of the world-wide CONCORD-3 study of patients diagnosed with cancer during the 15 years 2000–2014 in 71 countries and territories show that the five-year net survival of Slovenian patients with hepatocellular carcinoma has been improving (Figure 5). For patients diagnosed during the most recent period (2010–2014), Slovenia ranked 22nd among the 26 participating European countries.

CLINICAL COMMENTARY

Mirko Omejc

Hepatocellular carcinoma is the most common primary liver cancer. In most cases it develops in patients with chronic liver disease, cirrhosis as a result of hepatitis B or C, alcoholic liver disease, or non-alcoholic fatty liver disease. Resection and radiofrequency ablation of the affected liver parts are the basic potentially curative treatment modalities, or else are used as bridging therapy until possible liver transplantation. Depending on the stage of the disease, other treatment choices are transarterial chemoembolization, transarterial radioembolization, electrochemotherapy, ethanol-lipiodol embolization and systemic therapy as palliative treatment. Which treatment is the most appropriate for an individual patient depends on the size and localization of the tumour, the hepatic parenchymal function, and the patient's general condition. In addition to liver transplantation, surgical resection is the only curative method. In the observed five-year periods (1997–2016), the number of patients treated for hepatocellular carcinoma has increased. Treatment was carried out at only three main institutions, the University Medical Centre Ljubljana, the University Medical Centre Maribor, and the Institute of Oncology Ljubljana, where all the necessary specific infrastructure and knowledge required for the treatment of hepatocellular carcinoma are available. Only about 13% of patients were treated surgically and this proportion did not change significantly during the observed period. Also during this period, the proportion of patients who did not receive any specific treatment did not decrease significantly and represents more than two-thirds of patients.

The survival of patients with hepatocellular carcinoma is still low, which is certainly in a large part attributable to the high proportion of untreated patients. Owing to the nature of the disease, a hallmark of which is impaired liver function, the five-year survival rate of patients with the localized disease is also low. Nevertheless, an improvement in survival in this group of patients has been observed, especially in the last five-year period, which is probably due to the modern treatment methods that have become established during this time. The effectiveness of surgical treatment, which can result in a five-year survival rate of up to 50%, is not reflected in the entire patient population due to the small number of patients treated in this way. The poorer survival of older patients may be due to the long duration of cirrhosis and thus the significantly more advanced liver disease in this age group. On the one hand, this is reflected in a higher incidence of carcinoma in this age group and on the other, a markedly worse prognosis, since the prognosis is affected primarily by the liver disease rather than the carcinoma itself.

Despite the efforts of gastroenterologists to detect hepatocellular carcinoma at an early stage during follow-ups of patients with liver cirrhosis, the distribution by stage of disease at diagnosis has not changed significantly and the proportion of regional and distant stages is still higher than the proportion of the localized disease. Nearly 70% of patients do not receive specific treatment. The treatment of hepatocellular carcinoma is multidisciplinary and multimodal, therefore quality treatment is only possible in clinical institutions that subspecialize in the treatment of such patients.

Vaneja Velenik

Hepatocellular carcinoma (HCC) is an aggressive cancer that occurs in chronic liver disease and cirrhosis and is often diagnosed at an already advanced stage, which is also confirmed by the data of the present analysis. Concomitant liver dysfunction and advanced disease further limit curative treatment, and patient survival remains accordingly poor.

It is not surprising that the proportion of HCC that is not microscopically confirmed is increasing, as appropriate and reliable imaging diagnostics are sufficient for confirmation—a rare exception among solid cancers.

Surgery is still the curative treatment of choice for localized HCC. For a locoregionally advanced disease, local ablative methods (radiofrequency ablation—RFA, microwave ablation—MWA) and catheter-based locoregional therapy (chemoembolization—TACE, radioembolization—TARE) are also used. The choice of individual treatment depends on the characteristics of the tumour, comorbidities and the patient's general condition. The most widely used method is conventional transarterial chemoembolization, where various combinations of cytostatics, embolic agents, and oily contrast agents are delivered to the tumour. Two randomized trials showed that this method results in statistically better survival compared to good supportive care alone.

Previously, radiotherapy was not used for the local treatment of inoperable HCC due to the high sensitivity of the liver to irradiation. Advances in radiotherapy techniques (3D-conformal, intensity-modulated) and its implementation (management of respiration-induced organ motion, image-guided radiotherapy) have led to stereotactic body radiotherapy. Stereotactic body radiotherapy allows the high-dose ablative irradiation of the tumour in several fractions. Due to the steep drop in radiation dose outside the tumour margins, the toxicity is low, thus damage to the healthy liver parenchyma and surrounding structures and organs is minimal. Data from the literature shows that the method is safe and completely non-invasive, while allowing good local control (three-year local control up to 97%) and overall survival (two-year survival 40–70%), especially given the limited treatment options available to most patients. The stereotactic body radiotherapy of primary and secondary liver tumours was introduced at the Institute of Oncology Ljubljana in 2018.

Until 2008, there was no effective systemic therapy that was shown to improve the survival of patients with advanced HCC. However, since two placebo-controlled randomized phase III studies demonstrated that the tyrosine kinase inhibitor sorafenib improves survival by almost three months, increasing it from six to nine months in otherwise untreated disease, sorafenib became a new standard of care for advanced HCC.

Janja Ocvirk, Tanja Mesti

The survival of patients of both sexes has been steadily increasing in all periods since 1997, mainly due to the improved survival of patients with the localized stage disease. The survival of patients with regional or distant HCC has remained the same since 2002. Better diagnostics, as well as better and standardized surgical techniques and local treatments, are important factors behind the increasing survival of patients with a localized disease. In patients with an advanced disease, a stable survival trend can be observed on account of systemic treatment with the tyrosine kinase inhibitor sorafenib, which for ten years was the only effective therapeutic option for these patients.

Survival is increasing in all age groups, especially in patients aged 20 to 49 years, in part due to the increased proportion of patients who have cancer detected at an early stage and are in better physical condition, as well as systemic treatment. With age, the increase in survival diminishes, meaning that it is highest in the 20 to 49 age group, lower in the 50 to 74 age group, and lowest in the 75–94 age group. This can be attributed to the polymorbidity and frailty of older patients.

Since 2016, many new drugs—regorafenib, lenvatinib, ramucirumab, cabozantinib, pembrolizumab and nivolumab—have proved effective in the treatment of advanced HCC. Thus, it can be expected that this will also be reflected in future analyses of HCC survival and mortality.

References

Au JS, Frenette CT. Management of hepatocellular carcinoma: current status and future directions. Gut Liver 2015; 9(4): 437–48.

Balogh J, Victor D, Asham EH, et al. Hepatocellular carcinoma: a review. J Hepatocell Carcinoma 2016; 3: 41–53.

Crissien AM, Frenette C. Current management of hepatocellular carcinoma. Gastroenterol Hepatol 2014; 10(3): 153–61.

El–Serag HB. Hepatocellular carcinoma. N Engl J Med 2011; 365: 1118–27.

Llovet JM, Real MI, Montana X, Planas R, Coll S, Aponte J, et al. Arterial embolisation or chemoembolization versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet 2002; 359(9319): 1734–9.

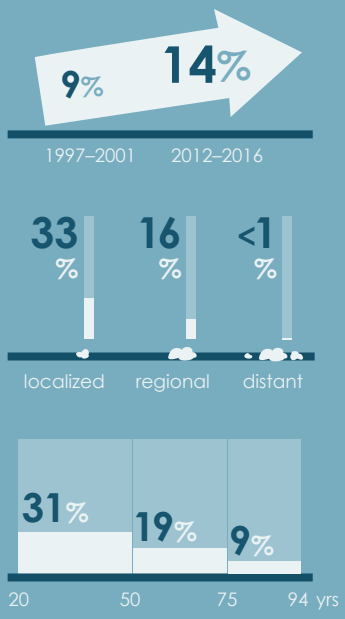
Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008; 359(4): 378–90.

Robbins JR, Schmid RK, Hammad AY, et al. Stereotactic body radiation therapy for hepatocellular carcinoma: Practice patterns, dose selection and factors impacting survival. Cancer Med 2019; 8(3): 928–38.

Vivarelli M, Montalti R, Risaliti A. Multimodal treatment of hepatocellular carcinoma on cirrhois: an update. World J Gastroenterol 2013; 19(42): 7316–26.

C23–C24

GALLBLADDER AND BILE DUCTS

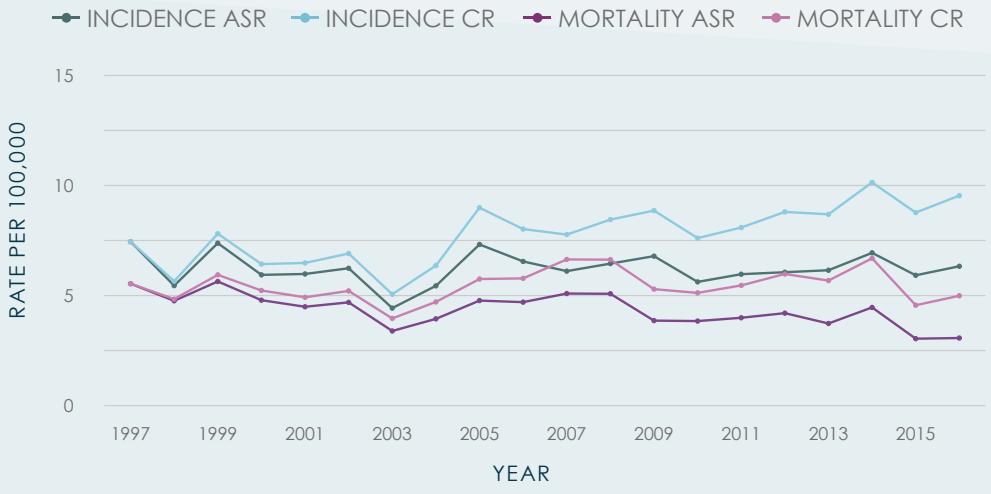


EPIDEMIOLOGY

In the last five-year period (2012–2016), 189 people per year on average were diagnosed with gallbladder and bile duct cancer in Slovenia, 84 men and 105 women, and 115 people died, 48 men and 67 women. As shown in Figure 1, the incidence rates of gallbladder and bile duct cancer gradually increased. Between 2007 and 2016, the crude incidence rate for gallbladder and bile duct cancer in both sexes combined increased by a statistically significant 1.9% per year. In men, the crude incidence rate for gallbladder and bile duct cancer increased by a statistically significant 4.7% per year; in women, it remained roughly the same. Between 2007 and 2016, the crude mortality rate of gallbladder and bile duct cancer in both sexes combined decreased by 2.1% per year. It decreased by a statistically significant 4.5% per year in women and increased by 1.9% per year in men, though the increase was not statistically significant.

FIGURE 1

The crude (CR) and age-standardized (ASR) incidence and mortality rates of gallbladder and bile duct cancer in Slovenia in 1997–2016.



At the end of 2016, there were 355 people in Slovenia who had been diagnosed with gallbladder and bile duct cancer at some point in their lives. Of those, the diagnosis had been established less than one year ago in 101 people, one to four years ago in 122 people, and over ten years ago in 63 people.

The survival analysis included 3,022 cases of patients aged 20 to 94 years; 135 cases (4%) were excluded because they were diagnosed on the day of death or because they did not fulfil the age inclusion criteria.

Throughout the observed period, in around 40% of cases, the disease occurred in the gallbladder (C23). In about 60% of cases, it occurred in other and unspecified parts of the biliary tract (C24), namely 43% in the extrahepatic bile duct (C24.0), 14% in the Ampulla of Vater (C24.1), and in 1% as an overlapping lesion of the biliary tract (C24.8). In 1% of cases, the site was unspecified (C24.9).

	Sex		Age			Stage			Total
	Men	Women	20–49 yrs	50–74 yrs	75–94 yrs	Localized	Regional	Distant	
1997–2001	241	383	27	356	241	104	229	195	624
1997–2001 %	38.6	61.4	4.3	57.1	38.6	16.7	36.7	31.3	
2002–2006	259	412	25	341	305	95	253	231	671
2002–2006 %	38.6	61.4	3.7	50.8	45.5	14.2	37.7	34.4	
2007–2011	321	485	32	367	407	149	298	273	806
2007–2011 %	39.8	60.2	4.0	45.5	50.5	18.5	37.0	33.9	
2012–2016	411	510	19	425	477	199	375	320	921
2012–2016 %	44.6	55.4	2.1	46.2	51.8	21.6	40.7	34.7	

TABLE 1

Number and proportion of patients with gallbladder and bile duct cancer by sex, age, stage and period of diagnosis in Slovenia in 1997–2016.

Depending on the specific observation period, between 36–42% of patients did not have their disease confirmed microscopically. Among the microscopically confirmed cases, adenocarcinoma was the most common histological type, occurring in 90% of cases in the last five-year period. In a bit over one percent of cases, the histological type was not specified.

In all the observed periods, more women than men were diagnosed with gallbladder and bile duct cancer. Between 1997 and 2006, the largest proportion of persons were aged 50 and 74 years at diagnosis, while between 2007 and 2016 most were aged 75–94. The disease was most commonly diagnosed in the regional stage, and only marginally less often in the distant stage (Table 1).

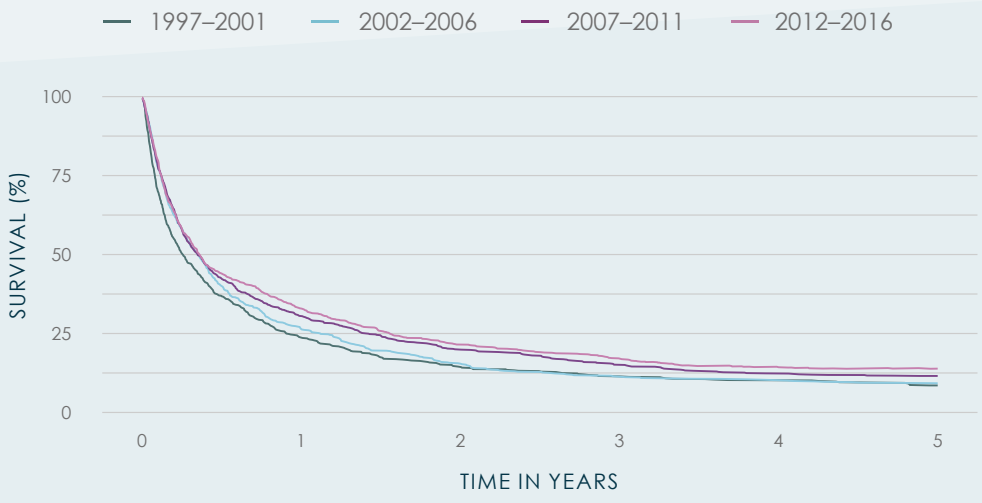


FIGURE 2

Net survival of patients with gallbladder and bile duct cancer by period of diagnosis in Slovenia in 1997–2016.

Regarding the specific primary treatment of gallbladder and bile duct cancer between 1997 and 2016, most patients were treated with surgery alone (34%). Systemic treatment was given to 4% of patients and less than 1% of patients received radiotherapy. Throughout the observed period, more than 61% of patients did not receive specific primary treatment; the proportion of patients who did not receive specific primary treatment does not significantly differ between any of the observed five-year periods.

TABLE 2

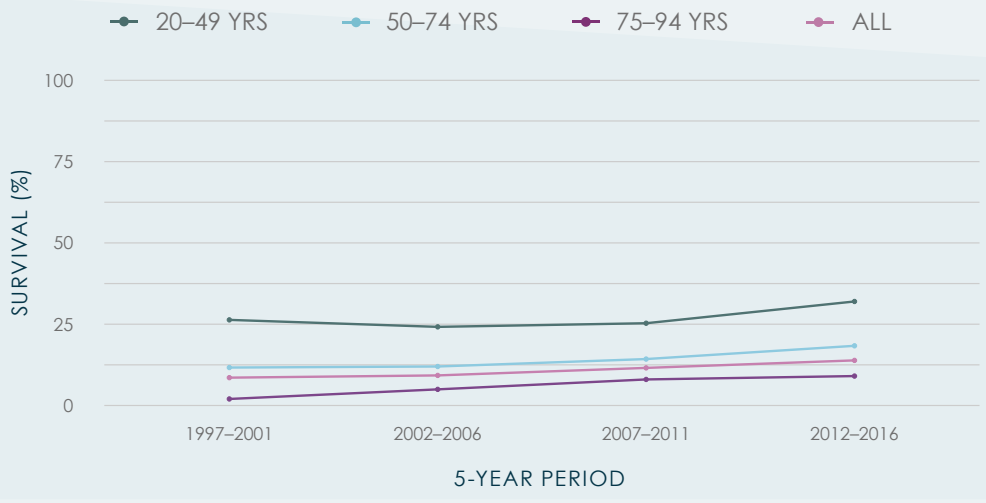
One-, three-, and five-year observed and net survival (with a 95% confidence interval-CI) of patients with gallbladder and bile duct cancer by sex and period of diagnosis in Slovenia in 1997–2016.

Survival / Period			1997–2001	(95% CI)	2002–2006	(95% CI)	2007–2011	(95% CI)	2012–2016	(95% CI)
Observed	1-year	all	23.1	20.0–26.7	25.6	22.5–29.2	29.5	26.5–32.9	31.9	29.1–35.1
		men	29.6	24.3–36.0	32.1	26.8–38.3	35.5	30.7–41.2	34.8	30.5–39.7
		women	19.1	15.5–23.4	21.6	18.0–26.0	25.6	22.0–29.8	29.6	25.9–33.9
	3-year	all	10.6	8.4–13.3	10.4	8.4–13.0	13.8	11.6–16.4	15.8	13.6–18.3
		men	15.4	11.5–20.7	12.0	8.6–16.7	15.9	12.4–20.4	17.0	13.7–21.1
		women	7.6	5.3–10.7	9.5	7.0–12.8	12.4	9.8–15.7	14.8	12.0–18.3
	5-year	all	7.4	5.6–9.8	7.8	6.0–10.1	9.9	8.1–12.2	11.6	9.7–14.0
		men	10.0	6.8–14.6	8.5	5.7–12.7	10.9	8.0–14.9	12.2	9.3–16.1
		women	5.7	3.8–8.6	7.3	5.2–10.3	9.3	7.0–12.3	11.2	8.7–14.4
Net	1-year	all	23.9	20.7–27.6	26.6	23.4–30.3	30.6	27.5–34.0	32.9	30.0–36.2
		men	30.8	25.3–37.4	33.6	28.2–40.1	37.0	31.9–42.9	36.0	31.5–41.1
		women	19.6	16.0–24.1	22.2	18.5–26.7	26.3	22.6–30.7	30.5	26.7–34.9
	3-year	all	11.6	9.2–14.6	11.5	9.1–14.4	15.1	12.7–18.0	17.3	14.9–20.2
		men	17.1	12.7–23.0	13.2	9.4–18.7	17.5	13.5–22.5	18.6	15.0–23.0
		women	8.1	5.6–11.6	10.3	7.6–13.9	13.6	10.7–17.3	16.3	13.2–20.1
	5-year	all	8.6	6.4–11.4	9.3	7.1–12.1	11.6	9.4–14.3	14.2	11.8–17.1
		men	11.9	8.0–17.5	9.9	6.6–15.0	12.9	9.4–17.7	14.7	11.2–19.3
		women	6.5	4.3–9.9	8.7	6.2–12.3	10.6	8.0–14.1	13.7	10.6–17.8

Throughout the observed period, gallbladder and bile duct cancer surgery was performed in at least eight hospitals, most often at the University Medical Centre Ljubljana (54%) and University Medical Centre Maribor (34%). At the Celje General Hospital, Jesenice General Hospital, Izola General Hospital, Murska Sobota General Hospital, Nova Gorica General Hospital and Novo Mesto General Hospital, less than 5% of operations were performed. In the last five-year period, as part of their primary treatment patients received systemic treatment at the Institute of Oncology Ljubljana (34%), the University Medical Centre Ljubljana (34%), the University Medical Centre Maribor (28%), the Celje General Hospital (4%), and Slovenj Gradec General Hospital (2%).

FIGURE 3

Five-year net survival of patients with gallbladder and bile duct cancer by age group in Slovenia in 1997–2016.



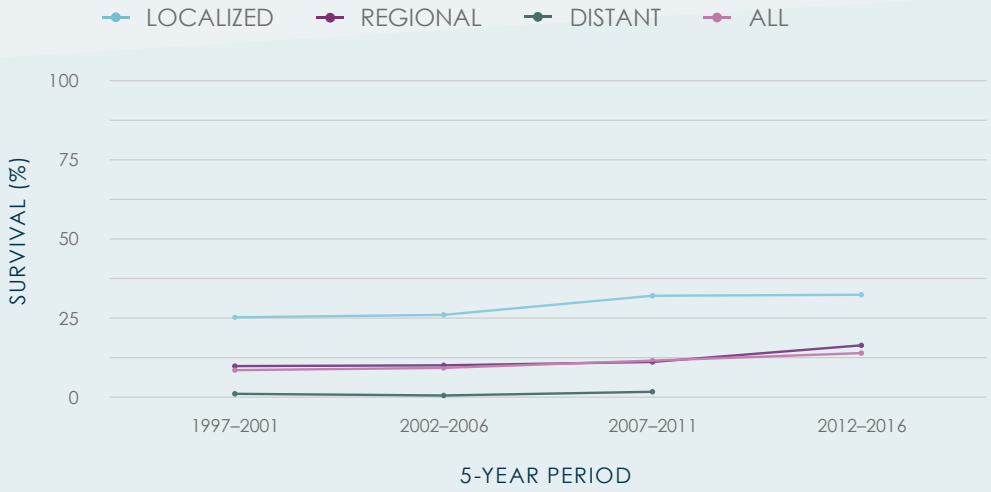


FIGURE 4

Five-year net survival of patients with gallbladder and bile duct cancer by stage in Slovenia in 1997–2016.

The net survival of patients with gallbladder and bile duct cancer has been gradually improving with the increasing year of diagnosis (Figure 2, Table 2). In the 20 years under review, the five-year net survival improved by slightly less than 6 percentage points. Throughout the observed period, there were no major differences between the sexes in the five-year net survival of patients with gallbladder and bile duct cancer (Table 2).

In Slovenia, compared to other selected cancers, gallbladder and bile duct cancer ranks 19th in men and 22nd in women by five-year net survival.

Figure 3 shows the impact of age on the survival of patients with gallbladder and bile duct cancer. The five-year net survival is lowest in patients aged 75–94 years. In all periods, the survival of people aged 20 to 49 at diagnosis was better compared to people aged 50 to 74, being on average 12 percentage points higher.

The importance of stage at diagnosis is shown in Figure 4. In the last period, the five-year net survival of patients was slightly less than 33% for the localized stage of the disease and 16% for the regional stage, while there were almost no survivors after five years among patients with the distant stage of the disease at diagnosis. During 1997–2016, the five-year net survival of patients with gallbladder and bile duct cancer has been slowly improving for all stages of the disease.

CLINICAL COMMENTARY

Mirko Omejc

The number of patients diagnosed with gallbladder and bile duct cancer increased in the observed period (1997–2016). Approximately two-thirds of patients with gallbladder and bile duct cancer are diagnosed at a regional or distant stage, meaning that only palliative treatment is possible for these patients. Their survival is low and has changed only little during the observed period. The greatest improvement in survival was seen in the group of younger patients, aged up to 50 years, and for the localized stage of the cancer. Although surgical resection is the only potentially curative treatment, it has been performed in 37% of patients. Two-thirds of patients did not receive any specific treatment, and this did not change significantly during the observed period. There has been a centralization of patient treatment at the University Medical Centres in Ljubljana and Maribor and at the Institute of Oncology Ljubljana, institutions with technical requirements and expertise in the treatment of such patients. Even in patients who have undergone potentially curative resection, the likelihood of recurrence is high. This is why a multidisciplinary approach in the treatment of patients with gallbladder and bile duct cancer, which also enables quality palliative treatment, is so important.

The increasing popularity of laparoscopic cholecystectomies has led to an increase in the incidence of gallbladder cancer. More than half of the cases are diagnosed histologically after cholecystectomy due to cholecystitis or cholecystolithiasis, which is also reflected in the fragmentation of first treatments shown in this analysis. If an incidental cancer diagnosed in the localized stage (T1b, T2, T3) is not histologically confirmed during surgery, a repeat surgery is indicated by oncological principles. The extent to which and where in Slovenia reoperations are carried out is not clear from the present analysis.

Although gallbladder and bile duct cancer is a rare group of cancers, including in Slovenia, it is an important cause of cancer death due to its aggressive course and early metastasis. The mortality rate is very similar to the incidence rate. The five-year survival in the world is 50% for stage I gallbladder cancer (most commonly incidentally diagnosed) and only 3% for a distant disease, which is comparable to the disease outcomes here in Slovenia. Surgery is the only potentially curative treatment and its success depends on the stage, tumour biology and surgical radicality. Recurrence occurs early in the course of the disease, in 88% in the first two years after surgery and as systemic recurrence in 85%. Early distant recurrence suggests that in most cases, micrometastatic disease is already present at diagnosis, highlighting the benefit of neoadjuvant systemic treatment. Its advantages are: the immediate treatment of micrometastases; good patient compliance; the selection of patients who respond to treatment, do not have disease progression and are therefore more suitable for undergoing surgery, while other patients are spared unnecessary surgery along with possible complications; and tumour reduction with a greater potential for radical resection. Unfortunately, the available studies suggest that the systemic treatment of gallbladder cancer is not as effective as treatment for other gastrointestinal tract malignancies. The response is smaller and disease progression is more frequent. Preoperative radiochemotherapy is usually indicated for locally inoperable disease or when there are contraindications for surgery. Most often, we use modern radiotherapy techniques that are intensity-modulated, volumetric with classical fractionation, and include concomitant treatment with capecitabine or stereotactic radiotherapy with a high ablative dose of irradiation in several fractions.

Both the NCCN guidelines and the ESMO guidelines for gallbladder and bile duct cancers recommend adjuvant chemotherapy or radiochemotherapy after R0 resection and histopathologically affected regional lymph nodes or after non-radical surgery. There are no randomized trials comparing the advantage of one or the other, resulting in the use of different postoperative approaches. Despite the advantages of postoperative treatment, the results of the NCDC analysis and the treatment analysis in Slovenia confirm that only a third of patients received it. In Slovenia, a handful of patients received postoperative chemotherapy and only a few individuals received radiochemotherapy, and even this only in the last observed periods.

References

Bridgewater J, Galle PR, Khan SA, et al. Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. J Hepatol 2014; 60: 1268–89.

Fornaro L, Cereda S, Aprile G, et al. Multivariate prognostic factors analysis for second-line chemotherapy in advanced biliary tract cancer. Br J Cancer 2014; 110: 2165–9.

Fuks D, Regimbeau JM, Le Treut YP, et al. Incidental gallbladder cancer by the AFC-GBC-2009 Study Group. World J Surg 2011; 35(8): 1887–97.

Valle JW, Borbath I, Khan SA, et al. Biliary cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2016; 27 (Suppl 5): 28–37.

Mitin T, Enestvedt CK, Jemal A, et al. Limited use of adjuvant therapy in patients with resected gallbladder cancer despite a strong association with survival. J Natl Cancer Inst 2017; 109(7): 1–9.

National Comprehensive Cancer Network. NCCN Guidelines – hepatobiliary cancers. Plymouth: National Comprehensive Cancer Network; 2021. Available from: https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary_blocks.pdf

Sharma A, Dwary AD, Mohanti BK, et al. Best supportive care compared with chemotherapy for unresectable gallbladder cancer: a randomized controlled study. J Clin Oncol 2010; 28: 4581–6.

van der Gaag NA, Kloek JJ, de Bakker JK, et al. Survival analysis and prognostic nomogram for patients undergoing resection of extrahepatic cholangiocarcinoma. Ann Oncol 2012; 23: 2642–94.

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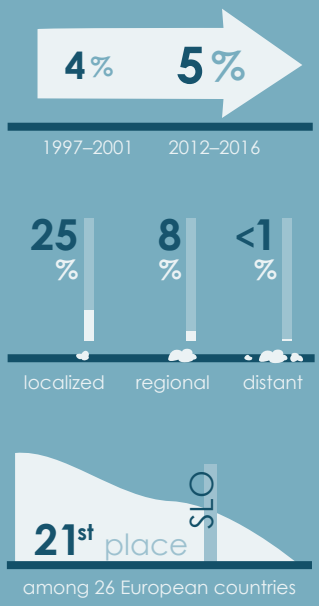
PANCREAS

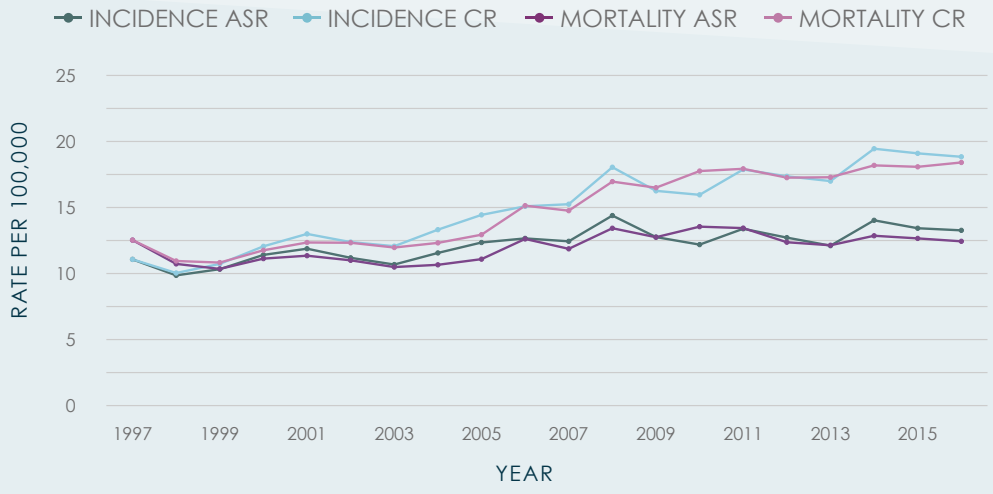


EPIDEMIOLOGY

In the last five-year period (2012–2016), 379 people per year on average were diagnosed with pancreatic cancer in Slovenia, 195 men and 184 women, and 368 people died, 187 men and 181 women. As shown in Figure 1, the pancreatic cancer incidence rate increased throughout the observed period; in the last ten years, incidence increased by 2% per year (2.8% for men and for 1.4% for women). The overall trend and the trend in men are statistically significant. Just over 70% of incidence rate growth can be attributed to an ageing population. Between 2007 and 2016, the crude mortality rate of pancreatic cancer increased by 1.7% per year in both sexes; in men statistically significantly by 1.9% and in women by 1.5%. The crude or standardized mortality rate is close to or even exceeds the crude or standardized incidence rate throughout the observed period. This is explained by the detection of the disease in the regional and distant stages at the time of diagnosis, the aggressive nature of the disease and the limited treatment options available.

FIGURE 1

The crude (CR) and age-standardized (ASR) incidence and mortality rates of pancreatic cancer in Slovenia in 1997–2016.



At the end of 2016, there were 421 people living in Slovenia who had been diagnosed with pancreatic cancer at some point in their lives. Of those, the diagnosis had been established less than one year ago in 189 people, one to four years ago in 134 people, and more than ten years ago in 39 people.

The survival analysis included 5,763 cases of patients aged 20 to 94; 303 cases (5%) were excluded because they were diagnosed on the day of death, or because they did not fulfil the age inclusion criteria.

	Sex		Age			Stage			Total
	Men	Women	20–49 yrs	50–74 yrs	75–94 yrs	Localized	Regional	Distant	
1997–2001	502	515	87	617	313	106	311	475	1017
1997–2001 %	49.4	50.6	8.6	60.7	30.8	10.4	30.6	46.7	
2002–2006	608	651	103	744	412	84	422	629	1259
2002–2006 %	48.3	51.7	8.2	59.1	32.7	6.7	33.5	50.0	
2007–2011	800	846	75	907	664	109	555	865	1646
2007–2011 %	48.6	51.4	4.6	55.1	40.3	6.6	33.7	52.6	
2012–2016	950	891	71	996	774	162	609	1018	1841
2012–2016 %	51.6	48.4	3.9	54.1	42.0	8.8	33.1	55.3	

TABLE 1

Number and proportion of patients with pancreatic cancer by sex, age, stage and period of diagnosis in Slovenia in 1997–2016.

Over the observed periods, most cases (42–44%) occurred in the head of the pancreas (C25.0). In 6–11%, the disease occurred in the tail of the pancreas (C25.2) and in 5–8%, in the body of the pancreas (C25.1). In 4–5% of cases, the disease occurred as an overlapping lesion of the pancreas (C25.8). In less than 1%, however, the disease occurred in the pancreatic duct (C25.3), in endocrine pancreas (C25.4), and other parts of the pancreas (C25.7). In 34–40% of cases of pancreatic cancer the site was not specified (C25.9).Depending on the specific observation period, between 40–47% of cases did not have their disease confirmed microscopically. In all periods, the most common histological type among all microscopically confirmed cases was adenocarcinoma, which occurred in 87% of cases in the last five-year period. In 10% of cases, the histological type was not specified.

In all observed periods, a similar number of men and women were diagnosed with pancreatic cancer, the majority of patients were aged 50–74 years. The disease was most commonly diagnosed in the distant stage (Table 1), and this proportion has been increasing.

Regarding the specific primary treatment of pancreatic cancer between 1997 and 2016, 13% of patients were treated with surgery alone and 12% of patients were treated with systemic therapy alone. Slightly under 5% of patients received systemic therapy in combination with surgery. Less than 2% of patients received radiotherapy. Across the entire observed period, 69% of patients did not receive spe-

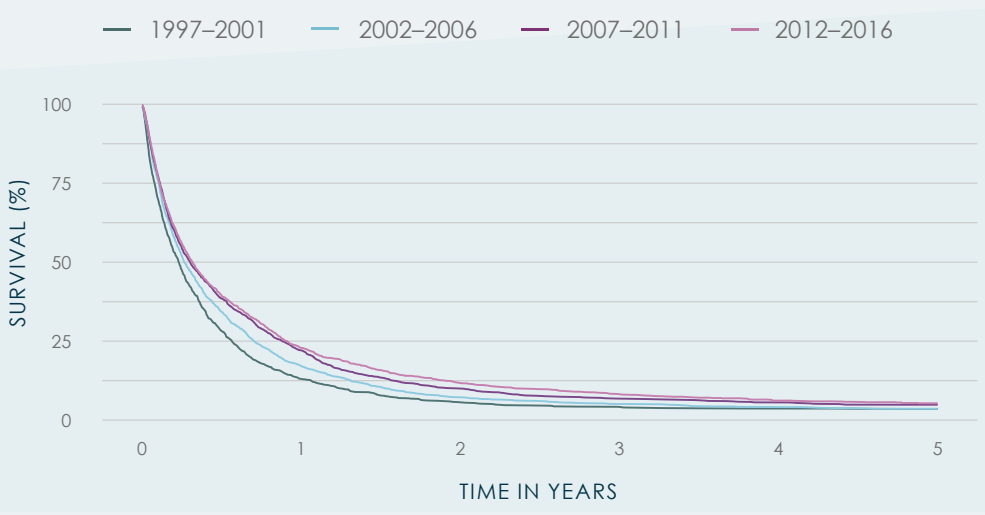


FIGURE 2

Net survival of patients with pancreatic cancer by period of diagnosis in Slovenia in 1997–2016.

cific primary treatment. The proportion of patients who did not receive specific primary treatment decreased in the observed five-year periods (1997–2001: 80%; 2012–2016: 64%).

TABLE 2

One-, three- and five-year observed and net survival (with a 95% confidence interval–CI) of patients with pancreatic cancer by sex and period of diagnosis in Slovenia in 1997–2016.

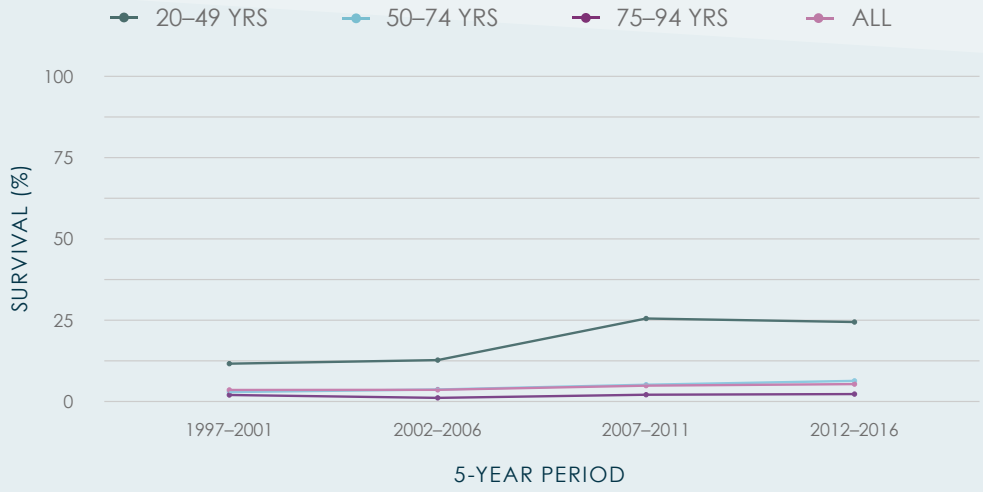
Survival		/ Period	1997–2001	(95% CI)	2002–2006	(95% CI)	2007–2011	(95% CI)	2012–2016	(95% CI)
Observed	1-year	all	12.7	10.8–14.9	16.7	14.8–18.9	21.6	19.7–23.7	22.4	20.6–24.4
		men	12.0	9.4–15.2	17.5	14.7–20.8	23.2	20.4–26.3	21.5	19.0–24.3
		women	13.4	10.8–16.7	16.0	13.4–19.1	20.1	17.6–23.0	23.3	20.7–26.3
	3-year	all	3.8	2.8–5.2	4.8	3.7–6.1	6.4	5.3–7.7	7.7	6.6–9.0
		men	4.2	2.8–6.4	4.1	2.8–6.1	6.5	5.0–8.5	6.8	5.4–8.6
		women	3.5	2.2–5.5	5.4	3.9–7.4	6.3	4.8–8.1	8.6	6.9–10.7
	5-year	all	3.0	2.1–4.2	3.3	2.4–4.4	4.4	3.6–5.6	4.8	3.8–6.0
		men	3.2	2.0–5.2	3.0	1.9–4.7	4.9	3.6–6.6	4.0	2.9–5.7
		women	2.7	1.6–4.6	3.5	2.4–5.3	4.0	2.9–5.6	5.6	4.2–7.5
Net	1-year	all	13.1	11.1–15.4	17.1	15.1–19.4	22.2	20.2–24.3	22.9	21.0–24.9
		men	12.4	9.8–15.7	18.0	15.1–21.4	23.8	21.0–27.0	22.1	19.6–24.9
		women	13.7	11.0–17.1	16.3	13.7–19.5	20.6	18.0–23.6	23.8	21.1–26.8
	3-year	all	4.2	3.1–5.7	5.1	4.0–6.6	6.8	5.7–8.2	8.2	7.0–9.6
		men	4.8	3.2–7.2	4.5	3.1–6.6	7.0	5.4–9.1	7.4	5.8–9.3
		women	3.6	2.3–5.7	5.7	4.2–7.9	6.7	5.1–8.7	9.0	7.3–11.2
	5-year	all	3.5	2.5–5.0	3.6	2.6–4.9	4.9	3.9–6.1	5.3	4.3–6.7
		men	4.3	2.7–6.8	3.3	2.1–5.3	5.4	4.0–7.4	4.7	3.4–6.6
		women	2.8	1.7–4.8	3.8	2.5–5.8	4.3	3.1–6.1	6.0	4.5–8.0

Throughout the observed period, pancreatic cancer surgery was performed in at least three hospitals; in the last five-year period, the majority of surgical procedures were performed at the University Medical Centre Ljubljana (62%), the University Medical Centre Maribor (32%), and Izola General Hospital (5.5%). In the last five-year period, most patients received systemic treatment at the Institute of Oncology Ljubljana (44%), the University Medical Centre Ljubljana (33%), and the University Medical Centre Maribor (20%) as part of their primary treatment. A small number of patients also received systemic treatment at Celje General Hospital (1.2%), Nova Gorica General Hospital (0.7%) and Slovenj Gradec General Hospital (0.2%).

The net survival of patients with pancreatic cancer did not change significantly with year of diagnosis (Figure 2, Table 2). In the 20 years under review, five-year net survival improved by slightly less than 2 percentage points. Throughout the observed period, there were no major differences between the sexes in the five-year net survival of patients with pancreatic cancer (Table 2). In Slovenia, compared

FIGURE 3

Five-year net survival of patients with pancreatic cancer by age group in Slovenia in 1997–2016.



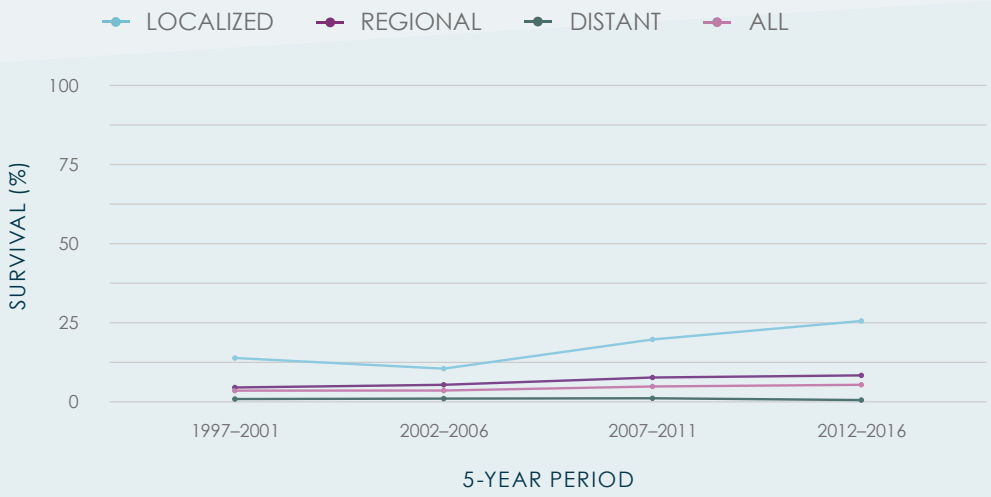


FIGURE 4

Five-year net survival of patients with pancreatic cancer by stage in Slovenia in 1997–2016.

to other selected cancers, pancreatic cancer ranks 22nd in men and 24th in women by five-year net survival.

Figure 3 shows the impact of age on the survival of patients with pancreatic cancer. Five-year net survival is lowest in people aged 75 –94 years and is only slightly better in people aged 50 to 74. In people

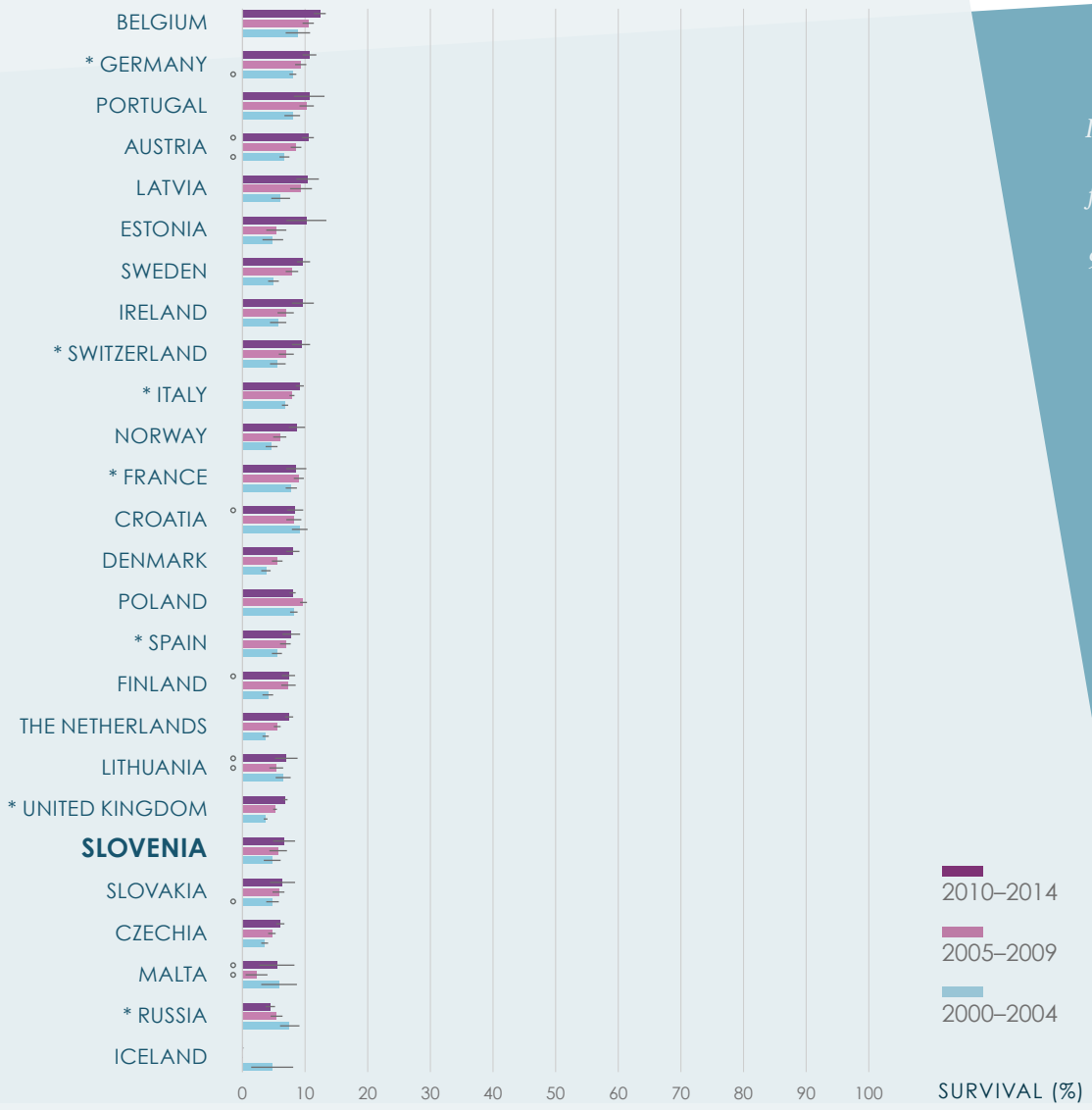


FIGURE 5

International comparison of age-standardized five-year net survival for pancreatic cancer (with 95% confidence intervals) in patients diagnosed in 2000–2004, 2005–2009 and 2010–2014 (CONCORD-3).

** Data doesn't cover a 100% of the country's population.*

° Survival estimate is less reliable.

aged 20 to 49 at diagnosis, survival has improved markedly in the last two periods, on average by 13 percentage points, and has thus been over 20% for some time.

The importance of stage at diagnosis is shown in Figure 4. In the last period, five-year net survival of patients with localized disease was 25% and has improved by 11 percentage points compared to 1997–2001. Five-year net survival of patients with regional disease is 8%, whereas in patients with distant disease at diagnosis, it is less than 1%.

The results of the world-wide CONCORD-3 study of patients diagnosed with cancer during the 15 years between 2000 and 2014 in 71 countries and territories show that five-year net survival of Slovenian patients with pancreatic cancer has been improving (Figure 5). For patients diagnosed during the most recent period (2010–2014), Slovenia ranked 21st among the 26 participating countries in Europe.

CLINICAL COMMENTARY

Mirko Omejc

Pancreatic cancer typically spreads quietly, lacking signs and symptoms, which means that the disease has often reached an advanced stage by the time of diagnosis. Even in early-stage of pancreatic cancer, the mortality rate is high due to aggressive growth and spreading. It is clinically manifested by extensive perineural and retroperitoneal infiltration, vascular invasion, local recurrence, and early local and distant metastases. Research in recent years has presented a number of new questions, but unfortunately yielded only a few answers that contribute to the increased survival of patients. There is a wealth of new findings about this disease, yet progress in treatment is limited. The number of patients treated for pancreatic cancer almost doubled in the observed period (1997–2016). Despite considerable efforts and improved diagnostic options, there has been little change in the ratio between the locally limited and the regional and distant stages. In the majority of patients, the disease had already had metastasized at the time of diagnosis. In more than 90% of patients, the disease was already in the regional or distant stage at the time of treatment. Furthermore, a large proportion of deaths from pancreatic cancer also occurred in patients with presumably locally limited disease stage. Nevertheless, it is in this group of patients that the greatest improvement in survival has occurred in the last decade.

In Slovenia, increasing incidence is leading to changes in the detection and treatment of pancreatic cancer, similarly as in the rest of the world. In parallel with the increase in incidence, the number of resections has also increased. Tumour-free resection (R0) is the most important prognostic factor. Pylorus-preserving cephalic duodenopancreatectomy has become an established surgical treatment; it is better tolerated by the patient and enables an improved quality of life after surgery with a survival rate comparable to classic Whipple surgery. Extensive lymphadenectomy does not improve survival outcomes compared to standard lymph node dissection. Postoperative mortality and postoperative complications are inversely proportional to the number of resections. In centres that perform a large number of surgical procedures, mortality has fallen below 5% over the last decade, and patient survival in these centres has increased. Since 2000, treatment in Slovenia has been centralized in three larger centres that provide oncological surgery. A team approach and multimodal treatment are established in these centres. During this period, the proportion of patients treated with surgery alone decreased and the proportion of those receiving surgery in combination with another treatment increased. The improvement in survival is particularly pronounced during this period, especially in patients under 50 years of age. At the same time, it is interesting to note that the proportion of patients with localized cancer at the time of diagnosis has decreased and the proportion of regionally and distantly advanced cancer at the time of diagnosis has increased, which speaks in favour of improved diagnostics in recent years. The increase in the number of patients with local and distant spread of the disease can also be attributed to improved technical and diagnostic possibilities, which also enable safe and accurate diagnostic procedures in patients with jaundice. The improvement in survival is most striking in younger patients with localized cancer. Elderly patients are often less suitable for extensive surgery and additional treatment due to comorbidities, so survival has not changed much in this group. The increase in survival during the observed period can be attributed to greater accuracy in determining disease stage, better selection of patients for surgery, and lower early

postoperative mortality due to improved postoperative intensive care and oncology treatment, which is a result of a team approach to treating patients with pancreatic cancer. However, there are still more than two thirds of patients who did not receive specific treatment.

Vaneja Velenik

Survival data in the present cohort analysis are similar to those worldwide: the mortality rate and incidence rates are almost equal, with a five-year survival rate of less than 6%. Although it is 25% in patients with localized disease, they represent only 9% of all patients. More than half (55%) have distant stage disease at diagnosis, and their survival is only 0.5%.

In assessing the prognosis of the disease at diagnosis, it is paramount to assess the resectability of the tumour. Tumours are classified as resectable, borderline resectable, locally advanced, or metastatic according to the location, proximity, or contact with adjacent vessels or organs and the presence of metastases. Only 15–20% of patients have resectable disease at diagnosis, and 30–40% have non-metastatic but unresectable disease and are therefore assessed as locally advanced. Differences in survival between studies may be a result of inconsistent criteria among different guidelines for distinguishing marginally resectable from locally advanced unresectable cancers. Surgery is the only treatment option that may cure patients with resectable cancer. Due to the high percentage of systemic (80%) and local recurrences (20%), survival of even radically operated patients is poor; therefore, adjuvant treatment is recommended either with chemotherapy alone or in combination with chemoradiotherapy. Our data show that only a few patients in Slovenia have received such treatment. Neoadjuvant treatment is recommended for borderline resectable tumours. Most often, this is chemotherapy, followed by chemoradiotherapy in the event of local progression. In Slovenia, this treatment regime was rare in the observed periods.

There are no standardized international guidelines for the treatment of the group of patients with locally advanced pancreatic cancer. If such patients cannot be included in an ongoing study, we follow one of the existing guidelines. The ESMO guidelines recommend either chemotherapy with gemcitabine or chemoradiotherapy with fluoropyrimidines. As an alternative to chemoradiotherapy, the guidelines optionally recommend stereotactic radiotherapy of the tumour. In clinical practice in recent years, as recommended by the updated NCCN and ASCO guidelines, a combination of irinotecan and oxaliplatin (FOLFIRINOX regimen) or nabpaclitaxel in combination with gemcitabine has been used in the chemotherapy regimen. Although both the NCCN and ASCO guidelines include stereotactic radiotherapy of the tumour as a follow-up or alternative treatment option, stereotactic radiotherapy regimens and doses in individual clinical trials vary greatly. The optimal sequence of radiochemotherapy and stereotactic radiotherapy also remains unclear.

References

American Society of Clinical Oncology. ASCO guidelines – Gastrointestial cancers. United States of America, American Society of Clinical Oncology; 2021. Available from: https://www.asco.org/research-guidelines/quality-guidelines/guidelines/gastrointestinal-cancer

Ducreux M, Cuhna AS, Caramella C, et al. Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015; 26 (Suppl 5): 56–68.

Khorana AA, Mangu PB, Berlin J, et al. Potentially Curable Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2016; 34: 2541.

Merchant N, Berlin J. Past and future of pancreas cancer: are we ready to move forward together? J Clin Oncol 2008; 26: 3478–80.

National Comprehensive Cancer Network. NCCN Guidelines – pancreatic cancer. Plymouth: National Comprehensive Cancer Network; 2021. Available from: https://www.nccn.org/professionals/physician_gls/pdf/pancreatic_blocks.pdf

Omejc M. Rak trebušne slinavke v Sloveniji. Anketa kirurških oddelkov za leti 1999–2000 (Pancreatic carcinoma in Slovenia : results of national questionnary 1999-2000). In: Pleskovič A, ed. Kirurgija trebušne slinavke: zbornik simpozija (Pancreatic surgery: proceedings of the symposium), Ljubljana. Ljubljana: University Medical Centre, Divison of Surgery; 2002. p. 135–9.

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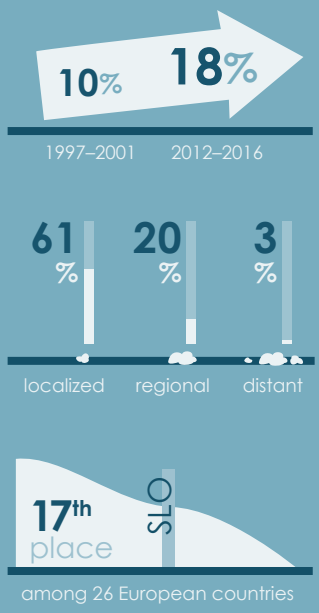
LUNGS

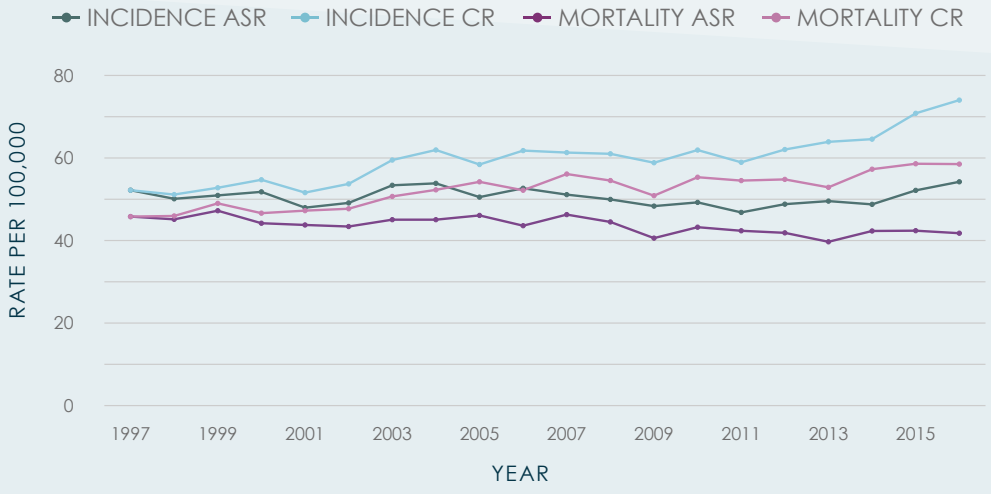


EPIDEMIOLOGY

In the last five-year period (2012–2016), 1,380 people on average were diagnosed with lung cancer in Slovenia, 923 men and 457 women, and 1,163 people died, 796 men and 367 women. As shown in Figure 1, incidence rate of lung cancer has been rising again since 2011. Between 2007 and 2016, the lung cancer incidence rate increased statistically significantly by 2.0% per year. Although lung cancer affects more men than women, the incidence of this cancer is increasing faster in women than in men, a trend which has also been observed in Slovenia for other smoking-related cancers. In the last ten years, the lung cancer incidence rate in women has increased statistically significantly by 4.9% per year. From 2007 to 2016, the crude mortality rate of lung cancer increased by 0.8% per year in both sexes; in women statistically significantly by 3.2% per year. In men, the crude mortality rate decreased by 0.2% per year.

FIGURE 1

The crude (CR) and age-standardized (ASR) incidence and mortality rates of lung cancer in Slovenia in 1997–2016.



At the end of 2016, there were 3,294 people living in Slovenia who had ever been diagnosed with lung cancer. Of those, the diagnosis had been established less than one year ago in 955 people, one to four years ago in 1,237 people, and over ten years ago in 541 people.

The survival analysis included 23,415 cases of patients aged 20 to 94; 762 cases (3%) were excluded because they were diagnosed on the day of death, or because they did not fulfil the age inclusion criteria.

Over the observed periods, the disease occurred in the trachea (C33) in only 0.4% of cases. In most cases, the disease occurred in the bronchus and the lung (C34), namely in the upper lobe (C34.1) in 50%, in lower lobe (C34.3) in 26%, and in the main bronchus (C34.0) and the middle lobe (C34.2) in 6%. In less than 2% of cases the disease occurred as an overlapping lesion of the bronchus and the lung (C34.8). In 10% of cases the site was not specified (C34.9).

	Sex		Age			Stage			Total
	Men	Women	20–49 yrs	50–74 yrs	75–94 yrs	Localized	Regional	Distant	
1997–2001	3926	1075	547	3670	784	1147	1943	1767	5001
	% 78.5	21.5	10.9	73.4	15.7	22.9	38.9	35.3	
2002–2006	4303	1404	440	4102	1165	928	2180	2415	5707
	% 75.4	24.6	7.7	71.9	20.4	16.3	38.2	42.3	
2007–2011	4225	1751	331	4128	1517	879	1975	2994	5976
	% 70.7	29.3	5.5	69.1	25.4	14.7	33.1	50.1	
2012–2016	4489	2242	218	4728	1785	1108	1950	3615	6731
	% 66.7	33.3	3.2	70.2	26.5	16.5	29.0	53.7	

TABLE 1

Number and proportion of patients with lung cancer by sex, age, stage and period of diagnosis in Slovenia in 1997–2016.

Depending on the specific observation period, between 6–8% of patients did not have a microscopically confirmed disease. In all periods, the most common histological types among all microscopically confirmed cases were adenocarcinoma (43% of cases in the last period), squamous cell carcinoma (28%), and small cell carcinoma (17%). Over the observed period, the proportion of adenocarcinomas has gradually increased, while the proportion of squamous cell carcinomas has decreased. In less than 2% of cases, the histological type was not specified.

In all observed periods, more men than women were diagnosed with lung cancer, the majority of patients were aged 50–74 years. The disease was most commonly diagnosed in the distant stage (Table 1).

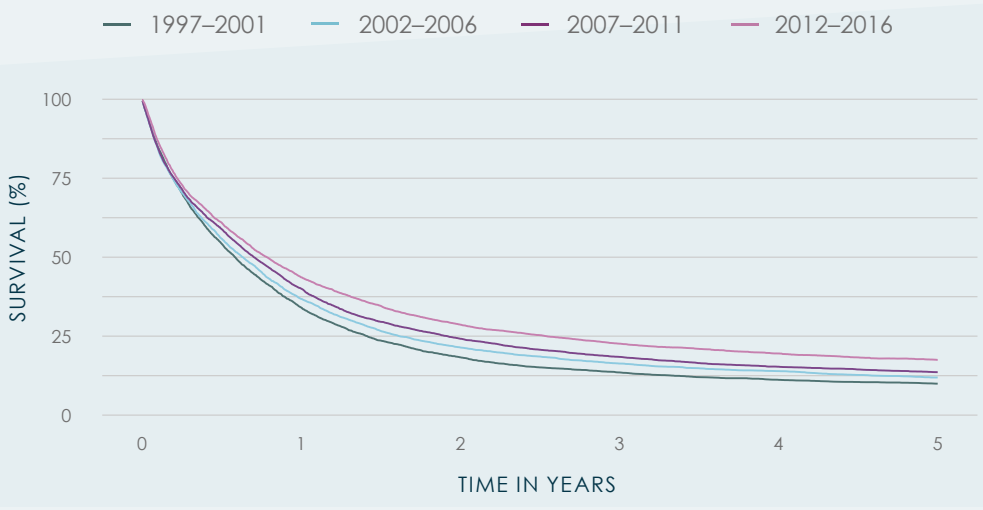


FIGURE 2

Net survival of patients with lung cancer by period of diagnosis in Slovenia in 1997–2016.

Regarding the specific primary treatment of lung cancer, between 1997 and 2016, the largest proportion of patients (23%) received radiotherapy alone, and 17% of patients were treated with radiotherapy and systemic therapy. 33% of patients received systemic therapy alone or in combination. Across the entire observed period, the proportion of patients who were treated with surgery was 19%, while 30% of patients did not receive specific primary treatment; the proportion of patients who did not receive specific primary treatment decreased in the observed five-year periods (1997–2001: 33%; 2012–2016: 27%).

TABLE 2

One-, three- and five-year observed and net survival (with a 95% confidence interval–CI) of patients with lung cancer by sex and period of diagnosis in Slovenia in 1997–2016.

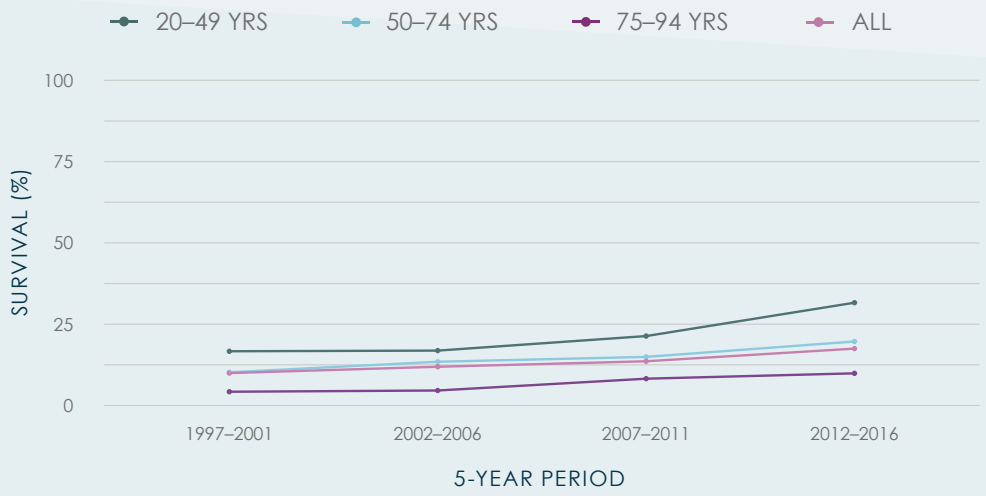
Survival / Period			1997–2001	(95% CI)	2002–2006	(95% CI)	2007–2011	(95% CI)	2012–2016	(95% CI)
Observed	1-year	all	33.1	31.8–34.4	35.8	34.6–37.1	39.0	37.8–40.3	42.6	41.5–43.8
		men	32.4	31.0–33.9	34.2	32.8–35.7	36.6	35.2–38.1	39.5	38.1–41.0
		women	35.7	32.9–38.7	40.7	38.2–43.4	44.7	42.5–47.1	48.8	46.8–50.9
	3-year	all	12.4	11.5–13.4	15.1	14.2–16.1	17.2	16.2–18.2	21.3	20.3–22.3
		men	12.0	11.1–13.1	14.2	13.2–15.2	15.2	14.1–16.3	18.4	17.3–19.6
		women	13.9	12.0–16.1	18.0	16.1–20.2	22.0	20.1–24.0	27.1	25.3–29.0
	5-year	all	8.7	8.0–9.5	10.5	9.8–11.4	12.1	11.3–12.9	15.9	15.0–16.9
		men	8.2	7.4–9.1	9.8	8.9–10.7	10.5	9.6–11.5	13.6	12.6–14.7
		women	10.5	8.8–12.5	12.9	11.3–14.8	15.8	14.2–17.6	20.5	18.8–22.4
Net	1-year	all	34.1	32.8–35.5	36.8	35.5–38.1	40.1	38.8–41.4	43.6	42.4–44.8
		men	33.5	32.0–35.0	35.3	33.9–36.8	37.8	36.3–39.3	40.6	39.2–42.1
		women	36.3	33.5–39.3	41.4	38.9–44.1	45.6	43.2–48.0	49.5	47.5–51.7
	3-year	all	13.5	12.6–14.6	16.3	15.4–17.4	18.4	17.4–19.5	22.7	21.7–23.8
		men	13.2	12.2–14.4	15.5	14.4–16.7	16.5	15.3–17.7	19.9	18.7–21.2
		women	14.6	12.6–16.9	18.9	16.9–21.2	23.1	21.2–25.3	28.2	26.4–30.3
	5-year	all	10.0	9.1–10.9	11.9	11.0–12.9	13.6	12.7–14.6	17.7	16.6–18.8
		men	9.6	8.6–10.7	11.3	10.3–12.4	12.1	11.0–13.2	15.5	14.3–16.8
		women	11.4	9.5–13.6	13.9	12.1–16.0	17.3	15.5–19.3	22.1	20.2–24.1

Throughout the observed period, lung cancer surgery was performed in three centres: in the last five-year period, the majority of surgical procedures were performed at the University Medical Centre Ljubljana (38%), Surgery Bitenc (33%) and the University Medical Centre Maribor (20%). As part of their primary treatment in the last five-year period, patients received systemic therapy at the Institute of Oncology Ljubljana (56%), the University Clinic Golnik (29%), and the University Medical Centre Maribor (15%).

The net survival of patients with lung cancer by year of diagnosis has been gradually improving (Figure 2, Table 2). In the 20 years under review, five-year net survival improved by slightly less than

FIGURE 3

Five-year net survival of patients with lung cancer by age group in Slovenia in 1997–2016.



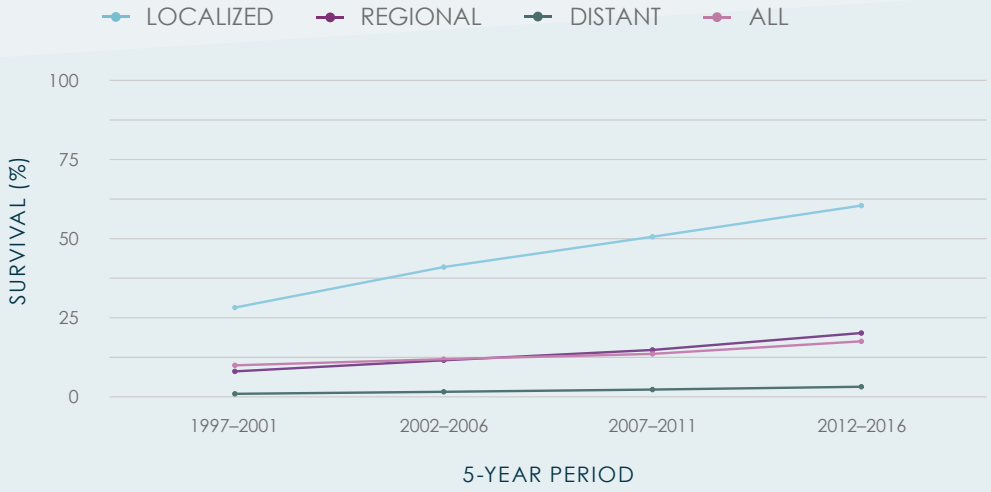


FIGURE 4

Five-year net survival of patients with lung cancer by stage in Slovenia in 1997–2016.

eight percentage points. Regarding the five-year net survival of patients with lung cancer, women have a slightly better survival rate than men throughout the observed period; the difference varies between two and seven percentage points depending on the specific period, and has consistently been increasing (Table 2).

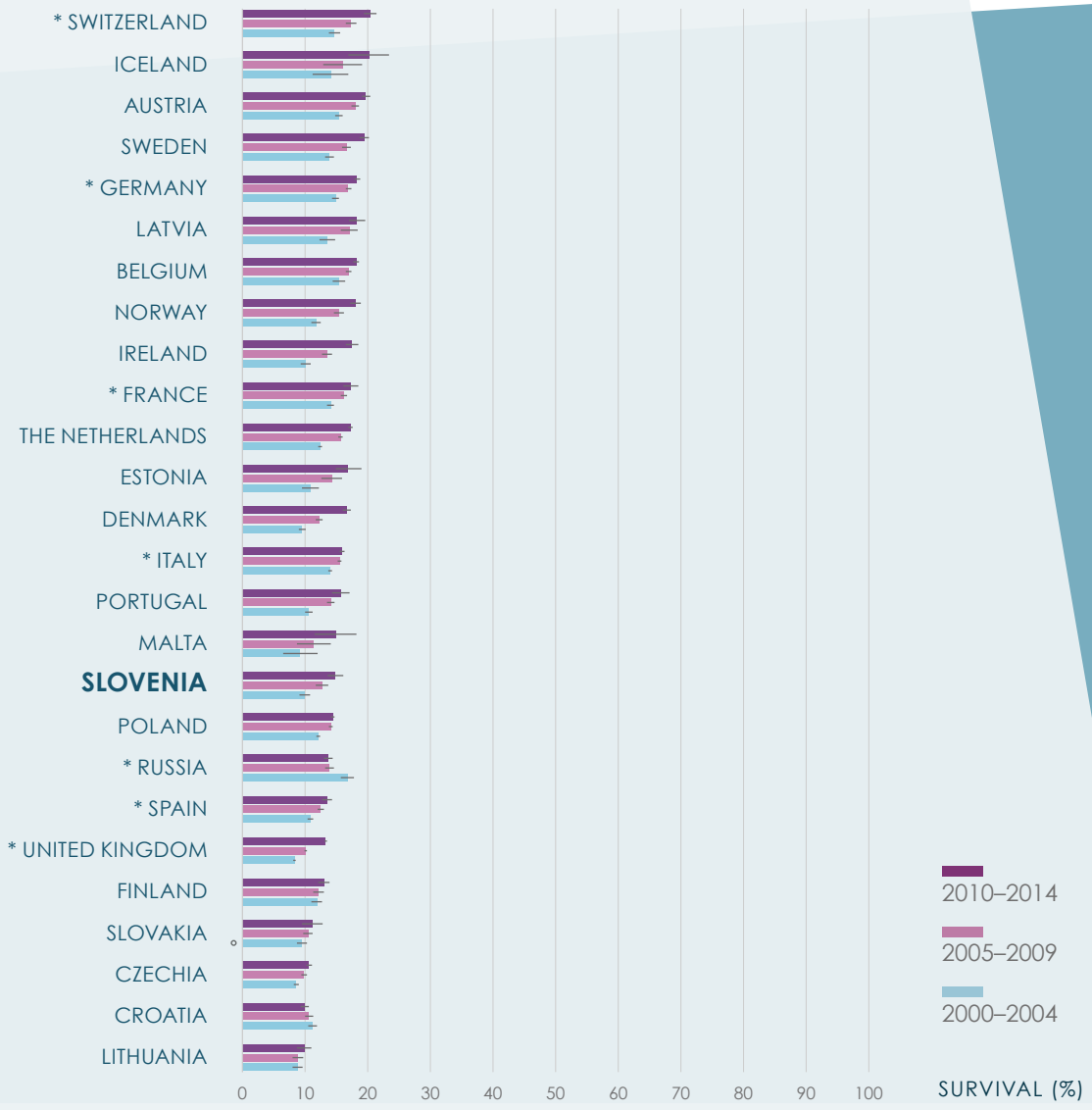


FIGURE 5

International comparison of age-standardized five-year net survival for lung cancer (with 95% confidence intervals) in patients diagnosed during 2000–2004, 2005–2009 and 2010–2014 (CONCORD-3).

** Data doesn't cover a 100% of the country's population.*

° Survival estimate is less reliable.

In Slovenia, compared to other selected cancers, lung cancer ranks 18th in men and 19th in women by five-year net survival.

Figure 3 shows the impact of age on the survival of patients with lung cancer. Five-year net survival is lowest in people aged 75–94 years and has improved slightly over the last two periods. The survival of patients aged 20–49 at diagnosis was better in all five-year periods compared to other age groups and improved by almost 15 percentage points between 2012 and 2016 compared to the first observed five-year period.

The importance of stage at diagnosis is shown in Figure 4. In the last period, five-year net survival of patients with localized lung cancer exceeded 60%. Five-year net survival of patients with regional disease is 20%, whereas in patients with distant disease at diagnosis, it is slightly over 3%. Five-year net survival of patients with lung cancer improved slightly between 1997 and 2016 in all stages.

The results of the world-wide CONCORD-3 study of patients diagnosed with cancer during the 15 years between 2000 and 2014 in 71 countries and territories show that five-year net survival of Slovenian patients with lung cancer has been improving (Figure 5). For patients diagnosed during the most recent period (2010–2014), Slovenia ranked 17th among the 26 participating countries in Europe.

CLINICAL COMMENTARY

Tomaž Štupnik

Of all lung cancer treatment options, surgery gives patients the greatest chance of cure; therefore, a significant increase in the proportion of operated patients over the last 20 years has certainly made a significant contribution to improving five-year survival. The most obvious turning points occurred in 2002 and 2012.

In the period 1997–2001, patients treated with surgery (935) represented 82% of patients who had localized disease (1,147). In the periods 2002–2006 and 2007–2011, the number of patients treated with surgery suddenly increased to 1,039 and 1,015, respectively, which meant that the proportion of patients treated with surgery exceeded the number of patients with localized disease by 12% and 15%. After 2002 more and more patients with regionally advanced disease were operated on in addition to patients with localized disease. The expansion of surgical treatment indications was the result of improved disease staging, which was due to computed tomography (CT), endobronchial ultrasound (US), and later, PET/CT, as well as the result of advances in thoracic surgery.

Due to more precise surgery, in the majority of patients who would once have undergone lung removal, the same radicality could be achieved by lung lobe removal, which many more patients with lung cancer can tolerate, especially patients aged over 65. These patients also benefited greatly from the fact that in the late 1990s, instead of cutting into the chest using posterolateral thoracotomy, we began to use much less painful anterolateral thoracotomy.

As the proportion of pneumonectomies decreased from 20–25% to 5–10%, the average age of patients with lung cancer undergoing surgery increased from approximately 55 to 65 years of age, resulting in the biggest improvement in five-year survival in the group of patients aged 75–94.

A revolution in the surgical treatment of patients with lung cancer occurred between 2012 and 2016, with the introduction of minimally invasive videothoracoscopic surgery into the field of lung cancer surgery; with this development, the number of operated patients increased suddenly from 1,015 to 1,449, and the proportion of operated patients exceeded 21% having been hovering around 17–19% over the previous five year periods.

The first videothoracoscopic lobectomy for lung cancer was performed in Slovenia in 2008; in the following decade, the proportion of patients undergoing videothoracic surgery quickly exceeded 50%,

and it became the gold standard for the surgical treatment of lung cancer. Videothoracoscopic surgery has significantly reduced the risk of postoperative complications and thus extended the indications for surgical treatment to some groups of patients that were previously not suitable candidates for open surgery.

Given recent breakthroughs in the field of early detection and treatment of lung cancer, we can optimistically expect that in the future the proportion of surgically treated patients will double, and that the majority of lung cancers will be diagnosed in early stages and removed by videothoracoscopic segment resection with an almost negligible risk of postoperative complications.

Martina Vrankar

The incidence of lung cancer has been increasing over the last 20 years, mainly due to an increase in incidence in women. In the last five-year period, one-third of all patients with lung cancer were women, while in the first five years of the observed period, cases in females made up only slightly more than one-fifth. The reason is attributed to the different pattern of smoking between the sexes in the past: the rise of smoking among women came later, with women's emancipation, which is reflected in an increased incidence in the recent period, as the estimated latency period for lung cancer is 20 years.

Although the diagnostics of lung cancer has advanced significantly in the last five-year period, the same cannot be said for shortening the time to diagnosis. The improvement in diagnostics is reflected in a change in the proportion of patients at different stages of the disease, in so-called stage migration. Accordingly, in the last 20 years, we have seen a decline in the proportion of localized lung cancer, an even greater decline in the proportion of regionally advanced disease, and an increase in the proportion of distant metastasis from 35% in the first five-year period to 54% in the last observed period. The greatest contribution to the improvement of diagnostics has been made by 18F-FDG PET/CT, which all patients now undergo to rule out dissemination of the disease. Of late, in the early stages before treatment, we have also increasingly been using ultrasound techniques in the cytological verification of mediastinal lymph nodes, which makes staging of the disease even more accurate. Despite improved diagnostics, the proportion of microscopically confirmed lung cancer has remained more or less unchanged over the entire 20-year period. Almost 8% of patients have no cytological or histological confirmation of their lung cancer.

The proportion of patients who did not receive oncology treatment after diagnosis has been declining in the last 20 years, but in the latest five-year period, this group of patients still made up a good quarter of all patients, which can be attributed to their age and comorbidities.

Between 2012 and 2016 most patients (45%) received radiotherapy as part of primary treatment, either alone as palliative or radical treatment, or in combination with surgery and/or systemic therapy. The total proportion of patients who received radiotherapy as part of primary treatment remained the same by period, but the ratio changed in favour of combination therapy, mainly with chemotherapy. Since the majority of patients in this group have non-metastatic inoperable locally advanced lung cancer, we can conclude that in the last period we have become more radical in our approach to the treatment of potentially curable patients. More advanced new radiotherapy techniques, increased accuracy and performance of radiotherapy equipment and improved supportive therapy in oncology treatment have allowed us to achieve more radical treatment with fewer radiotherapy-related adverse effects.

The survival of patients with lung cancer is improving. As expected, the best five-year survival is in the localized lung cancer group, rising from 28% in the first period to 61%. Five-year survival of locally advanced lung cancer and disseminated lung cancer also improved, from 8% to 20% and 1% to 3%, respectively. Improved survival despite the effect of the stage migration from lower to higher disease stages shows the remarkable progress in lung cancer treatment over the last 20 years. Better surgical techniques with fewer complications, new radiotherapy techniques with more accurate and powerful equipment, and advances in systemic therapy with new drugs such as targeted therapy and immunotherapy have more than doubled the five-year survival rate of each group.

Several challenges lie ahead that need to be addressed to help improve lung cancer treatment outcomes. The first is faster diagnostics that would allow patients to be treated quickly and appropriately. Patients lose significant time on a waiting list alongside other patients who do not have cancer and for whom a delay in examination does not come with such fatal consequences. The current health care system is certainly not geared towards reducing waiting times for patients with suspected lung cancer, and action will be needed to manage these patients more quickly. The survival data offer another important aspect: diagnosis at an earlier stage ensures better survival, and increasingly more data confirm that lung cancer screening contributes to this. However, several questions arise: it is not entirely clear how to identify an at-risk group, how often screening should take place, and how to include screening in the current health care system. The third challenge is prevention, which should address young people in particular and discourage them from smoking, which is still the most important risk factor for lung cancer.

Tanja Čufer

Lung cancer is one of the most common cancers, the incidence of which is still increasing in Slovenia. Between 2012–2016, slightly more than 6,700 people were diagnosed with lung cancer, which is about 10% more than in the previous five-year period. Overall, the number and proportion of women among patients is increasing, recently accounting for 33% of all patients. Given that women started smoking in large numbers only at the end of the last century, we can expect a further increase in morbidity in the coming years.

The good news, however, is that mortality from lung cancer is not increasing as much as incidence, and that age-standardized mortality is even declining a little. Nevertheless, lung cancer management is still far from optimal. How can we improve it? We have reliable data that screening reduces lung cancer mortality in smokers. However, there are still many dilemmas about how to organize screening without prolonging the already lengthy period from the first signs of symptomatic lung cancer to diagnosis, and that at the same time, the side effects of screening for the individual and the financial cost for society would not be too high. Unfortunately, the proportion of patients with disseminated lung cancer at the time of diagnosis is increasing and this trend must be reversed.

The next step to better lung cancer management is more effective treatment. Survival of patients with localized lung cancer has improved from the beginning of this century. Twice as many patients are cured now and the trend is rising. However, the success of the treatment of locally advanced and disseminated lung cancer is only slowly improving. Since 2010, new, more effective systemic treatments have been introduced: targeted therapies and immunotherapy, which have already improved patients' three- to five-year survival in developed countries. There was also an increase in the survival of patients diagnosed between 2012 and 2016, especially among women, who are more likely to receive targeted treatment due to the greater presence of molecular tumour-specific targets (in EGFR or ALK).

Challenges await us in the treatment of elderly, vulnerable patients, who are increasingly suffering from lung cancer and already account for about a quarter of all patients. The answer probably lies in the additional geriatric assessment of these patients and the centralization of their care in tertiary centres. Lung cancer management would certainly be further improved by hospital registries, which would give us a more in-depth and reliable picture of diagnostics and treatment, as well as treatment outcomes across hospitals regionally. Currently available data on the site and modalities of primary treatment are not sufficient for such analyses.

Slovenia ranks approximately in the middle when it comes to five-year survival of patients with lung cancer in Europe. However, the time when we are able to assess the quality of care for patients with lung cancer is yet to come. Historically very poor lung cancer survival will improve significantly in the coming years with the arrival of novel treatment options. Lung cancer will thus become one of the cancers for which we will measure the quality of care for patients with cancer in the future, and we wish to at least maintain our current position, if not improve it.

References

Aberle DR, Adams AM, Berg CD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011; 365: 395–409.

Begum SS, Papagiannopoulos K, Falcoz PE, et al. Outcome after video-assisted thoracoscopic surgery and open pulmonary lobectomy in patients with low VO2 max: a case-matched analysis from the ESTS database. Eur J Cardiothorac Surg 2016; 49: 1054–8.

Čufer T, Košnik M. Klinični register bolnikov z rakom pljuč (Clinical registry of lung cancer patients). Onkologija 2013; 17: 8–13.

Čufer T, Ovčariček T, O'Brien ME. Systemic therapy of advanced non-small cell lung cancer: major-developments of the last 5-years. Eur J Cancer 2013; 49: 1216–25.

Deng B, Cassivi SD, de Andrade M, et al. Clinical outcomes and changes in lung function after segmentectomy versus lobectomy for lung cancer cases. J Thorac Cardiovasc Surg 2014; 148: 1186–92.

National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011; 365(5): 395–409.

Postmus PE, Kerr KM, Oudkerk M, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2017; 28: 1–21.

Ramlau R, Cufer T, Berzinec P, Dziadziuszko R, Olszewski W, Popper H, et al. Epidermal growth factor receptor mutation-positive non-small-cell lung cancer in the real-world setting in Central Europe: The INSIGHT Study. J Thorac Oncol 2015; 10: 1370–4.

Rich A, Baldwin D, Alfageme I, Beckett P, Berghmans T, Brincat S, et al. Achieving thoracic oncology data collection in Europe: a precursor study in 35 Countries. BMC Cancer 2018; 18: 1144.

Štupnik T, Vidmar S, Kramer S, Hari P. Videotorakoskopske resekcije pri raku pljuč. Isis 2008; 57(4): 81-–82.

Triller N, Bereš V, Rozman A. Delays in the diagnosis and treatment of lung cancer: Can the period between the onset of symptoms and the diagnosis and treatment be shortened? Zdrav Vestn 2010; 79(9): 618–22.

Vidmar S. Vpliv prognostičnih dejavnikov pri reseciranem, nemikrocelularnem karcinomu pljuč, stadijev I, II in IIIa, na nadaljnji potek bolezni in preživetje : disertacija (Influence of prognostic factors for further course and survival of resected, non-microcellular lung carcinoma, stage I, II and IIa ; Doctoral Thesis). Ljubljana: Medical Faculty of University of Ljubljana; 1996.

Vrankar M, Stanič K. Long-term survival of locally advanced stage III non-small cell lung cancer patients treated with chemoradiotherapy and perspectives for the treatment with immunotherapy. Radio Oncol 2018; 52: 281–88.

Vrankar M, Zwitter M, Bavčar T, et al. Induction gemcitabine in standard dose or prolonged low-dose with cisplatin followed by concurrent radiochemotherapy in locally advanced non-small cell lung cancer: a randomized phase II clinical trial. Radio Oncol 2014; 48: 369–80.

Vrdoljak E, Bodoky G, Jassem J, et al. Expenditures on oncology drugs and cancer mortality-to-incidence ratio in Central and Eastern Europe. Oncologist 2019; 24: 30–7.

Wu Y, Li P, Zhangl H, Honghe Z, et al. Diagnostic value of fluorine 18 fluorodeoxyglucose positron emission tomography/computed tomography for the detection of metastases in non-small-cell lung cancer patients. Int J Cancer 2013; 132: 37–47.

Yousaf-Khan U, van der Aalst C, de Jong PA, et al. Final screening round of the NELSON lung cancer screening trial: the effect of a 2.5-year screening interval. Thorax 2017; 72: 48–56.

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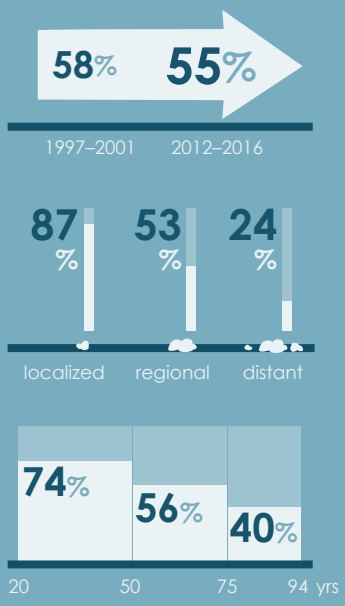
SOFT TISSUES



EPIDEMIOLOGY

In the last five-year period (2012–2016), 80 people per year on average were diagnosed with malignant soft tissue tumours in Slovenia, 34 men and 46 women, and 43 people died, 17 men and 26 women. Figure 1 shows the time trend of malignant soft tissue tumours. Due to the small number of cases throughout the observed period, it is difficult to talk about a consistent trend. Over the last ten years, there has been a noticeable increase in the crude incidence rate of 2.5% per year; in men by 1.4% and in women with a statistically significant 3.1% per year. Between 2007 and 2016, the crude mortality rate of malignant soft tissue tumours increased by 2.6% per year in both sexes combined, by 5.5% in men and by 1.6% in women. The increase is not statistically significant.

At the end of 2016, there were 856 people living in Slovenia who had been diagnosed with a malignant soft tissue tumour at some point in their lives. Of those, the diagnosis had been established less than one year ago in 73 people, one to four years ago in 205 people, and over ten years ago in 443 people.

FIGURE 1

The crude (CR) and age-standardized (ASR) incidence and mortality rates of malignant soft tissue tumours in Slovenia in 1997–2016.

The survival analysis included 1,232 cases of patients aged 20 to 94 years; 92 cases (7%) were excluded because they were diagnosed on the day of death or because they did not fulfil the age inclusion criteria.

Throughout the observed period, most cases (55–68%) occurred in other connective and soft tissue (C49), where in the largest proportion (24–36%), the disease developed in the connective and soft tissue of a lower limb, including the hip (C49.2), and in 8–11% in the connective and soft tissue of an upper limb, including the shoulder (C49.1). In the retroperitoneum and peritoneum (C48), the disease occurred in 27–41%; most often (11–22%), the disease occurred in the retroperitoneum (C48.0) and in 4–20% in specified parts of the peritoneum (C48.1). In the peripheral nerves and the autonomic nervous system (C47), the disease occurred in approximately 5%, most commonly (in less than 2%) in the peripheral nerves of the lower limb, including the hip (C47.2). In the heart (C38.0), the disease occurred in less than 1% of cases.

	Sex		Age			Stage			Total
	Men	Women	20–49 yrs	50–74 yrs	75–94 yrs	Localized	Regional	Distant	
1997–2001	109	125	84	107	43	113	89	24	234
1997–2001 %	46.6	53.4	35.9	45.7	18.4	48.3	38.0	10.3	
2002–2006	142	171	85	167	61	96	139	62	313
2002–2006 %	45.4	54.6	27.2	53.4	19.5	30.7	44.4	19.8	
2007–2011	136	183	64	172	83	85	136	90	319
2007–2011 %	42.6	57.4	20.1	53.9	26.0	26.7	42.6	28.2	
2012–2016	154	212	62	208	96	97	170	90	366
2012–2016 %	42.1	57.9	16.9	56.8	26.2	26.5	46.5	24.6	

TABLE 1

Number and proportion of patients with malignant soft tissue tumours by sex, age, stage and period of diagnosis in Slovenia in 1997–2016.

Depending on the individual observed period, the disease was microscopically confirmed in 97–100%. Only 14 patients did not have their disease confirmed microscopically during the entire observed period. In all periods, among all the microscopically confirmed cases, the most common histological types were leiomyosarcoma, the proportion of which decreased throughout the observed periods, liposarcoma, which occurred in a similar proportion in all periods, and unspecified sarcoma, adenocarcinoma and fibrosarcoma, the proportion of which gradually increased through periods. In the last observed period, between 2012 and 2016, unspecified sarcoma (23%), liposarcoma (20%) and adenocarcinoma (15%) occurred most frequently. In approximately 0.5% of cases, the histological type was not defined.

In all periods, more men than women were diagnosed with malignant soft tissue tumours: the majority of patients were aged 50 to 74 years. The disease was most commonly diagnosed in the regional stage (Table 1).

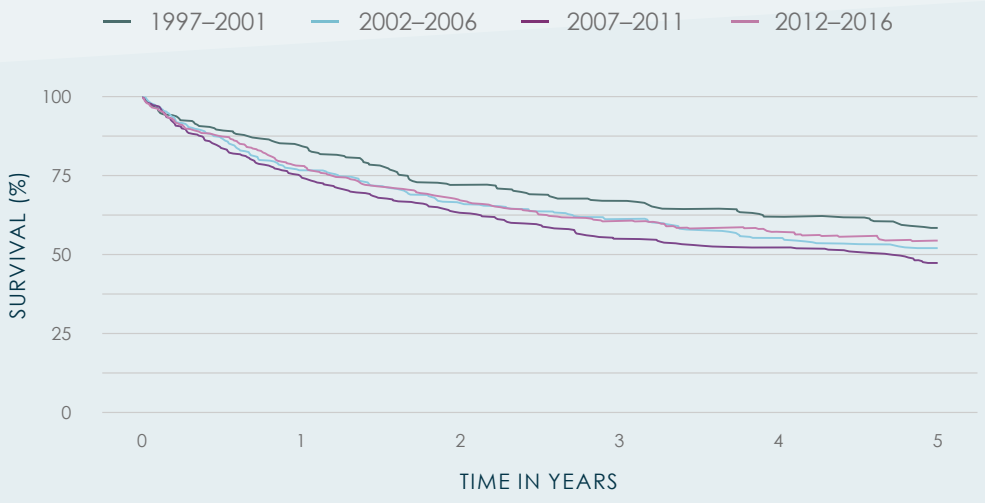


FIGURE 2

Net survival of patients with malignant soft tissue tumours by period of diagnosis in Slovenia in 1997–2016.

Regarding the specific primary treatment of malignant soft tissue tumours, between 1997 and 2016, the largest proportion of patients (45%) were treated with surgery alone, 18% of patients were treated with a combination of surgery and radiotherapy, and 14% with a combination of surgery and systemic therapy. Twenty-four percent of patients received systemic treatment alone or in combination. Throughout the observed period, 8% of patients did not receive specific primary treatment; the proportion of patients who did not receive specific primary treatment increased during the observed five-year periods (1997–2001: 6%; 2012–2016: 9%).

TABLE 2

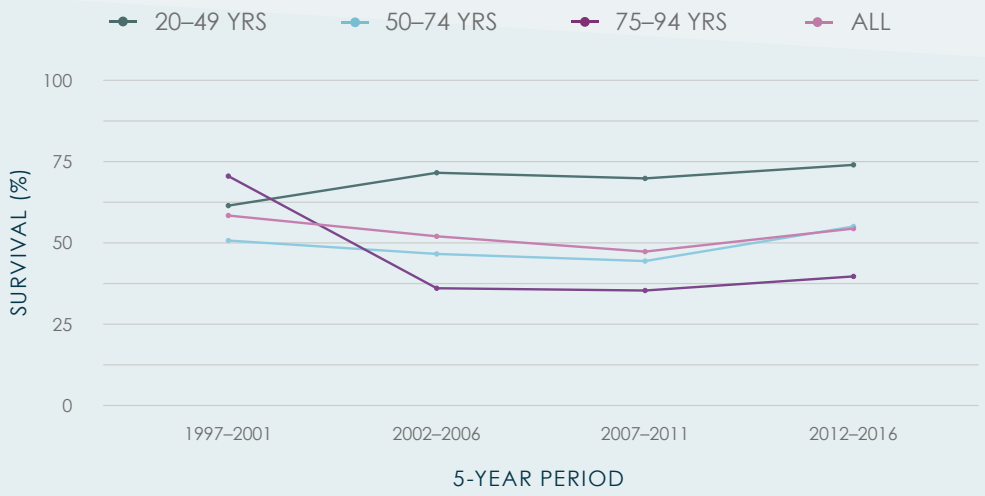
One-, three-, and five-year observed and net survival (with a 95% confidence interval-CI) of patients with malignant soft tissue tumours by sex and period of diagnosis in 1997–2016.

Survival / Period			1997–2001	(95% CI)	2002–2006	(95% CI)	2007–2011	(95% CI)	2012–2016	(95% CI)
Observed	1-year	all	82.5	77.8–87.5	75.1	70.4–80.0	73.4	68.7–78.4	76.5	72.3–81.0
		men	80.7	73.7–88.5	72.5	65.6–80.3	74.3	67.3–82.0	76.6	70.2–83.6
		women	84.0	77.8–90.7	77.2	71.2–83.8	72.7	66.5–79.4	76.4	70.9–82.4
	3-year	all	61.5	55.6–68.1	56.9	51.6–62.6	52.0	46.8–57.8	57.6	52.8–62.9
		men	59.6	51.1–69.6	55.6	48.0–64.4	55.9	48.1–64.9	59.1	51.8–67.4
		women	63.2	55.3–72.3	57.9	51.0–65.8	49.2	42.5–57.0	56.6	50.3–63.7
	5-year	all	49.6	43.6–56.4	46.7	41.4–52.5	42.6	37.5–48.4	50.0	44.9–55.7
		men	50.5	41.9–60.8	49.3	41.7–58.2	50.0	42.3–59.2	52.2	44.6–61.1
		women	48.8	40.8–58.4	44.4	37.6–52.6	37.2	30.8–44.9	48.4	41.8–56.0
Net	1-year	all	84.6	79.7–89.8	76.6	71.8–81.7	74.9	70.0–80.0	78.1	73.8–82.7
		men	83.0	75.6–91.0	74.1	66.9–82.0	75.9	68.7–83.8	78.7	72.2–85.9
		women	85.7	79.3–92.5	78.7	72.5–85.4	74.0	67.7–81.0	77.6	72.0–83.7
	3-year	all	67.9	60.4–74.0	61.1	55.4–67.2	55.2	49.6–61.4	60.9	55.6–66.6
		men	64.9	55.6–75.8	59.0	50.9–68.4	59.3	50.8–69.1	63.4	55.4–72.5
		women	68.4	59.9–78.1	62.5	55.0–71.0	51.9	44.8–60.2	59.0	52.3–66.6
	5-year	all	58.2	50.8–66.6	51.9	45.8–58.7	47.5	41.7–54.1	54.6	48.8–61.1
		men	61.3	51.1–73.7	54.8	46.2–65.0	56.0	47.2–66.6	58.0	48.9–68.7
		women	55.0	45.1–67.0	49.4	41.4–58.9	41.1	33.9–49.7	52.0	44.8–60.3

In all periods, malignant soft tissue tumour surgeries were performed in at least 12 hospitals. In the last five-year period, most of them were performed at the Institute of Oncology Ljubljana (65%), the University Medical Centre Ljubljana (23%), and at the University Medical Centre Maribor (8%). As part of their primary treatment, in the last five-year period, patients received systemic therapy at three institutions, namely the Institute of Oncology Ljubljana (89%), the University Medical Centre Maribor (10%), and the Nova Gorica General Hospital (1%).

FIGURE 3

Five-year net survival of patients with malignant soft tissue tumours by age group in Slovenia in 1997–2016.



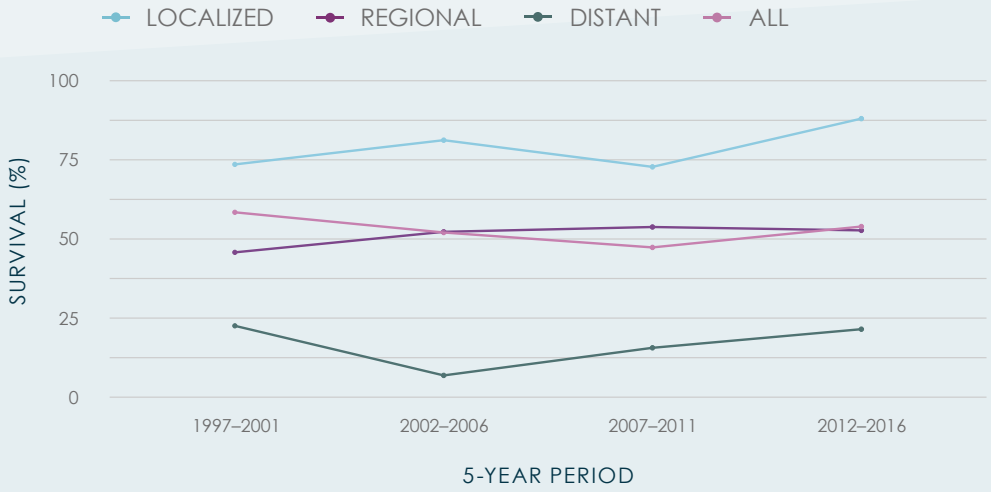


FIGURE 4

Five-year net survival of patients with malignant soft tissue tumours by stage in Slovenia in 1997–2016.

The net survival in malignant soft tissue tumours varies depending on the year of diagnosis, but the differences between the individual observed periods were not statistically significant. The five-year net survival was highest (58%) between 1997 and 2001 and lowest (47%) between 2007 and 2011 (Figure 2, Table 2). In all the observed periods, men had a higher five-year net survival than women; the difference across the periods was 5–15 percentage points (Table 2).

In Slovenia, compared to other selected cancers, malignant soft tissue tumours rank 11th in men and 11th in women by five-year net survival.

Figure 3 shows the impact of age on the survival of patients with malignant soft tissue tumours. Due to the small number of cases, the five-year net survival of patients with malignant soft tissue tumours in the 1997–2001 period indicates a higher variability between age groups compared to other five-year periods, but the differences in survival are not statistically significant. Between 2002 and 2016, the five-year net survival was lowest in patients aged 75–94 years. The survival of patients aged 20 to 49 at diagnosis is better compared to other age groups and improved by 12 percentage points between 2012 and 2016 compared to the first observed period (Figure 3).

The importance of the stage at diagnosis is shown in Figure 4. The five-year net survival of patients with the localized stage of the disease was slightly over 87% in the last period. The five-year net survival of patients with the regional stage was 53%, whereas in patients with the distant stage of the disease at diagnosis, it was 24%. Due to the small number of cases, the time trend of the five-year net survival of patients with malignant soft tissue tumours between 1997 and 2016 indicates higher variability between the five-year periods for all stages, but the differences in survival were not statistically significant.

CLINICAL COMMENTARY

Marko Novak, Lorna Zadravec Zaletel, Mojca Unk

Soft tissue sarcomas are a group of rare and heterogeneous malignancies, accounting for only 1% of all malignancies. The disease has a very good prognosis in the early stage and an extremely poor prognosis in the distant stage with the presence of distant metastases. According to international and Slovenian recommendations, treatment at a sarcoma reference centre is essential for achieving the best treatment outcome. The only such institution in Slovenia is the Institute of Oncology Ljubljana. Diagnosis and treatment require a multidisciplinary approach, involving a (cyto)pathologist, radiologist, oncology surgeon, radiotherapist, and medical oncologist, all specialising in treating patients with sarcomas.

On average, around 80 people are diagnosed with this disease in Slovenia every year. The incidence is slowly but steadily increasing, probably partly due to the ageing of the population, and partly due to better access to radiological examinations, while greater exposure to carcinogens in the environment may also play a role. In the 2007–2011 period, the proportion of patients with non-metastatic disease vs. metastatic disease at diagnosis declined, but increased again in the last observed period. There is no clear explanation for this; it may be a reflection of the better awareness of patients and general practitioners or better access to imaging examinations.

The Slovenian and international recommendations regarding diagnostics and treatment are clear, however, only about half of patients receive primary treatment at the recommended institution. It is worrying that, despite all the efforts of the experts, this percentage has recently been declining (compared to the period between 2007 and 2011).

The predominant treatment for soft tissue sarcomas is surgical and thus, surgery accounts for the largest proportion of specific primary treatment. In recent years, we have seen new evidence that treatment outcomes are improving thanks to the use of multimodal treatment, supplementing surgery with radiotherapy and systemic therapy. In the last decade, a higher proportion of patients received radiotherapy before or after surgery. This, alongside more accurate imaging, is probably one of the main reasons for the improved survival of patients with the localized disease. It is also pleasing to see that patients with primary metastatic disease are living longer than they did previously, most likely due to the introduction of new systemic treatments, better supportive care, and the inclusion of both surgical and radiation therapy in the treatment of patients in the distant stage of the disease.

Nevertheless, the survival of Slovenian patients remains below the European average (EUROCARE-5 study). Given that providing appropriate primary treatment is the most important factor for the final outcome, the Slovenian results of treatment of patients with soft tissue tumours could be improved if more patients were treated in accordance with the international and Slovenian recommendations for the treatment of soft tissue sarcomas.

References

Brennan M, Singer S, Maki R, et al. Sarcomas of the soft tissues and bone. In: DeVita V Jr, Hellman S, Rosenberg SA, eds. Cancer: Principles and Practice of Oncology. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 1581–631.

Casali PG, Abecassis N, Bauer S, et al. Soft tissue and visceral sarcomas: ESMO–EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018; 29 (Suppl 4): 268–9.

Minicozzi P, Otter R, Primic-Žakelj M, S. Francisci S, eds. Survival of Cancer Patients in Europe, 1999–2007: The EUROCARE-5 Study. Eur J Cancer 2015; 51 (15): 2099-268.

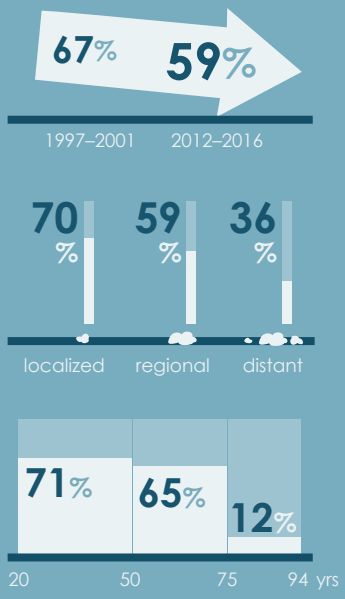
Novak M, Blatnik O, Pižem J, et al. Smernice za diagnostiko, zdravljenje in sledenje bolnikov s sarkomi mehkih tkiv in kosti. Onkologija 2018; 22 (Suppl 2): 52–81.

Primic-Žakelj M, Zadnik V, Žagar T, et al. Preživetje bolnikov z rakom, zbolelih v letih 1991-2005 v Sloveniji (Survival of cancer patients in Slovenia in the period 1991–2005). Ljubljana: Institute of Oncology; 2009.

Stiller CA, Botta L, Brester DH, et al. Survival of adults with cancers of bone or soft tissue in Europe-Report from the EUROCARE-5 study. Cancer Epidemiol 2018; 56: 146–153.

C40–C41

BONE AND ARTICULAR CARTILAGE



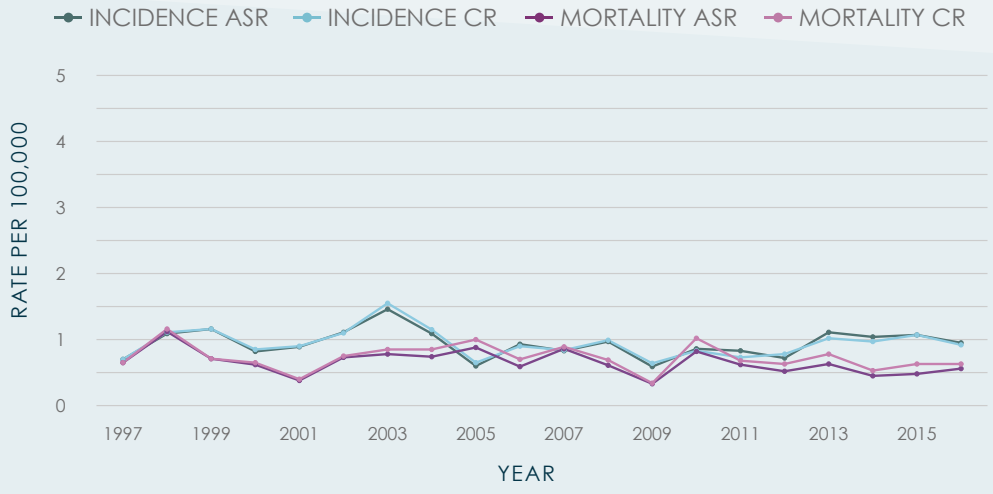
EPIDEMIOLOGY

In the last five-year period (2012–2016), 19 people per year on average were diagnosed with malignant bone tumours in Slovenia, 10 men and 9 women, and 13 people died, 5 men and 8 women. Figure 1 shows the time trend of malignant bone tumours. Due to the small number of cases throughout the observed period, it is difficult to talk about a consistent trend. Over the last ten years, there has been a noticeable increase of 3.1% per year, by 5.1% in men and by 1.5% in women per year, which is not statistically significant. Between 2007 and 2016, the crude mortality rate of malignant bone tumours in both sexes combined decreased by 1.8% per year. It decreased in a statistically significant way by 12.2% in men and increased by 11.7% per year in women, though the increase in women was not statistically significant.

At the end of 2016, there were 177 people living in Slovenia who had been diagnosed with a malignant bone tumour at some point in their lives. Of those, the diagnosis had been established less than one year ago in 10 people, one to four years ago in 23 people, and over ten years ago in 113 people.

FIGURE 1

The crude (CR) and age-standardized (ASR) incidence and mortality rates of malignant bone tumours in Slovenia in 1997–2016.



The survival analysis included 292 cases of patients aged 20 to 94 years; 89 cases (23%) were excluded because they were diagnosed on the day of death or because they did not fulfil the age inclusion criteria.

Throughout the observed period, most cases (23–40%) occurred in the long bones of the lower limb (C40.2), 14–21% in the pelvis bones, sacrum and coccyx (C41.4), 11–15% in the bones of the skull and face (C41.0) and 6–12% in the scapula and long bones of the upper limb (C40.0). Over the years, the incidence of bone tumours in the ribs, sternum and clavicle has increased (C41.3) (1997–2001: 7%; 2012–2016: 20%). In other sites, the disease occurs only occasionally.

Only two patients did not have their disease confirmed microscopically during the entire observed period. Among all the microscopically confirmed cases, in all periods, the most common histological types were chondrosarcoma, which occurred in 43% of cases in the last period, and osteosarcoma, which occurred in 32% of cases in the last period.

	Sex		Age			Stage			Total
	Men	Women	20–49 yrs	50–74 yrs	75–94 yrs	Localized	Regional	Distant	
1997–2001	36	39	26	40	9	27	32	8	75
1997–2001 %	48.0	52.0	34.7	53.3	12.0	36.0	42.7	10.7	
2002–2006	48	37	32	41	12	26	38	7	85
2002–2006 %	56.5	43.5	37.7	48.2	14.1	30.6	44.7	8.2	
2007–2011	32	31	33	25	5	27	25	10	63
2007–2011 %	50.8	49.2	52.4	39.7	7.9	42.9	39.7	15.9	
2012–2016	35	34	29	30	10	23	31	12	69
2012–2016 %	50.7	49.3	42.0	43.5	14.5	33.3	44.9	17.4	

TABLE 1

Number and proportion of patients with malignant bone tumours by sex, age, stage and period of diagnosis in Slovenia in 1997–2016.

A similar number of men and women were diagnosed with a malignant bone tumour over three of the five-year periods. The exception is the 2002–2006 period, when 13 percentage points more men than women were diagnosed. Between 1997 and 2006, on average, 46% of people diagnosed with bone tumours were aged 50 to 74, 42% of people 20 to 49, and 12% of people 75 to 94. The disease was most commonly diagnosed in the regional stage, and in a slightly lesser proportion in the localized stage (Table1).

Regarding the specific primary treatment of malignant bone tumours between 1997 and 2016, most patients (48%) were treated with surgery alone, 18% of patients were treated with surgery and systemic therapy, 9% with surgery and radiotherapy, 5% with surgery, radiotherapy and systemic therapy,

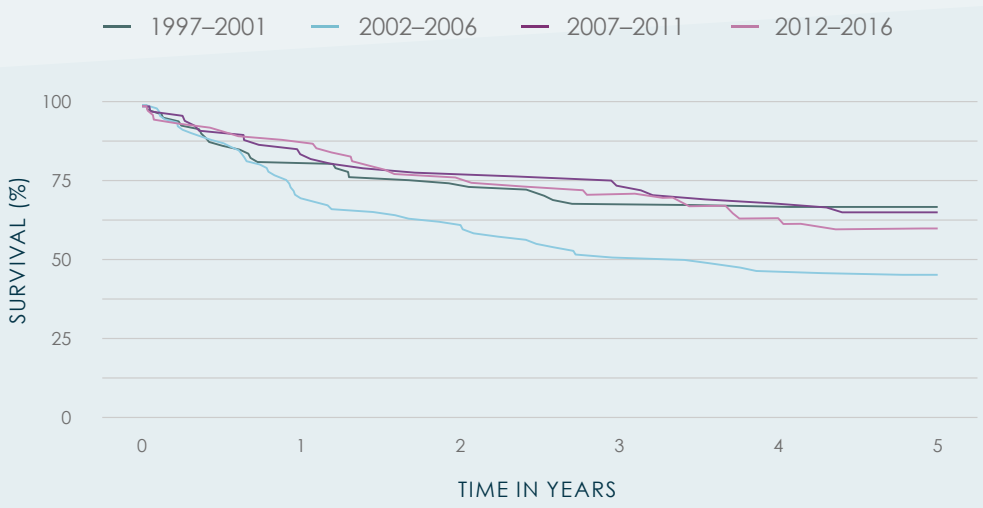


FIGURE 2

Net survival of patients with malignant bone tumours by period of diagnosis in Slovenia in 1997–2016.

and 5% with systemic therapy alone. Throughout the observed period, a total of 10% of patients did not receive specific primary treatment; the proportion of patients who did not receive specific primary treatment does not significantly differ between any of the observed periods.

In all periods, surgery for malignant bone tumours was performed in at least three hospitals. In the last five-year period, most of them were performed at the University Medical Centre Ljubljana (68%), the Institute of Oncology Ljubljana (18%), and the University Medical Centre Maribor (14%). As part of their primary treatment, in the last five-year period, the patients only received systemic therapy at the Institute of Oncology Ljubljana.

TABLE 2

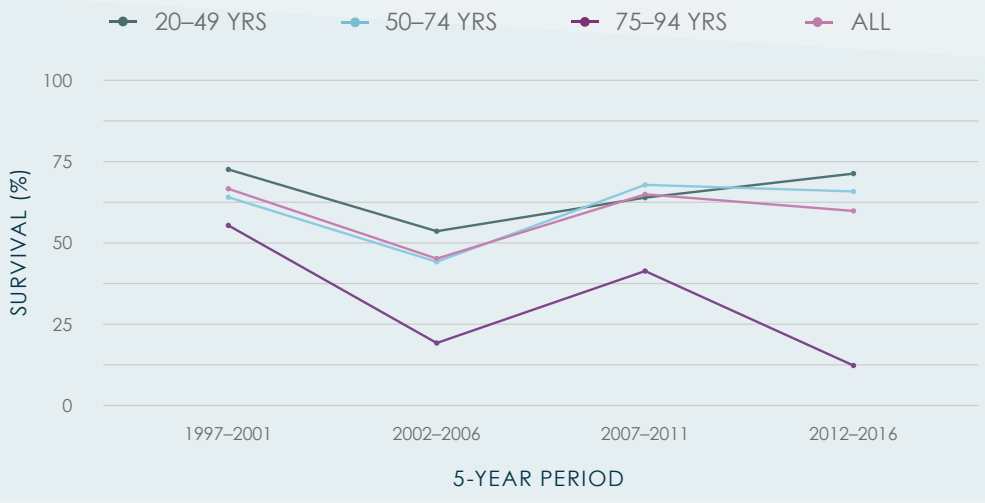
One-, three-, and five-year observed and net survival (with a 95% confidence interval–CI) of patients with malignant bone tumours by sex and period of diagnosis in Slovenia in 1997–2016.

Survival / Period			1997–2001	(95% CI)	2002–2006	(95% CI)	2007–2011	(95% CI)	2012–2016	(95% CI)
Observed	1-year	all	79.8	71.1–89.5	68.2	59.0–78.9	82.5	73.7–92.5	87.0	79.4–95.3
		men	77.8	65.3–92.6	72.9	61.4–86.6	75.0	61.4–91.6	88.6	78.6–99.8
		women	81.6	70.2–94.9	62.2	48.3–79.9	90.3	80.5–100.0	85.3	74.2–98.1
	3-year	all	64.9	54.9–76.7	48.2	38.7–60.1	71.4	61.1–83.5	68.0	57.8–80.0
		men	66.7	52.9–84.0	50.0	37.7–66.4	59.4	44.6–79.1	73.9	60.5–90.1
		women	63.2	49.6–80.6	46.0	32.4–65.2	83.9	71.9–97.9	61.8	47.4–80.5
	5-year	all	62.2	52.1–74.3	41.2	31.9–53.1	61.9	51.0–75.1	57.2	46.2–70.9
		men	63.9	50.0–81.7	39.6	27.9–56.1	50.0	35.4–70.7	63.7	49.1–82.7
		women	60.6	46.9–78.3	43.2	29.9–62.6	74.2	60.3–91.3	50.4	35.4–71.7
Net	1-year	all	80.9	72.1–90.7	69.4	59.9–80.3	83.4	74.5–93.3	87.9	80.2–96.3
		men	78.5	66.1–93.4	74.3	62.6–88.1	76.2	62.7–92.7	89.3	79.4–100.4
		women	83.0	71.5–96.3	63.0	48.8–81.4	90.6	80.8–101.5	85.9	74.8–98.7
	3-year	all	67.6	56.9–80.4	50.6	40.6–63.2	73.4	62.7–85.8	70.6	59.9–83.2
		men	68.7	54.6–86.6	53.7	40.7–70.8	62.1	46.8–82.5	77.6	63.7–94.6
		women	66.5	51.7–85.7	46.7	32.6–66.7	84.3	72.5–98.2	62.7	48.1–81.9
	5-year	all	66.7	55.6–80.0	45.2	34.9–58.4	64.9	53.6–78.7	58.9	46.8–74.1
		men	66.7	52.3–85.1	45.7	32.4–64.4	53.8	38.5–75.2	65.7	48.9–88.3
		women	66.0	50.7–86.1	44.2	30.4–64.4	75.9	61.9–93.1	51.8	36.5–73.3

The net survival of patients with malignant bone tumours does not change significantly with respect to the year of diagnosis. The exception is the 2002–2006 period, where survival is on average 18 percentage points lower than in the other five-year periods, but this difference is not statistically significant (Figure 2, Table 2). During the entire observed period, for malignant bone tumours, no major differences between the sexes in the five-year net survival were observed (Table 2).

FIGURE 3

Five-year net survival of patients with malignant bone tumours by age group in Slovenia in 1997–2016.



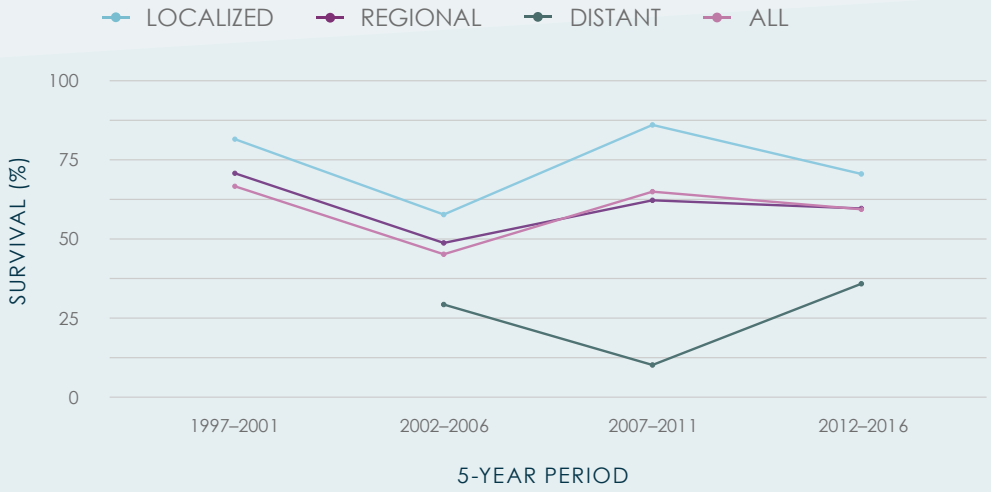


FIGURE 4

Five-year net survival of patients with malignant bone tumours by stage in Slovenia in 1997–2016.

In Slovenia, compared to other selected cancers, malignant bone tumours rank 7th in men and 12th in women by five-year net survival.

Figure 3 shows the impact of age on the survival of patients with malignant bone tumours. The five-year net survival is lowest in patients aged 75–94. The survival of people aged 20 to 49 at diagnosis is on average 5 percentage points better throughout the observed period compared to people aged 50 to 74.

The importance of the stage at diagnosis is shown in Figure 4. The five-year net survival of patients with the localized stage of the disease was slightly over 70% in the last period. The five-year net survival of patients with the regional stage was 59%, whereas in patients with the distant stage of the disease at diagnosis, it was 36%. Due to the small number of cases, the time trend of the five-year net survival of patients with malignant bone tumours between 1997 and 2016 indicates substantial variability between the five-year periods for all stages, but the differences in survival are not statistically significant.

CLINICAL COMMENTARY

Blaž Mavčič

Primary malignant bone tumours are sarcomas. The estimated incidence of bone sarcomas in Europe is about 0.9 per 100,000 population per year, which in Slovenia would mean 18 patients per year across all age groups, and an expected 360 new cases in 20 years. The number of 381 registered patients in Slovenia between 1997 and 2016 thus exceeds the expected European average by only 6 percentage points and can be explained by the demographic structure of the Slovenian population, which is gradually ageing. In Slovenia, surgery for the treatment of bone sarcomas of the limbs and spine is mostly performed at the University Medical Centre Ljubljana at the Orthopaedic Clinic, while localizations in the chest (Clinical Department for Thoracic Surgery) and bones of the skull and face (Clinical Department for Neurosurgery, Clinical Department for Maxillofacial Surgery) are less common.

There were significant changes in the surgical treatment of bone sarcomas from 1997 to 2016. Patients have greater access to magnetic resonance imaging in the diagnostic phase, in the planning of surgical resection, and for postoperative monitoring. In most cases, conservation procedures with wide resection are performed without the radical removal of entire compartments, although amputation is still necessary in about 10% of bone sarcomas of the limbs. Reconstructions after the resection of large parts of bone were still performed with custom-made allografts and endoprostheses in the 1990s, whereas after 2000, modular tumour endoprostheses with the intraoperative adjustment of implant dimensions and silver-plated metal surfaces were introduced to reduce the incidence of infections. In

the field of cartilaginous tumours, the World Health Organization classification in 2013 introduced a new entity replacing chondrosarcoma grade 1 with atypical cartilaginous tumours. This diagnosis is an exception among low-grade sarcomas, as atypical cartilaginous tumours on the extremities are no longer indications for extensive resection, but are usually treated with intralesional emptying and filling with bone cement.

Advances in conservation interventions and limb endoprostheses have unfortunately not had an impact on the overall survival of patients. As in the USA and Western European countries (five-year survival in the range of 55–66%), the five-year survival rates of adult patients in Slovenia is still around 60%, which means that it has not improved in the last 20 years, while the proportion of the cases discovered in the distant stage has actually been increasing. The only encouraging trend is an improvement in the five-year survival of patients with a metastatic disease. Data for the 1997–2016 period for Slovenia confirms the findings from the literature: older patients with bone sarcomas have a shorter survival and poorer response to chemotherapy compared to children and adolescents. In line with the demographic picture in Slovenia, an increase in the number of cases in the elderly is expected in the coming decades, so the survival rate may even worsen.

References

Franchi A. Epidemiology and classification of bone tumors. Clin Cases Miner Bone Metab 2012; 9: 92–5.

Goedhart LM, Gerbers JG, Ploegmakers JJ, et al. Delay in diagnosis and its effect on clinical outcome in high-grade sarcoma of bone: A referral oncological centre study. Orthop Surg 2016; 8: 122–8.

Jeys LM, Thorne CJ, Parry M, et al. A Novel system for the surgical staging of primary high-grade osteosarcoma: The Birmingham Classification. Clin Orthop Relat Res 2017; 475: 842–50.

Medellin MR, Fujiwara T, Clark R, et al. Mechanisms of failure and survival of total femoral endoprosthetic replacements. Bone Joint J 2019; 101-B: 522–8.

Nagano A, Matsumoto S, Kawai A, et al. Osteosarcoma in patients over 50 years of age: Multi-institutional retrospective analysis of 104 patients. J Orthop Sci 2020; 25(2): 319-323.

Ogura K, Higashi T, Kawai. Statistics of bone sarcoma in Japan: Report from the Bone and Soft Tissue Tumor Registry in Japan. J Orthop Sci 2017; 22: 133–43.

Racano A, Pazionis T, Farrokhyar F, et al. High infection rate outcomes in long-bone tumor surgery with endoprosthetic reconstruction in adults: a systematic review. Clin Orthop Relat Res 2013; 471: 2017–27.

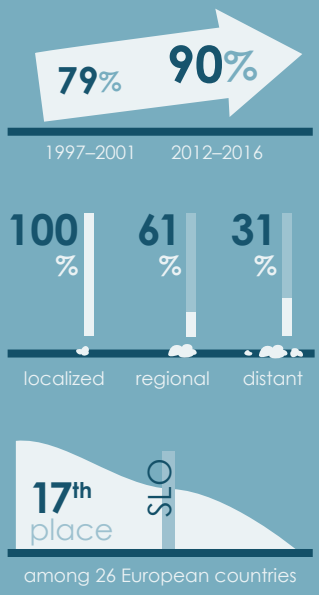
Schmidt-Braekling T, Streitbuerger A, Gosheger G, et al. Silver-coated megaprostheses: review of the literature. Eur J Orthop Surg Traumatol 2017; 27: 483–9.

Stevenson JD, Laitinen MK, Parry MC, et al. The role of surgical margins in chondrosarcoma. Eur J Surg Oncol 2018; 44: 1412–8.

Thevenin-Lemoine C, Destombes L, Vial J, et al. Planning for bone excision in Ewing sarcoma: Post-chemotherapy MRI more accurate than pre-chemotherapy MRI assessment. J Bone Joint Surg Am 2018; 100: 13–20.

C43

CUTANEOUS MELANOMA



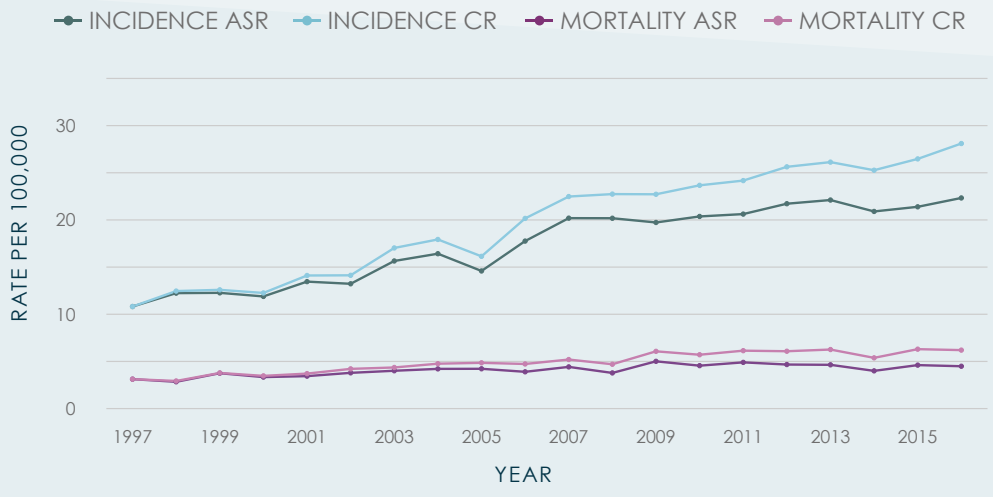
EPIDEMIOLOGY

In the last five-year period (2012–2016), 542 people per year on average were diagnosed with cutaneous melanoma in Slovenia, 286 men and 256 women, and 124 people died, 69 men and 55 women. As shown in Figure 1, the cutaneous melanoma incidence rate increased throughout the observed period: in the last ten years, it increased by 2.4% per year (4.4% per year for men and 0.5% per year for women). Growth is statistically significant in men and in both sexes together. One third of the growth in incidence rates can be attributed to an ageing population. Despite the steep increase in incidence, mortality remains relatively low, indicating a fairly good prognosis of the disease. Between 2007 and 2016, the crude mortality rate of cutaneous melanoma increased by 2% per year (2.8% in men and by 1.4% in women). The increases are not statistically significant.

At the end of 2016, there were 6,317 people living in Slovenia who had been diagnosed with cutaneous melanoma at some point in their lives. Of those, the diagnosis had been established less than

FIGURE 1

The crude (CR) and age-standardized (ASR) incidence and mortality rates of cutaneous melanoma in Slovenia in 1997–2016.



one year ago in 566 people, one to four years ago in 1,837 people, and over ten years ago in 2,227 people.

The survival analysis included 7,935 cases of patients aged 20–94; 74 cases (1%) were excluded because they were diagnosed on the day of death, or because they did not fulfil the age inclusion criteria.

Over the observed periods, the majority of cases of cutaneous melanoma (43–47%) occurred on the trunk (C43.5). In 20–25% of cases, the disease occurred on the lower limb, including the hip (C43.7), and in 13–18% on the upper limb, including the shoulder (C43.6). The disease occurred on a part of the face (C43.3) in 7% of cases on average, and on the scalp and neck (C43.4) in 5%. On the remaining sites (C43.0, C43.1, C43.2, and C43.8) the disease occurred in less than 2% of cases. The data show that in 2–4% of the cases the site was not specified (C43.9).

	Sex		Age			Stage			Total
	Men	Women	20–49 yrs	50–74 yrs	75–94 yrs	Localized	Regional	Distant	
1997–2001	580	633	427	621	165	993	172	36	1213
1997–2001 %	47.8	52.2	35.2	51.2	13.6	81.9	14.2	3.0	
2002–2006	789	902	518	872	301	1322	297	58	1691
2002–2006 %	46.7	53.3	30.6	51.6	17.8	78.2	17.6	3.4	
2007–2011	1129	1214	704	1220	419	1785	497	49	2343
2007–2011 %	48.2	51.8	30.1	52.1	17.9	76.2	21.2	2.1	
2012–2016	1417	1271	698	1366	624	2081	548	51	2688
2012–2016 %	52.7	47.3	26.0	50.8	23.2	77.4	20.4	1.9	

TABLE 1

Number and proportion of patients with cutaneous melanoma by sex, age, stage and period of diagnosis in Slovenia in 1997–2016.

The diagnosis of cutaneous melanoma is never made without microscopic confirmation of the tumour. In all periods, the most common histological type among all microscopically confirmed cases was superficial spreading melanoma, which occurred in 50% of cases in the last period. In 32% of cases, the histological type was not specified.

More women were diagnosed with cutaneous melanoma in the first three observed periods, and more men were diagnosed in the last period (2012–2016). The majority of patients were aged 50 to 74 years at the time of diagnosis. The disease was most commonly diagnosed in the localized stage (Table 1).

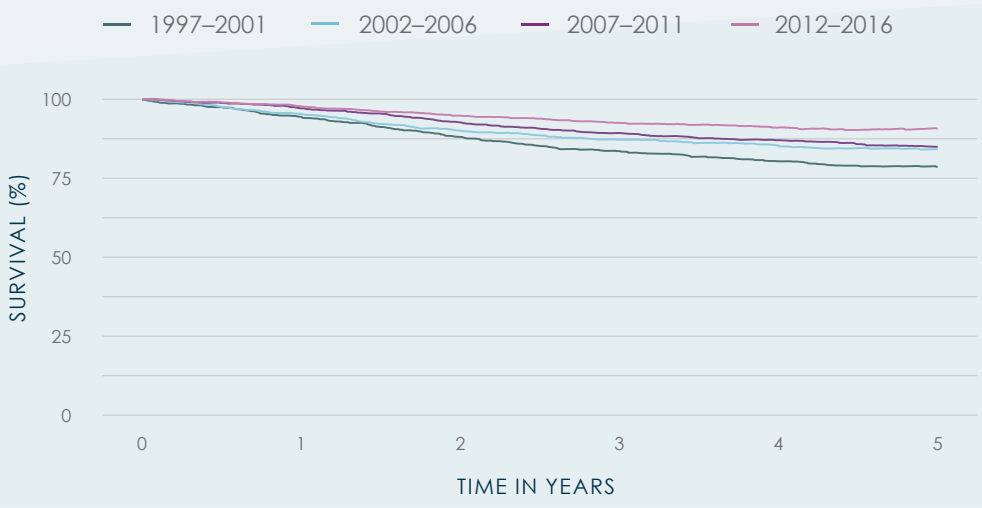


FIGURE 2

Net survival of patients with cutaneous melanoma by period of diagnosis in Slovenia in 1997–2016.

Regarding the specific primary treatment of cutaneous melanoma between 1997 and 2016, almost all patients (99%) were treated with surgery. Otherwise, 4% of patients received radiotherapy, mostly in combination with surgery. Less than 1% of patients received systemic therapy. Across the entire observed period, only 1% of patients did not receive a specific primary treatment.

TABLE 2

One-, three- and five-year observed and net survival (with a 95% confidence interval–CI) of patients with cutaneous melanoma by sex and period of diagnosis in Slovenia in 1997–2016.

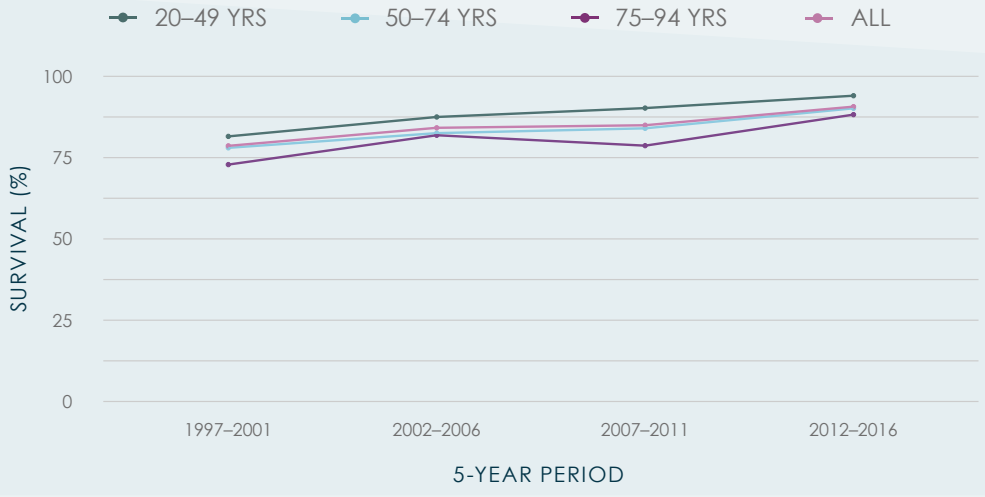
Survival / Period			1997–2001	(95% CI)	2002–2006	(95% CI)	2007–2011	(95% CI)	2012–2016	(95% CI)
Observed	1-year	all	92.5	91.0–94.0	92.9	91.7–94.1	95.1	94.2–95.9	95.4	94.6–96.2
		men	92.1	89.9–94.3	91.4	89.4–93.4	94.2	92.8–95.5	95.1	93.9–96.2
		women	92.9	90.9–94.9	94.2	92.7–95.8	95.9	94.8–97.0	95.8	94.7–96.9
	3-year	all	78.5	76.2–80.8	80.3	78.5–82.3	84.0	82.5–85.5	85.9	84.6–87.3
		men	75.0	71.6–78.6	78.4	75.6–81.3	81.2	79.0–83.5	83.8	81.9–85.7
		women	81.7	78.7–84.7	82.0	79.6–84.6	86.6	84.7–88.5	88.3	86.6–90.1
	5-year	all	70.4	67.9–73.0	73.0	70.9–75.2	76.6	74.9–78.3	79.6	78.0–81.3
		men	65.2	61.4–69.2	69.3	66.1–72.6	71.8	69.2–74.5	76.9	74.6–79.3
		women	75.2	71.9–78.6	76.3	73.6–79.1	81.1	78.9–83.3	82.7	80.5–85.0
Net	1-year	all	94.6	93.1–96.2	95.4	94.1–96.7	97.1	96.2–98.0	97.8	97.0–98.6
		men	94.6	92.4–96.9	94.4	92.3–96.4	96.7	95.3–98.1	97.8	96.7–99.0
		women	94.6	92.5–96.7	96.2	94.7–97.8	97.5	96.4–98.7	97.7	96.6–98.9
	3-year	all	83.7	81.1–86.3	87.2	85.0–89.4	89.2	87.6–90.9	92.6	91.1–94.1
		men	81.5	77.6–85.5	87.0	83.8–90.4	87.6	85.0–90.2	91.6	89.5–93.9
		women	85.7	82.3–89.1	87.2	84.4–90.2	90.7	88.6–92.9	93.6	91.5–95.7
	5-year	all	78.7	75.7–81.9	84.2	81.5–86.9	84.9	82.8–87.1	90.4	88.3–92.5
		men	75.4	70.9–80.3	83.9	79.8–88.2	81.8	78.5–85.2	90.0	87.0–93.2
		women	81.8	77.9–85.8	84.3	80.8–87.9	87.8	85.2–90.5	90.8	88.0–93.7

Throughout the observed period, surgery for cutaneous melanoma was performed in at least 15 hospitals and other health care institutions, most of them in the last five-year period at the Institute of Oncology Ljubljana (52%), the University Medical Centre Ljubljana (28%), and by private healthcare providers (15%). As part of their primary treatment, in the last five-year period, patients received systemic therapy and radiotherapy only at the Institute of Oncology Ljubljana.

The net survival of patients with cutaneous melanoma by year of diagnosis has been gradually improving (Figure 2, Table 2). In the 20 years under review, five-year net survival improved by almost 12 percentage points. Regarding the five-year net survival of patients with cutaneous melanoma throughout the observed period, women have a slightly better survival rate than men, on average by a good three percentage points (Table 2).

FIGURE 3

Five-year net survival of patients with cutaneous melanoma by age group in Slovenia in 1997–2016.



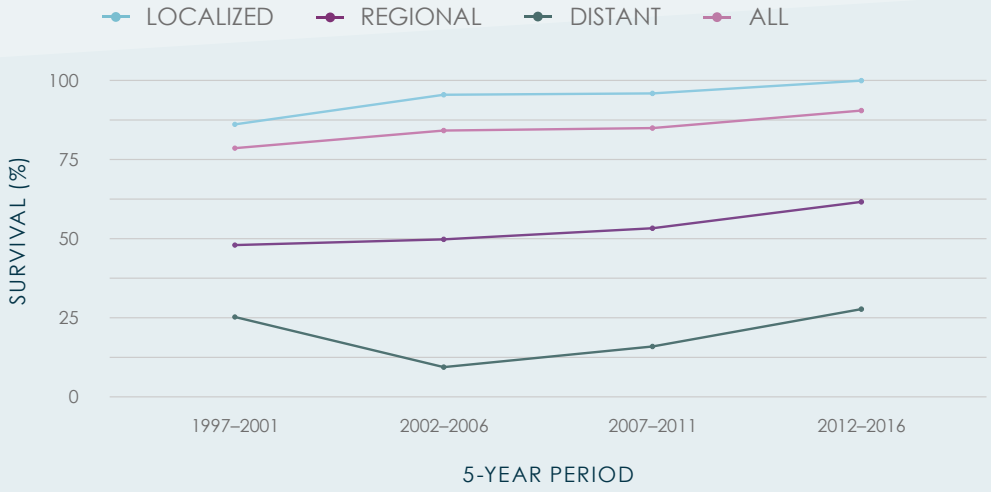


FIGURE 4

Five-year net survival of patients with cutaneous melanoma by stage in Slovenia in 1997–2016.

In Slovenia, compared to other selected cancers, cutaneous melanoma ranks 4th in men and 4th in women by five-year net survival.

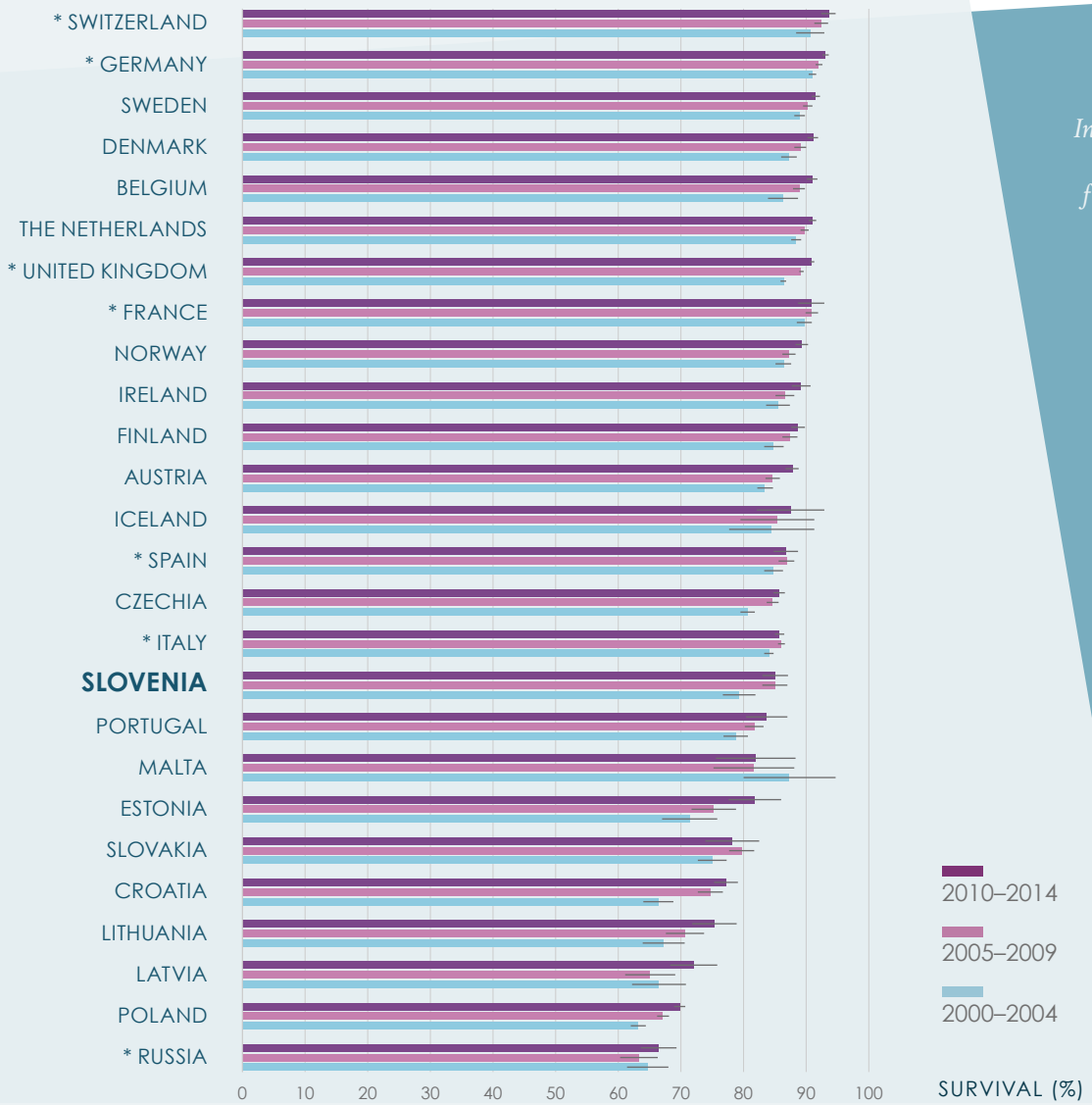


FIGURE 5

International comparison of age-standardized five-year net survival for cutaneous melanoma (with 95% confidence intervals) in patients diagnosed during 2000–2004, 2005–2009 and 2010–2014 (CONCORD-3).

** Data doesn't cover a 100% of the country's population.*

Figure 3 shows the impact of age on the survival of patients with cutaneous melanoma. Five-year net survival has been improving steadily in all age groups in all observed periods. It is lowest in people aged 75–94 at diagnosis, slightly better in people aged 50–74, and best in people aged 20–49. Survival of patients with cutaneous melanoma exceeded 70% in all observed groups in all observed periods.

The importance of stage at diagnosis is shown in Figure 4. Five-year net survival of patients with localized disease was almost 100% in the last five-year period, an improvement of 14 percentage points compared to 1997–2001. Five-year net survival of patients with regional disease is 61%, whereas in patients with distant disease at diagnosis, it is 31%. The temporal trend of five-year net survival of patients with cutaneous melanoma between 1997–2016 shows improvement in all stages.

The results of the world-wide CONCORD-3 study of patients diagnosed with cancer during the 15 years between 2000 and 2014 in 71 countries and territories show that five-year net survival of Slovenian patients with cutaneous melanoma in the last five-year period has not changed compared to the previous period (Figure 5). For patients diagnosed during the most recent period (2010–2014), Slovenia ranked 17th among the 26 participating countries in Europe.

CLINICAL COMMENTARY

Marko Hočevar, Primož Strojan, Janja Ocvirk

Excision under local anaesthesia and histological verification are required to confirm the diagnosis of melanoma. In patients with melanoma thinner than 1 mm, only re-excision under local anaesthesia is required to complete treatment. This entails about 50% of patients with melanoma, so it is not surprising that the proportion of those treated by private healthcare providers with a concession has increased 7.5-fold in the 20-year period under review.

The specific primary treatment of melanoma is surgery and the proportion of patients treated with surgery alone (more than 90%) has remained stable for the entire 20-year period. The proportions of patients treated with radiotherapy alone (0.3%), systemic treatment alone (0.1%) or with all three treatment modalities (0.2%) has also remained stable. In patients treated with surgery and then with adjuvant systemic therapy, a decrease from 1.2% to 0.8% and 0.2% is observed, which can be attributed to a decrease in interferon treatment. In the second and also in the third observed period, the proportion of patients treated with surgery and adjuvant radiotherapy also increased considerably. This coincides with the introduction of multidisciplinary treatment of patients and includes mainly patients with regionally advanced disease.

At time of diagnosis over time, fewer cases of localized disease are observed, while there is an increase in regionally advanced disease—a result of the introduction of sentinel lymph node biopsy in 1999 and thus the detection of regional metastases already in the clinically occult phase. The proportion of patients with disseminated disease at the time of diagnosis has remained stable throughout the observed period and amounts to 2–3%.

Five-year observed and net survival of the whole group of patients increased steadily during the observed period. The reason for this is to be found in the continuous improvement of the survival of patients with localized and regionally advanced disease (at the time of diagnosis). Thus, five-year survival improved in patients with localized disease, from 86% in 1997–2001 to 100% in 2012–2016, and in patients with regionally advanced disease, from 48% in 1997–2001 to 61% in 2012–2016. Both are attributed to earlier diagnosis and more precise staging of the disease at the time of diagnosis. In patients with localized disease, ever thinner melanomas are diagnosed, so that in the last period two thirds of all melanomas were thinner than 1.5 mm. At the same time, patients with clinically occult metastases in regional lymph nodes are now correctly classified in the regionally advanced stage, and no longer in the localized stage. In the group of patients with regionally advanced disease, between 2012 and 2016, 80% of metastases, diagnosed by sentinel lymph node biopsy, were clinically occult. After a decline in survival in the first three observed periods, there was a renewed improvement

between 2012 and 2016 in patients with distant metastases as a result of the introduction of new systemic treatments.

Survival of patients with melanoma with increasing age is expected to decline due to impaired immune system capacity. Nevertheless, we have observed an improvement in survival in all observed periods in all age groups.

A comparison of the survival of Slovenian patients with melanoma with survival in other European countries between 2010 and 2014 shows a very close correlation with gross domestic product in individual countries. Those with higher gross domestic product, and consequently better socio-economic status, achieve higher five-year net survival rates. As socio-economic status is an important prognostic factor in patients with melanoma, this observation is expected.

References

Zadnik V, Primic-Žakelj M, Žagar T, et al. Pregled obravnave bolnikov s kožnim melanomom v Sloveniji za incidenčna leta 2011-2016 (Overview of cutaneous melanoma treatment in Slovenia in period 2011-2016). Ljubljana: Institute of Oncology; 2017.

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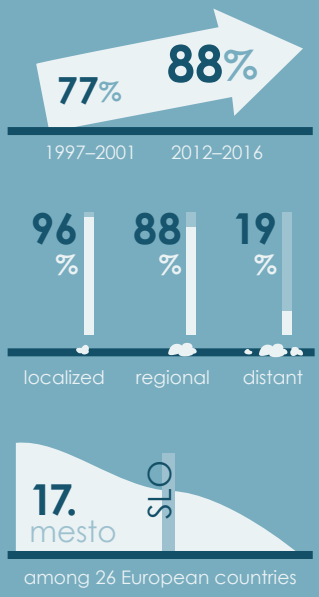
BREAST

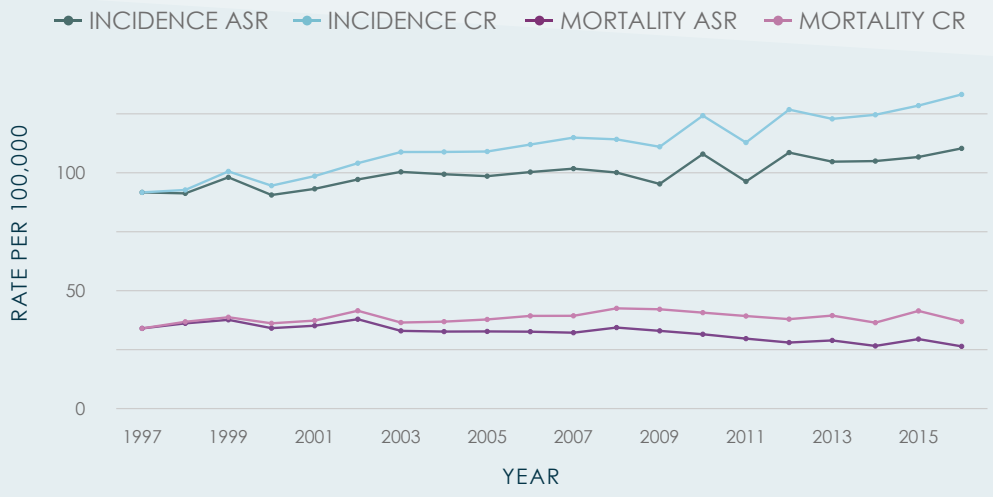


EPIDEMIOLOGY

In the last five-year period (2012–2016), 1,322 women on average were diagnosed with breast cancer and 400 women died each year. Breast cancer also occurs in men, but much less frequently, up to 10 cases per year on average. Only data for breast cancer in women are used in this analysis. As shown in Figure 1, incidence of breast cancer increased throughout the observed period. Between 2007–2016, the crude incidence rate of breast cancer in women increased by 1.7% per year, which is a statistically significant increase. About half of new cases can be attributed to population ageing. Breast cancer mortality rates are declining. Between 2007–2016, the crude mortality rate of breast cancer in women decreased by 1% per year. In 2008, Slovenia started introducing a screening programme for the early detection of breast cancer—the DORA programme. The programme expanded gradually and reached full coverage of the country in 2018; in 2014, it covered about 40% of women in the target population (aged 50–69). With the introduction of the national screening programme, a transient increase in the number of new cancer cases is expected, as cancer is actively sought in a targeted manner, while the long-term goal is to reduce mortality.

FIGURE 1

The crude (CR) and age-standardized (ASR) incidence and mortality rates of breast cancer in women in Slovenia in 1997–2016.



At the end of 2016, there were 17,317 women living in Slovenia who had been diagnosed with breast cancer at some point in their lives. Of those, the diagnosis had been established less than one year ago in 1,350 women, one to four years ago in 4,580 women, and over ten years ago in 7,225 women.

The survival analysis included 22,713 cases of patients aged 20–94; 245 cases (1%) were excluded because they were diagnosed on the day of death, or because they did not fulfil the age inclusion criteria.

Over the observed periods, in slightly less than half of patients the tumour site in the breast was not specified (C50.9), and among those in whom the site was specified, most cases, a good fifth (21–24%), appeared in the upper outer quadrant of the breast (C50.4). About 5% of breast cancers arose in the central portion (C50.1), the upper inner quadrant (C50.2), or the lower outer quadrant of the breast (C50.5).

WOMEN		Age			Stage			Total
		20–49 yrs	50–74 yrs	75–94 yrs	Localized	Regional	Distant	
1997–2001		1152	2822	813	2307	1955	467	4787
	%	24.1	59.0	17.0	48.2	40.8	9.8	
2002–2006		1185	3235	1049	2762	2261	406	5469
	%	21.7	59.2	19.2	50.5	41.3	7.4	
2007–2011		1164	3461	1260	2948	2472	437	5885
	%	19.8	58.8	21.4	50.1	42.0	7.4	
2012–2016		1333	3864	1375	3587	2530	441	6572
	%	20.3	58.8	20.9	54.6	38.5	6.7	

TABLE 1

Number and proportion of women with breast cancer by age, stage and period of diagnosis in Slovenia in 1997–2016.

Less than 4% of patients in each period (less than 0.5% in the last five-year period) did not have microscopically confirmed disease. Almost all cases of microscopically confirmed disease (more than 90%) were adenocarcinomas.

The largest proportion of women were diagnosed between the ages of 50–74. The disease was most commonly diagnosed in the localized stage (Table 1). In the last five-year period (2012–2016), an increase in cancer diagnosed in a localized stage was noted compared to previous periods, which may largely be attributed to the DORA programme, which detects cancer in earlier stages.

Regarding the specific primary treatment between 1997–2016, 44% of women with breast cancer were treated with surgery and concomitant systemic therapy and radiotherapy, while 30% of women

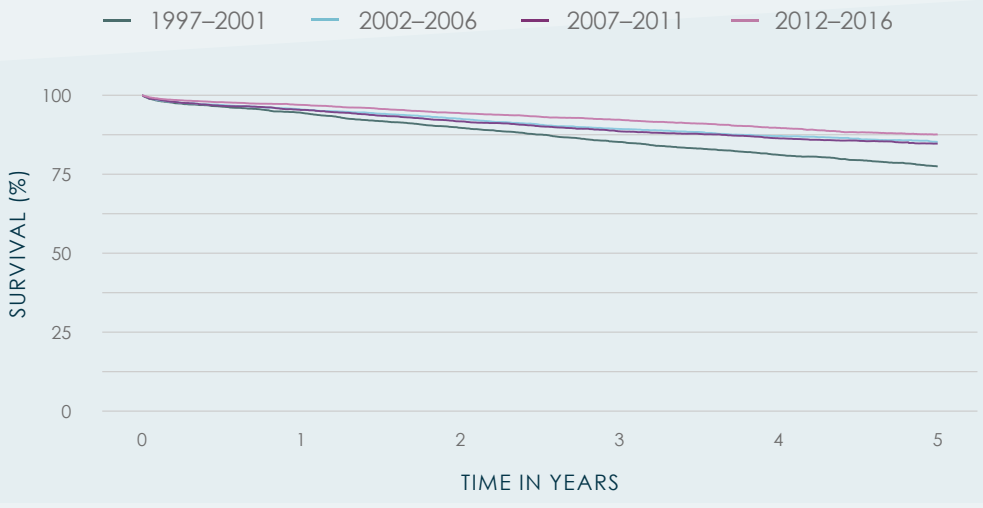


FIGURE 2

Net survival of women with breast cancer by period of diagnosis in Slovenia in 1997–2016.

received systemic therapy without radiotherapy in addition to surgery. During the observed period, the proportion of women who received all three forms of treatment as their primary treatment increased (1997–2001: 31%; 2012–2016: 55%). Across the entire observed period, 3% of patients did not receive specific primary treatment; the proportion of this group of patients was declining during the observed five-year periods.

TABLE 2

One-, three- and five-year observed and net survival (with a 95% confidence interval–CI) of women with breast cancer by period of diagnosis in Slovenia in 1997–2016.

WOMEN Survival / Period		1997–2001	(95% CI)	2002–2006	(95% CI)	2007–2011	(95% CI)	2012–2016	(95% CI)
Observed	1-year	92.6	91.9–93.4	93.6	93.0–94.3	93.5	92.9–94.2	95.3	94.7–95.8
	3-year	80.4	79.3–81.5	83.7	82.8–84.7	83.9	82.9–84.8	87.4	86.6–88.2
	5-year	70.2	68.9–71.5	76.2	75.1–77.3	77.1	76.1–78.2	79.8	78.8–80.9
Net	1-year	94.5	93.7–95.2	95.5	94.8–96.2	95.4	94.7–96.0	96.9	96.4–97.5
	3-year	85.2	84.0–86.5	89.3	88.2–90.4	88.6	87.6–89.7	92.2	91.3–93.1
	5-year	77.5	76.0–79.0	85.2	83.8–86.7	84.7	83.4–86.0	87.6	86.3–88.9

In any period, breast cancer surgery was performed in at least 12 hospitals, and in the last five-year period in nine. The majority of procedures were performed at the Institute of Oncology Ljubljana (71%), followed by the University Medical Centre Maribor (17%), Nova Gorica General Hospital (6%), Slovenj Gradec General Hospital (3%) and Celje General Hospital (2%). As part of their primary treatment, in the last five-year period, women received systemic therapy at the Institute of Oncology Ljubljana (almost 75%), University Medical Centre Maribor (19%), Nova Gorica General Hospital (4%), Slovenj Gradec General Hospital (2%), and Celje General Hospital (2%).

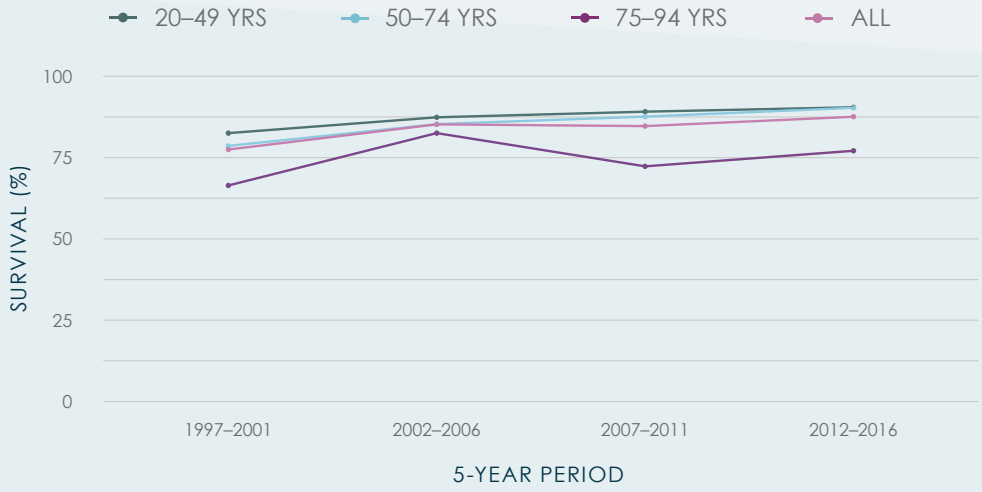
Survival of women with breast cancer gradually improved by year of diagnosis (Figure 2, Table 2). In the 20 years under review, five-year net survival improved by more than 10 percentage points.

In Slovenia, compared to other selected cancers, breast cancer ranks 2nd in women by five-year net survival.

Figure 3 shows the impact of age on the survival of women with breast cancer. Five-year net survival

FIGURE 3

Five-year net survival of women with breast cancer by age group in Slovenia in 1997–2016.



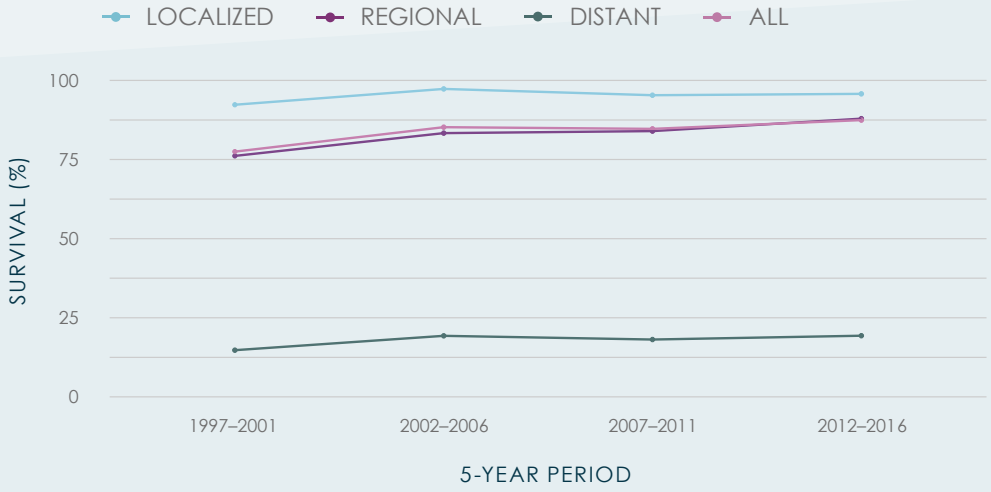


FIGURE 4

Five-year net survival of women with breast cancer by stage in Slovenia in 1997–2016.

is lowest in women aged 75–94. Survival of women aged 50–74 at diagnosis is approaching the net survival of those younger than 50 in the entire observed period. In the last five-year period (2012–2016), the net survival of women younger than 50 and women aged 50–74 is almost the same and is slightly more than 90%.

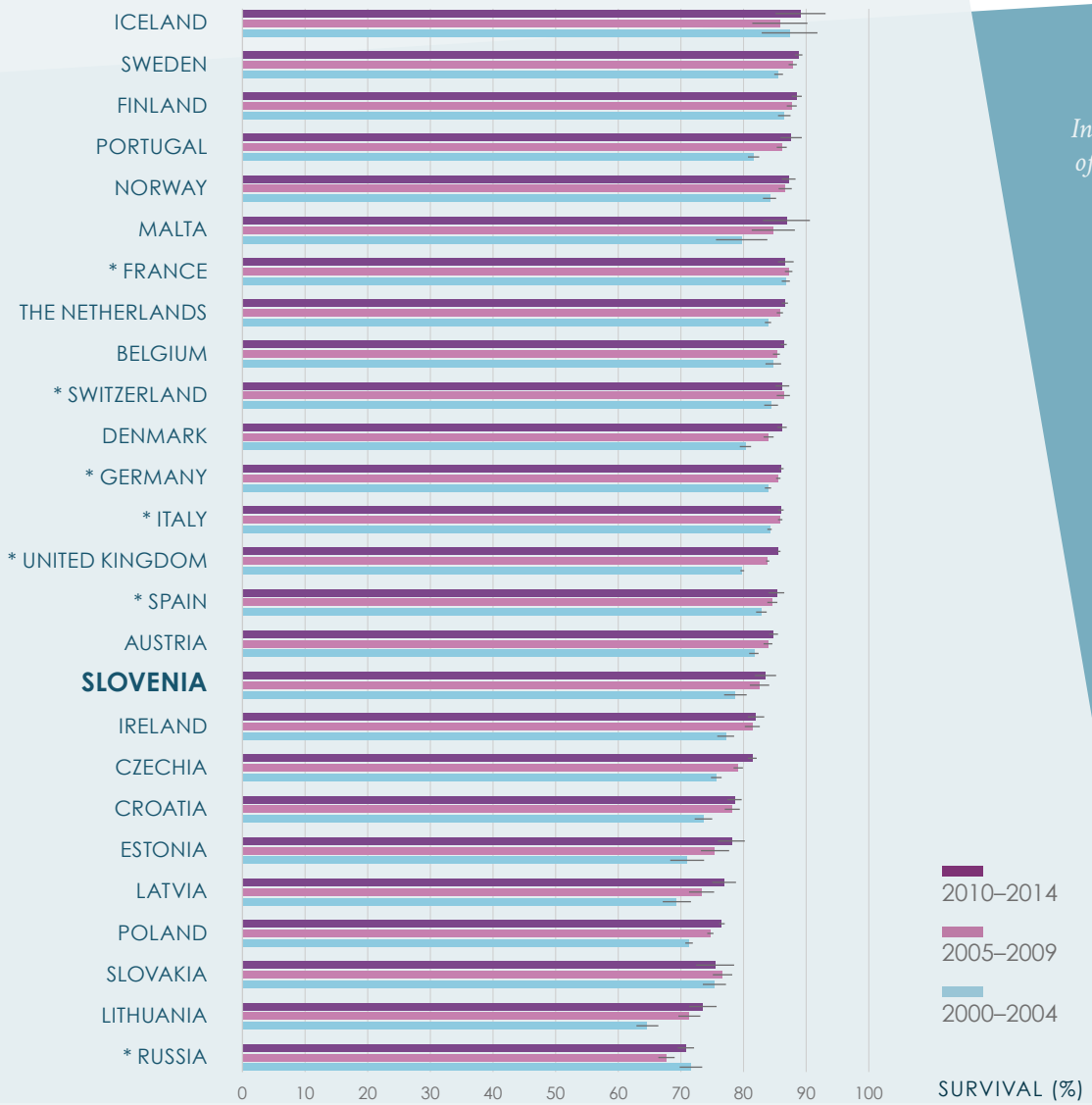


FIGURE 5

International comparison of age-standardized five-year net survival for breast cancer (with 95% confidence intervals) in women diagnosed during 2000–2004, 2005–2009 and 2010–2014 (CONCORD-3).

** Data doesn't cover a 100% of the country's population.*

The importance of stage at diagnosis is shown in Figure 4. Five-year net survival of women with localized breast cancer surpassed 96% in the last period. Five-year net survival of women with regional disease reached almost 88%, whereas in women with distant disease at diagnosis, it was slightly below 20%. The time trend of five-year net survival of women with breast cancer between 1997–2016 showed improvement for all stages, most notably for the regional stage.

The results of the world-wide CONCORD-3 study of patients diagnosed with cancer during the 15 years between 2000 and 2014 in 71 countries and territories show that five-year net survival of Slovenian women with breast cancer has been improving (Figure 5). For women diagnosed during the most recent period (2010–2014), Slovenia ranked 17th among the 26 participating countries in Europe.

CLINICAL COMMENTARY

Janez Žgajnar

The most important finding from the analysis of available data is that the survival of women with breast cancer in Slovenia continues to improve. The greatest progress was made in the first period (1997–2001), which was undoubtedly largely due to the more consistent application of systemic therapy as well as the introduction of new drugs. In the observed periods, stage distribution did not change significantly, though slightly fewer patients are now diagnosed in the distant stage of the disease (10% : 7%). However, this does not provide an explanation for the overall improved survival during this period. If we look at the specific primary treatment, we find that the proportion of women treated with all three modalities (surgery, systemic therapy, and radiotherapy) increased the most, from 31% in the first five-year period to 55% in the most recent period. Conversely, the proportion of women receiving locoregional treatment alone (surgery with or without radiotherapy) is declining. In addition to the new possibilities of systemic therapy, this trend is also the result having adopted a multidisciplinary approach to the treatment of all (or at least most) patients in Slovenia.

As expected, five-year survival is highest in the localized stage, where, naturally, progress in survival from 1997–2016 was also relatively modest in percentage terms (from 92% to 96%). In patients in whom the regional lymph nodes were affected, survival improved by almost 12% over the same period, but remained significantly lower compared to the localized stage (88% : 96%). There is still considerable room for improvement in lowering the average stage of the disease at diagnosis. The data cover periods when the DORA breast cancer screening programme either did not exist at all (before 2008) or was only available to a very limited extent, up to 2011. Thus, in 2011, when the DORA programme covered approximately 20% of the target population, 125 invasive cancers (approximately one-tenth of all cancers in Slovenia) were diagnosed, of which as many as 70% of cases were localized. For comparison, between 2007–2011, the average proportion of localized cancers in Slovenia was 50%. We can assume that with the full coverage of Slovenia by the DORA programme, the proportion of localized cancers will increase considerably.

The distribution of women by age groups indicates a decrease in the proportion of younger women (under the age of 50) and an increase in the proportion of women aged 75–94, which is a result of demographic trends. Survival is improving in all age groups except the oldest; the latter can be attributed both to the higher average stage of the disease at diagnosis (no screening) and to the inability of patients to tolerate all available treatments.

The vast majority of women with breast cancer started their specific primary treatment in one of two institutions, the Institute of Oncology Ljubljana or the University Medical Centre Maribor. In the other four institutions, where they want to continue treating patients with breast cancer, a total of only 11% (1.4-5.6%) or a total of 146 women per year received treatment in the 2012–2016 period, which does not reach the minimum standard for a single breast cancer centre according to European guidelines (150 patients per year).

From 2019 onwards, the redistribution of patients between the Institute of Oncology Ljubljana and the University Medical Centre Maribor is expected following the establishment of the DORA diagnostic centre in the latter and a further decline in the number of patients with breast cancer treated at Celje General Hospital and Slovenj Gradec General Hospital, as the DORA programme will cover the entire country. It is, therefore, high time to centralize the treatment of breast cancer in a maximum of three centres in Slovenia, where it makes sense to invest in staff and equipment.

Survival of women with breast cancer in Slovenia in the 2010–2014 period was slightly below the European average according to the CONCORD-3 survey. The important thing here is that survival is improving and that the gap with the best is getting smaller.

Tanja Marinko

A multidisciplinary approach is employed in the treatment of most patients with breast cancer. In all four observed periods, the majority of patients were treated with surgery, radiotherapy, and systemic therapy. The proportion of patients who received all three of the most important treatment modalities increased over time; thus, in the 1997–2001 period, it amounted to 31% (1,464 patients), and in the 2012–2016 period 55% (3,634 patients, which is more than twice as many as in the 1997–2001 period). In contrast, the proportion of patients treated with surgery and systemic therapy alone decreased (35% between 1997–2001 and 23% between 2012–2016), which means that we are increasingly opting for radiotherapy in the treatment of women with breast cancer. The trend is partly a reflection of the fact that the distribution of cancers by stage changed during the observed periods (the proportion of patients with localized breast cancer at the time of diagnosis increased from 48% in 1997–2001 to 55% in 2012–2016, and the proportion of diagnosed metastatic cancers decreased from 10% to 7%), as radiotherapy in non-metastatic breast cancer usually accompanies surgical treatment, and partly because patients with distant disease live longer (five-year survival: 1997–2001: 15%; 2012–2016: 19%) and therefore more often need palliative radiotherapy.

The proportion of women treated with radiotherapy alone is expected to be very small across the whole 20-year period (0.1–0.3%), as there are only a few patients for whom radiotherapy is the only suitable treatment.

Radiotherapy techniques for patients with breast cancer have advanced tremendously since 1997. Since 2007, we have been using 3D radiotherapy in patients with breast cancer at the Institute of Oncology Ljubljana, and recently, also other, even more sophisticated techniques that enable precise specification of dosing on both target and healthy tissue. This allows us to irradiate the target tissue more accurately and protect healthy tissues from radiation much better, which is especially important when the target is close to the heart. With modern radiotherapy techniques, we have been able to dramatically reduce radiotherapy-related cardiotoxicity and consequently improve the survival of patients with breast cancer.

In patients with non-metastatic disease, adjuvant radiotherapy has a significant effect on survival. The results of the latest research also suggest an improvement in survival in patients with oligometastatic disease who were treated with stereotactic radiotherapy. In the future, new, technologically extremely demanding approaches to radiotherapy that aim to destroy individual metastases (when these are few in number), combined with new types of systemic therapy, will undoubtedly help improve the survival of patients with metastatic breast cancer.

Simona Borštnar

The number of new patients with breast cancer has continued to rise over the last two decades. As such, breast cancer still firmly holds the first place among all cancers in women in Slovenia. It is encouraging that an increasing proportion of cancers are diagnosed when they are clinically and radiologically limited to the breast only (localized disease). Conversely, during this time, the proportion of patients with regional lymph node metastases (regional disease) decreased, and the proportion of patients with primarily distant cancer also decreased. The change in the distribution of stages may in

part be due to women's better awareness and better access to diagnostic tests. In addition, in recent years, we have begun to see the impact of the DORA screening programme, which was launched in 2008 and has gradually expanded to cover more and more of the country. This theory is supported by the fact that the stage migration has been most pronounced in the last five-year period.

As expected, survival continues to improve in women with both localized and regional disease, in both cases largely as a result of better and more widely used adjuvant systemic therapy, including the introduction of novel monoclonal antibodies in the treatment of HER2-positive cancers. The proportion of women receiving systemic therapy increased from 81% in 1997–2001 to 90% in 2012–2016. Five-year survival regardless of disease stage increased from 77% to 88% in the 20 years under review. An improvement of slightly less than 4 percentage points was observed during this period in localized cancer, where local treatment contributes the most to the cure, and survival improved a little more than 12 percentage points in regional disease, where the impact of systemic therapy is even more significant. In both localized and regional cancers, most of the improvement in survival was achieved between 2002 and 2006, and continued to improve over the following 10 years, but the growth is no longer statistically significant. The result is to be expected as the greatest shift in effective adjuvant systemic therapy was achieved at the turn of the millennium with the introduction of more effective chemotherapy regimens, the addition of taxanes, dose-dense regimens in patients at higher risk of disease recurrence, broader indications for adjuvant endocrine therapy, and aromatase inhibitors in postmenopausal patients. The introduction of trastuzumab in the treatment of HER2-positive cancers in 2005, which improves survival in this subgroup of women, did not lead to a significant improvement in the survival of the entire population of women with breast cancer, given that only 15% of patients have this disease subtype.

In contrast with the localized and regional stages of the disease, no improvement has been observed in the survival of patients with primary distant disease in the last 15 years, where a marked improvement in five-year survival was achieved at the turn of the millennium, from 15% in 1997–2001 to 19% in 2002–2006. This coincides with the wider use of anthracyclines and the introduction of taxanes and capecitabine, and new endocrine drugs (aromatase inhibitors) in hormone-dependent cancers, as well as the introduction of trastuzumab in patients with HER2-positive cancer, which started to be used in the treatment of distant disease five years earlier than in adjuvant therapy. There was no further improvement over the following decade. Similar results have been reported in some European countries (France, Sweden), while the results from America show a 27% five-year survival rate.

We are still finding poorer survival of women aged 75–94, which is not only true for Slovenia, but is a broader issue. These are mostly frail women with comorbidities, which often precludes appropriate adjuvant systemic therapy. An additional major problem is the lack of clinical trial results for this population of patients, as the majority of studies do not include them. It is gratifying that survival has improved over the last five-year period and is slightly closer to the survival of younger patients again. This is most likely due to the fact that this problem was detected several years ago and there has been a focus on the geriatric assessment of these patients and the implementation of appropriate, patient-friendly treatment, which also includes the escalation of treatment in those who are able to tolerate it.

With the DORA screening programme, which now covers the whole country, we can expect to see further stage migration in favour of an (even) higher proportion of patients with localized cancer in the coming period. This will help improve the survival of the entire population meaning that its survival curve, which now coincides with survival of patients with regional disease, will approach the curve of those with localized disease. In the primary distant cancer, however, the survival curve may reverse upward with the use of cyclin-dependent kinase 4/6 inhibitors, which we started using in 2018 and which about 70% of all women with disseminated disease receive together with endocrine therapy.

References

Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Lancet 2015; 386: 1341–52.

Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100 000 women in 123 randomised trials. Lancet 2012; 379: 432–44.

Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005; 365: 1687–717.

Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet 2014; 383: 2127–35.

Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomised trials. Lancet 2011; 378: 1707–16.

Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Increasing the dose intensity of chemotherapy by more frequent administration or sequential scheduling: a patient-level meta-analysis of 37 298 women with early breast cancer in 26 randomised trials. Lancet 2019; 393: 1440–52.

Gobbini E, Ezzalfani M, Dieras V, et al. Time trends of overall survival among metastatic breast cancer patients in the real-life ESME cohort. Eur J Cancer 2018; 96: 17–24.

Howlader N, Noone AM, Krapcho M, et al. (eds.). SEER cancer statistics review, 1975-2016, National Cancer Institute. Bethesda: National Cancer Institute; 2018. Available from: https://seer.cancer.gov/csr/1975_2016/

Mislang AR, Cheungb KL, Hamaker ME, et al. Controversial issues in the management of older adults with early breast cancer. Journal of Geriatric Oncology 2017; 8(6): 397–402.

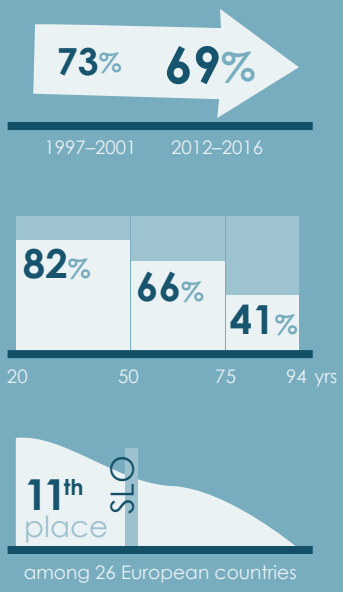
Palma DA, Olson R,Harrow S, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. Lancet 2019; 393: 2051–58.

Rehammar JC, Jensen MB, McGale P, et al. Risk of heart disease in relation to radiotherapy and chemotherapy with anthracyclines among 19,464 breast cancer patients in Denmark, 1977–2005. Radiother Oncol 2017; 123(2): 299–305.

Sundquist M, Brudin L, Tejler G. Improved survival in metastatic breast cancer 1985-2016. Breast 2017 Feb; 31: 46–50.

C53

CERVIX UTERI



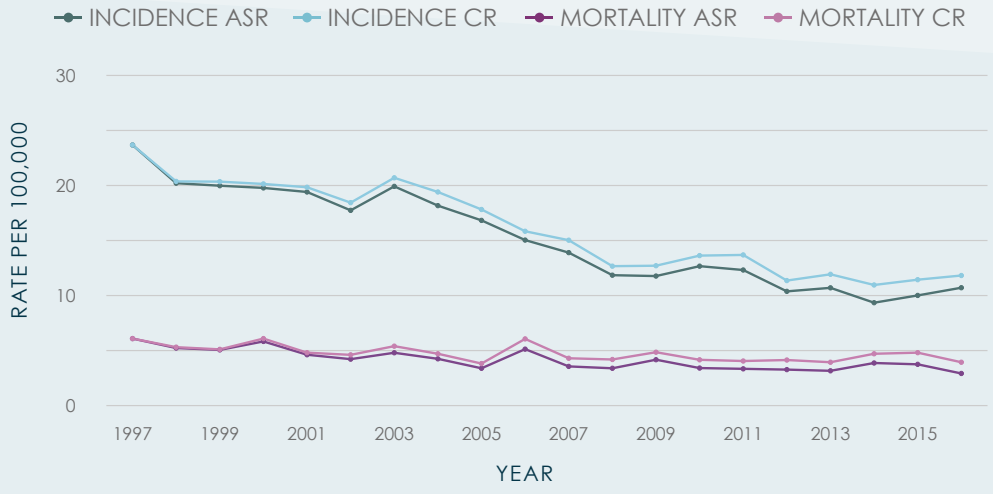
EPIDEMIOLOGY

In the last five-year period (2012–2016), on average 120 women in Slovenia were diagnosed with cervical cancer and 45 died each year. As shown in Figure 1, the cervical cancer incidence rate decreased throughout the observed period. Between 2007–2016, the crude incidence rate for cervical cancer decreased statistically significantly by 2.5% per year. Cervical cancer mortality rates did not change significantly. Between 2007 and 2016, the crude cervical cancer mortality rate decreased by 0.2% per year. In 2003 (after a pilot screening), Slovenia introduced a national screening programme for the detection of precancerous and early cancerous changes in the cervix—the ZORA programme. The purpose of the ZORA programme is to reduce cervical cancer incidence and mortality in Slovenia.

At the end of 2016, there were 3,523 women living in Slovenia who had been diagnosed with cervical cancer at some point in their lives. Of those, the diagnosis had been established less than one year ago in 114 women, one to four years ago in 340 women, and over ten years ago in 2,623 women.

FIGURE 1

The crude (CR) and age-standardized (ASR) incidence and mortality rates of cervical cancer in women in Slovenia in 1997–2016.



The survival analysis included 3,286 cases of patients aged 20 to 94; 11 cases (0.3%) were excluded because they were diagnosed on the day of death or because they did not fulfil the age inclusion criteria.

Over the entire period under review, in 47–93% of cases the tumour site was not specified (C53.9), and the number of cases without a specific site increases by year of diagnosis. Among the cases with specified sites, however, most (3–43%) occurred on the outer wall of the cervix (C53.1). 3–9% of cancers arose on the inner wall of cervix (C53.0) and 2–3% as an overlapping lesion of cervix uteri (C53.8).

Less than 1% of patients in each period did not have microscopically confirmed disease. The majority of cases of microscopically confirmed disease (more than 77% in the last period) were squamous cell carcinomas and 19% were adenocarcinomas.

WOMEN		Age			Stage			Total
		20–49 yrs	50–74 yrs	75–94 yrs	Localized	Regional	Distant	
1997–2001		614	362	80	586	431	32	1056
	%	58.1	34.3	7.6	55.5	40.8	3.0	
2002–2006		526	319	91	572	317	40	936
	%	56.2	34.1	9.7	61.1	33.9	4.3	
2007–2011		337	286	74	386	247	60	697
	%	48.4	41.0	10.6	55.4	35.4	8.6	
2012–2016		236	280	81	269	248	74	597
	%	39.5	46.9	13.6	45.1	41.5	12.4	

TABLE 1

Number and proportion of women with cervical cancer by age, stage and period of diagnosis in Slovenia in 1997–2016.

In the first three observed periods, the largest proportion of women were diagnosed between the ages of 20 and 49, and in the last period, between the ages of 50 and 74. The disease was most commonly diagnosed in the localized stage (Table 1).

Regarding the specific primary treatment of cervical cancer between 1997 and 2016, 45% of patients were treated with surgery alone and 20% received radiotherapy alone. Those patients receiving surgery and radiotherapy totalled 19%, 6% received radiotherapy and systemic therapy, and 11% of patients received systemic therapy alone or in combination. Across the entire observed period, 6% of patients did not receive specific primary treatment; the proportion of this group of patients was consistent during the observed five-year periods.

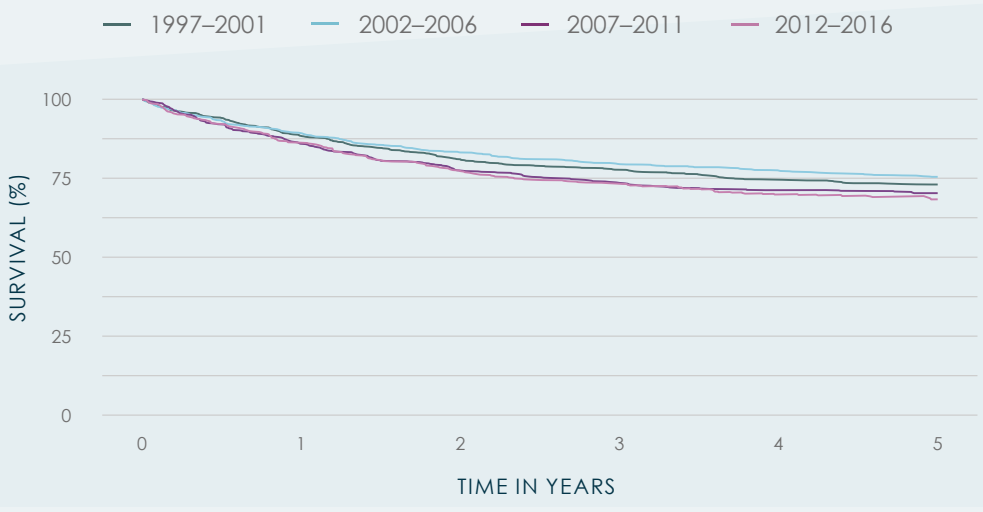


FIGURE 2

Net survival of women with cervical cancer by period of diagnosis in Slovenia in 1997–2016.

Throughout the observed period, cervical cancer surgery was performed in at least 15 hospitals. In the last five-year period, the majority of procedures were performed at the University Medical Centre Ljubljana (71%) and University Medical Centre Maribor (9%), as well as in other hospitals (less than 5%). In the last five-year period, patients received systemic therapy as part of their primary treatment at the Institute of Oncology Ljubljana (90%) and University Medical Centre Maribor (10%).

TABLE 2

One-, three- and five-year observed and net survival (with a 95% confidence interval–CI) of women with cervical cancer by period of diagnosis in Slovenia in 1997–2016.

WOMEN Survival / Period		1997–2001	(95% CI)	2002–2006	(95% CI)	2007–2011	(95% CI)	2012–2016	(95% CI)
Observed	1-year	87.9	85.9–89.9	88.7	86.7–90.7	85.2	82.6–87.9	85.4	82.6–88.3
	3-year	76.3	73.8–78.9	77.9	75.3–80.6	72.3	69.0–75.7	71.3	67.8–75.1
	5-year	71.0	68.3–73.8	73.2	70.4–76.1	68.1	64.7–71.7	66.2	62.4–70.2
Net	1-year	88.5	86.5–90.5	89.3	87.3–91.4	85.9	83.3–88.7	86.3	83.4–89.2
	3-year	77.8	75.2–80.5	79.5	76.8–82.4	73.7	70.3–77.2	73.4	69.7–77.3
	5-year	73.1	70.2–76.0	75.4	72.4–78.6	70.3	66.7–74.1	69.0	64.7–73.7

Survival of patients with cervical cancer remained similar in relation to the year of diagnosis (Figure 2, Table 2). In the 20 years under review, the five-year net survival rate was 69–75%. In Slovenia, compared to other selected cancers, cervical cancer ranks 7th in women by five-year net survival.

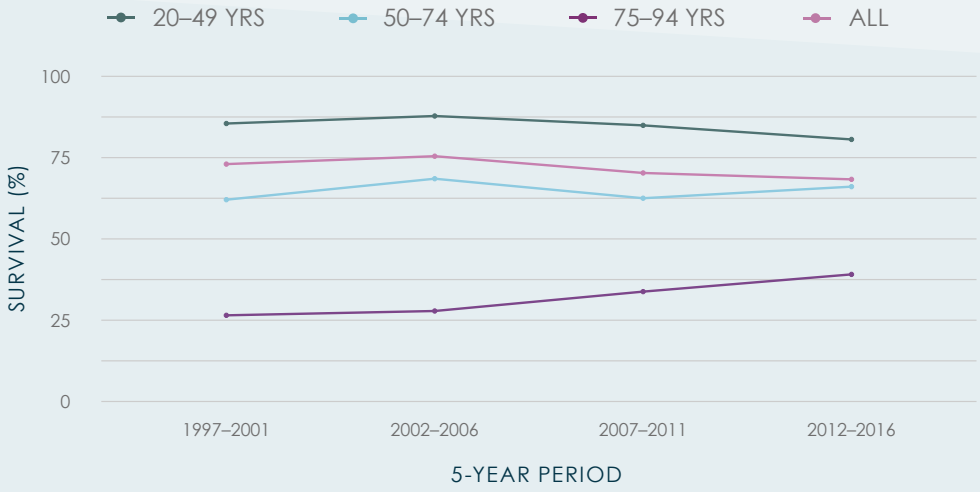
Figure 3 shows the impact of age on the survival of patients with cervical cancer. Five-year net survival is lowest in those aged 75–94 and has improved by 15 percentage points over the last five-year period (2012–2016) compared to the first (1997–2001). Survival of patients aged 50–74 at diagnosis is 62–69% in the entire observed period, and net survival of patients younger than 50 is 82–88%.

The importance of stage at diagnosis is shown in Figure 4. Five-year net survival of patients with localized disease exceeded 96% in the last two periods. Five-year net survival of patients with regional-stage disease approached 60%, whereas in patients with distant disease at diagnosis, it was only slightly above 11% in the last period.

The results of the world-wide CONCORD-3 study of patients diagnosed with cancer during the 15

FIGURE 3

Five-year net survival of women with cervical cancer by age group in Slovenia in 1997–2016.



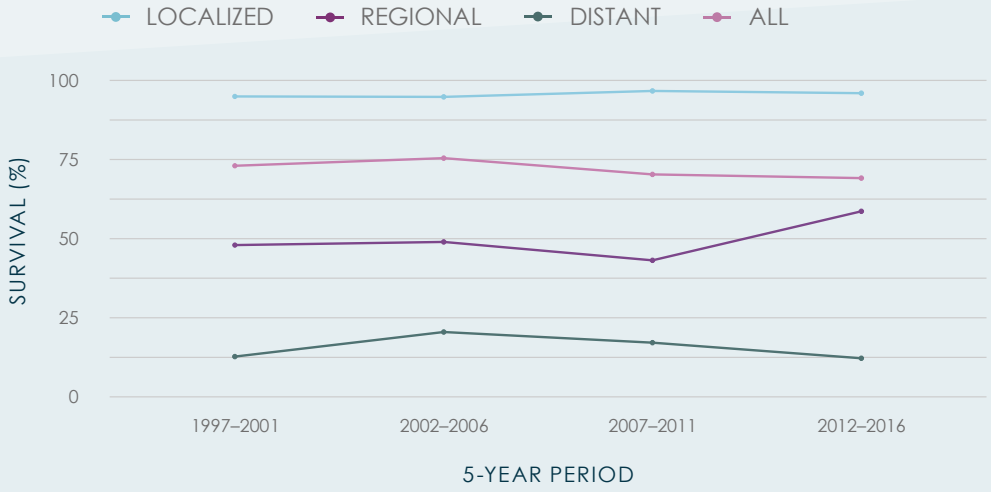


FIGURE 4

Five-year net survival of women with cervical cancer by stage in Slovenia in 1997–2016.

years between 2000 and 2014 in 71 countries and territories show that five-year net survival of Slovenian women with cervical cancer has been deteriorating slightly over the five-year periods, but the decline is not statistically significant (Figure 5). For women diagnosed during the most recent period (2010–2014), Slovenia ranked 11th among the 26 participating countries in Europe.

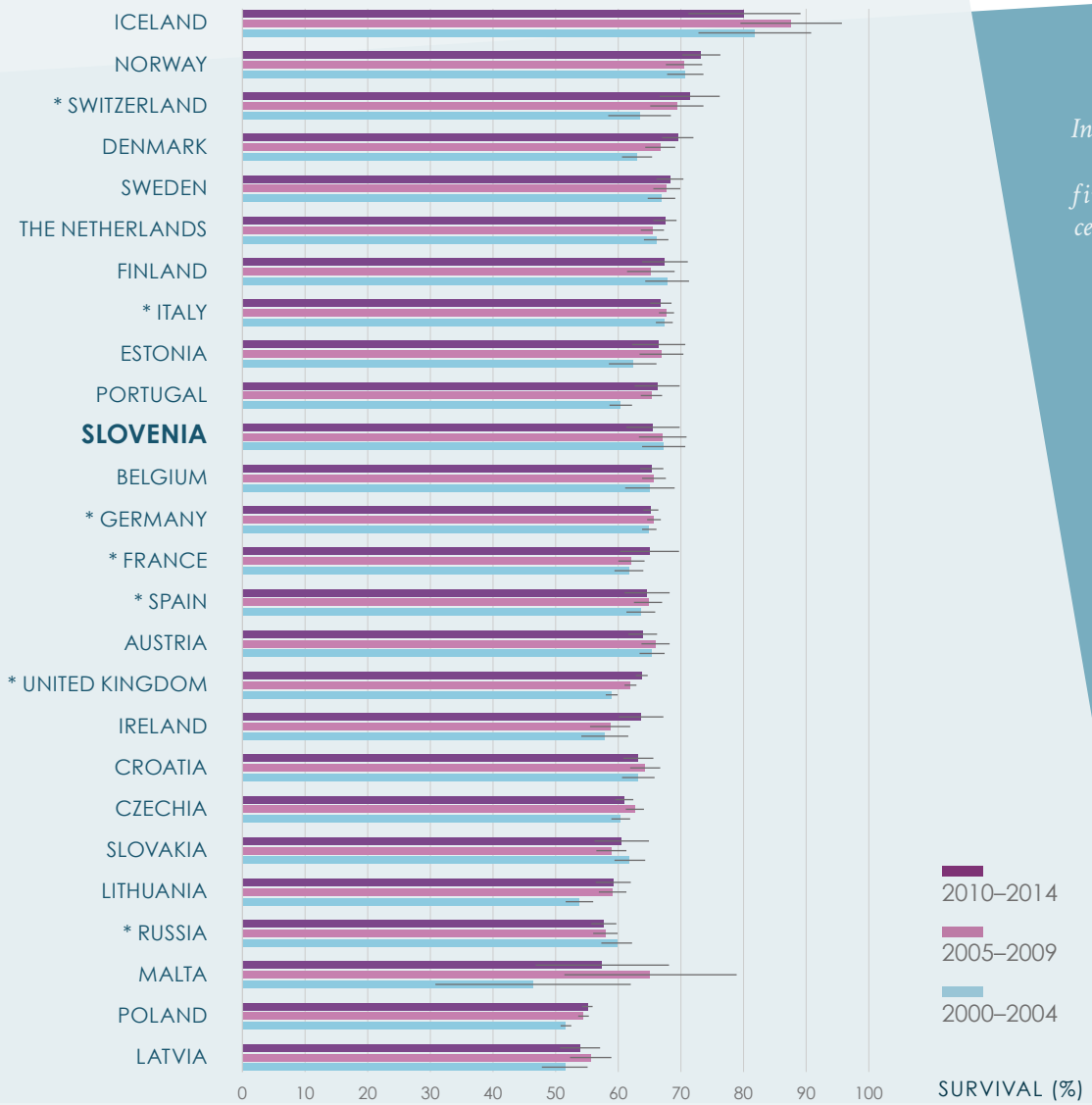


FIGURE 5

International comparison of age-standardized five-year net survival for cervical cancer (with 95% confidence intervals) in women diagnosed during 2000–2004, 2005–2009 and 2010–2014 (CONCORD-3).

** Data doesn't cover a 100% of the country's population.*

CLINICAL COMMENTARY

Borut Kobal

Thanks to the national screening programme for the early detection of precancerous and early cancerous changes of the cervix (the ZORA programme), the incidence of cervical cancer decreased during the 20 years under review. In this period, surgical treatment of this cancer has undergone the most significant changes. We gradually abandoned radical hysterectomy in stage IB2, while in stage IB1, in addition to the clinical assessment of the stage, we also began to consider the radiological assessment of parametrial invasion and pelvic lymph node metastasis. Thus, the proportion of patients who were treated with surgery alone in the 2012–2016 period fell to 40%. This is a result of having adopted guidelines for cervical cancer management in 2012, which introduced adjuvant radiotherapy based on a final assessment of histopathological prognostic factors: differentiation, depth of stromal invasion and the presence of lymphovascular invasion.

In addition to considering the oncological outcome of treatment, an individualized approach to the treatment of cervical cancer, which emphasises a more thorough preoperative assessment of the tumour, is important in order to maintain patients' quality of life. The quality of life is poorer when a combination of radical surgery and adjuvant radiotherapy is utilized.

In the observed periods, the largest proportion of women is in the 25–49 age group, many of whom are still in their reproductive period. Since 2011, we have treated these patients according to oncological treatment guidelines with a combination of laparoscopic lymphadenectomy and radical removal of the cervix (radical trachelectomy), which does not affect patients' fertility.

A minimally invasive surgical approach—laparoscopically assisted radical hysterectomy, laparoscopic radical hysterectomy—was introduced in 2014. Compared to open surgery, the advantages of the laparoscopic approach are less blood loss, shorter hospital stay, and faster recovery, with the same proportion of complications and comparable radicality of the procedure. As the latest data in the literature suggests that oncology treatment results are poorer, we expect that criteria will be developed to identify which patients are suitable for this approach.

Locally advanced cervical cancer is primarily treated with a combination of radiotherapy and concomitant chemotherapy. In 2010, in agreement with radiotherapists, we upgraded the imaging assessment of lymph node involvement using laparoscopic lymphadenectomy. The surgical approach also allows the removal of positive lymph nodes. This could further improve survival, which is reflected in the results of the 2012–2016 period in this group.

In the future, surgical treatment will be even more individualized and will be limited to the IA1–IB1 stages. The decision to treat a patient with radical surgery will be based on an imaging assessment of the stage (magnetic resonance imaging, expert ultrasound), sentinel lymph node biopsy or negative lymph nodes in the pelvis, while minimally invasive surgery will be intended only for patients with favourable prognostic factors.

Helena Barbara Zobec Logar

In patients with cervical cancer, radiotherapy is most often used as part of radical treatment and in the form of postoperative radiotherapy, and less frequently as palliative treatment in distant disease and in patients in poor general health. Before starting treatment, each patient's case is presented at a multidisciplinary consultation board, which makes a proposal for treatment. Radical radiotherapy is the treatment of choice from stage IB2 onwards or in tumours larger than 4 cm, and in lower stages when surgery is contraindicated or when the patient refuses it. Since 2006, patients have undergone MRI of the pelvis and PET/CT or CT of the abdomen or chest before treatment with radical radiotherapy. Based on the examinations, a lymphadenectomy can be performed before radical radiotherapy.

This can be pelvic with the removal of suspicious pelvic lymph nodes, or paraaortic in negative pelvic lymph nodes. Postoperative radiotherapy is used to treat patients with large tumours, deep stromal invasion of the cervix or lymphovascular invasion. Postoperative radiochemotherapy is used for patients with a close/positive surgical margin, parametrial invasion and positive lymph nodes. If possible, we try to avoid a combination of radical surgery and postoperative radiotherapy due to the greater possibility of late adverse effects of treatment.

In the 2012–2016 period, 22% of patients were treated with radiotherapy alone or in combination with chemotherapy, which is 4 percentage points less than between 2007 and 2011, while 31% of patients were treated with postoperative radiotherapy alone or in combination with chemotherapy, which is 8 percentage points more than between 2007 and 2011. A higher proportion of patients receiving combination therapy can be attributed to lymphadenectomy before radical radiotherapy. During the same period, the proportion of patients with localized disease decreased by slightly more than 10 percentage points, while the proportion of patients with regionally advanced disease increased by slightly more than 6 percentage points. The proportion of patients who received adjuvant systemic therapy as part of their primary treatment with radiotherapy and with or without surgery halved in the 2012–2016 compared to 2007–2011. The poorer five-year survival of all patients between 2012–2016 is the result of a 9 percentage-point increase in the proportion of patients with metastatic disease, 9 percentage-point increase in the proportion of older patients (aged 50–94), and 1 percentage-point increase in the proportion of untreated patients. Survival of patients with locoregional disease, where radiotherapy plays a major role, improved by 15 percentage points between 2012–2016 compared to 2007–2011, while the survival of patients with metastatic disease decreased by slightly more than 5 percentage points. The survival of patients with localized disease, however, remained almost unchanged and was an excellent 96%. Lower survival of patients with metastatic disease is most likely associated with comorbidities, which limit treatment options for older patients.

Five-year survival of patients with cervical cancer in Slovenia is in the top half of survival rankings among European countries and places us alongside Belgium and Portugal.

The challenges for the future are how to manage more intensive treatment of metastatic disease and treatment of older patients, and in prevention, how to get as many unresponsive women as possible from the target population to participate in the ZORA programme.

Erik Škof

Cervical cancer is a disease for which there is effective primary (vaccination) and secondary (early detection by screening) prevention. The ZORA screening programme, which was launched in 2003, is the main reason why incidence of the disease has almost halved. Women between the ages of 20 and 69 are actively invited to participate. The take-up rate exceeded 70%, which was the target of the programme. Most patients who develop cervical cancer today have not participated in a screening programme. Another effective measure to prevent cervical cancer is vaccination against oncogenic types of human papillomavirus, which are the leading cause of cervical cancer. In Slovenia, we have free vaccination of girls in the 6th grade of primary school. We currently have a 9-valent vaccine available. Because infection with this disease is sexually transmitted, it is also recommended to vaccinate boys before they become sexually active.

Most patients with cervical cancer are treated in a tertiary oncology centre, and are usually reviewed at a gynaecology-oncology consultation board, which proposes a type of specific oncological treatment. The primary treatment of the disease is surgery and/or radiotherapy. Systemic chemotherapy is used only as a palliative treatment for metastatic disease. This disease is characterized by occurring in younger women (median age: 45 years). Since the beginning of the ZORA screening programme, there has been an increase in the proportion of older patients with newly diagnosed cervical cancer, which confirms the assumption that the programme detects precancerous changes, the removal of which prevents cancer. This is further evidenced by the fact that patients who had not participated in the screening programme were more likely to be diagnosed with the disease in a distant stage, which is also the reason that the survival of all patients in the observed period declined — five-year survival in the 2012–2016 period was only 69%, which is the worst so far.

Although progress has been made in the survival of patients with early-stage cancer (five-year survival is 96%), the deterioration in overall survival can be explained by a marked (fourfold) increase in the proportion of patients with distant metastases at diagnosis in 2012–2016 compared with the 1997–2001 period. Although local treatment for this disease is very effective, the prognosis is very poor when distant metastases develop. Currently, systemic chemotherapy (taxane- or platinum-based combination) is classified as palliative treatment because the expected survival of patients treated with chemotherapy is only 12 to 13 months. However, when the condition of the patients allows the addition of the targeted therapy with bevacizumab, the expected survival is 17 months. Cervical cancer is a disease in which primary and secondary prevention have proven to be very effective. It is worrying that the proportion of patients diagnosed with advanced disease and thus with a poor prognosis is increasing, while in cases where the disease is detected at an early stage, the prognosis is excellent. Therefore, it is necessary to invest as much energy as possible into implementing proven effective preventive measures across the entire population in Slovenia.

References

Cibula D, Potter R, Planchamp F, et al. The European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology Guidelines for the management of patients with cervical cancer. Int J Gynecol Cancer 2018; 28: 641–55.

Delpech Y, Tulpin L, Bricou A, et al. Lymph node surgical staging for locally advanced cervical cancer. Gynecol Obstet Fertil 2010; 38: 30–5.

Magrina JF, Kho RM, Weaver AL, et al. Robotic radical hysterectomy: comparison with laparoscopy and laparotomy. Gynecol Oncol 2008; 109: 86–91.

Park JY, Kim DY, Kim JH, et al. Comparison of outcomes between radical hysterectomy followed by tailored adjuvant therapy versus primary chemoradiation therapy in IB2 and IIA2 cervical cancer. J Gyneco Oncol 2012; 23: 226–34.

Plante M, Renaud MC, Hoskins IA, et al. Vaginal radical trachelectomy: a valuable fertility-preserving option in the management of early-stage cervical cancer. A series of 50 pregnancies and review of the literature. Gynecol Oncol 2005; 98: 3–10.

Šegedin B, Merlo S, Arko D, et al. Priporočila za obravnavo bolnic z rakom materničnega vratu (Guidelines for treatment of patient with cervix uteri cancer). Onkologija 2019; 23(1): 54–72.

Tozzi R, Lavra F, Cassese T, et al. Laparoscopic debulking of bulky lymph nodes in women with cervical cancer: indication and surgical outcomes. BJOG 2009; 116: 688–92.

Uršič-Vrščaj M, Smrkolj Š, Petrič P, et al. Smernice za obravnavo bolnic z rakom materničnega vratu v Sloveniji (Guidelines for treatment of patients with cervix uteri cancer) . Ljubljana: Institute of Oncology; 2012. Available from: https://zora.onko-i.si/fileadmin/user_upload/dokumenti/strokovna_priporocila/2012_Smernice_RMV_web.pdf

Institute of Oncology Ljubljana. The ZORA Programme: Slovenian cervical cancer screening programme and registry. Ljubljana: Institute of Oncology; 2021. Available from: https://www.zora.onko-i.si

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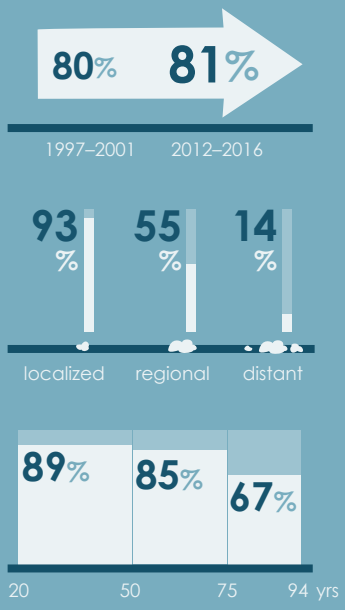
CORPUS UTERI



EPIDEMIOLOGY

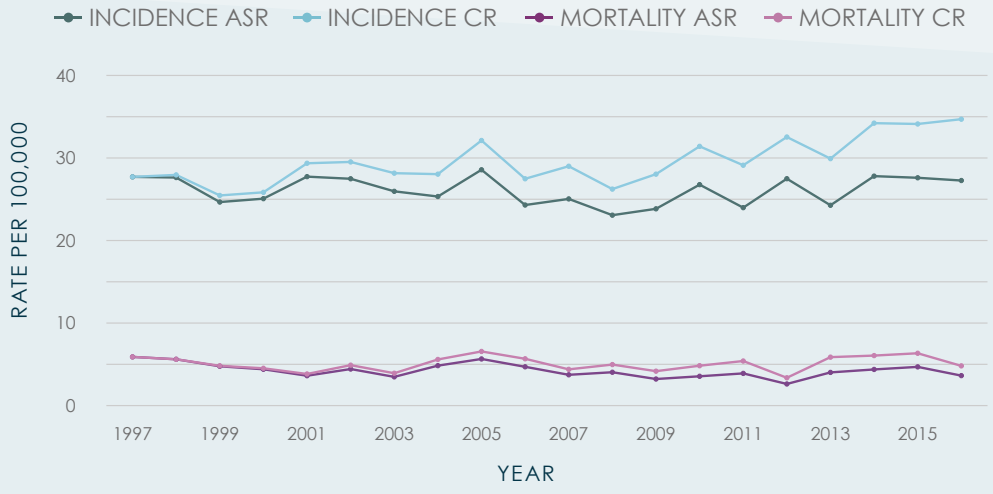
In the last five-year period (2012–2016), 344 women per year on average were diagnosed with cancer of the corpus uteri in Slovenia, and 55 women died. As shown in Figure 1, the incidence rate is gradually increasing. Between 2007–2016, the crude incidence rate increased by 2.7% per year. The increase is statistically significant, and can mostly be attributed to the ageing of women. Between 2007–2016, the crude mortality increased by 2.7% per year, an increase which is not statistically significant.

At the end of 2016, there were 4,686 women living in Slovenia who had ever been diagnosed with cancer of the corpus uteri. Of those, the diagnosis had been established less than one year ago in 341 women, one to four years ago in 1,082 women, and over ten years ago in 2,276 women.

The survival analysis included 6,036 cases of women aged 20–94; 34 cases (0.6%) were excluded because they were diagnosed on the day of death, or because they did not fulfil the age inclusion criteria.

FIGURE 1

The crude (CR) and age-standardized (ASR) incidence and mortality rates of women with corpus uteri cancer in Slovenia in 1997–2016.



Over the entire period under review, in 1–4% of cases the tumour site was not specified (C54.9). Among those with specified sites, however, most cases (more than 95%) occurred in the endometrium (C54.1). In the remaining sites (C54.0, C54.2, C54.3, C54.8), the disease occurred in less than 1%.

Less than 1% of patients in each five-year period did not have microscopically confirmed disease. The majority of cases of microscopically confirmed disease, more than 88% in the most recent period, were adenocarcinomas.

In the entire 20 years under review, the largest proportion of women were diagnosed between the ages of 50–74; over the observed period, incidence has gradually decreased in this age group and increased in the group of patients aged 75–94. The disease was most commonly diagnosed in the localized stage (Table 1).

WOMEN		Age			Stage			Total
		20–49 yrs	50–74 yrs	75–94 yrs	Localized	Regional	Distant	
1997–2001		129	1020	225	1056	204	87	1374
	%	9.4	74.2	16.4	76.9	14.9	6.3	
2002–2006		125	1026	326	1077	270	104	1477
	%	8.5	69.5	22.1	72.9	18.3	7.0	
2007–2011		114	981	380	1068	280	90	1475
	%	7.7	66.5	25.8	72.4	19.0	6.1	
2012–2016		129	1128	453	1276	312	101	1710
	%	7.5	66.0	26.5	74.6	18.3	5.9	

TABLE 1

Number and proportion of women with corpus uteri cancer by age, stage and period of diagnosis in Slovenia in 1997–2016.

Regarding the specific primary treatment between 1997–2016, almost 50% of patients of the corpus uteri were treated with surgery alone and 33% were treated with surgery and additional radiotherapy. Some 7% of patients received systemic treatment in any combination. There were 5% of patients without specific primary treatment across the entire period under review; the proportion of this group of women remained similar in all of the observed five-year periods.

Throughout the observed period, corpus uteri cancer surgery was performed in at least 15 hospitals. In the last five-year period, the majority of procedures were performed at the University Medical Centre Ljubljana (42%), the University Medical Centre Maribor (17%), the Institute of Oncology Ljubljana (11%), and Celje General Hospital (8%), and in other hospitals in 5% of cases or less. As part of their

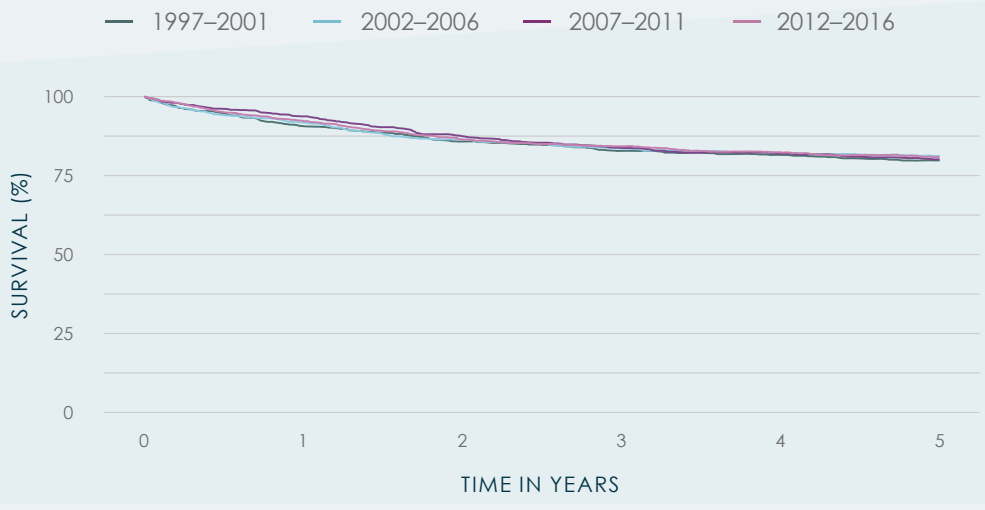


FIGURE 2

Net survival of women with corpus uteri cancer by period of diagnosis in Slovenia in 1997–2016.

primary treatment in the last five-year period, patients received systemic treatment at the Institute of Oncology Ljubljana (77%) and at the University Medical Centre Maribor (21%), while individual patients also received treatment at Murska Sobota General Hospital, Celje General Hospital, and Nova Gorica General Hospital.

Survival of patients with cancer of the corpus uteri did not change significantly in relation to the year of diagnosis (Figure 2, Table 2). In the 20 years under review, five-year net survival was around 80%.

TABLE 2

One-, three- and five-year observed and net survival (with a 95% confidence interval – CI) of women with corpus uteri cancer by period of diagnosis in Slovenia in 1997–2016.

WOMEN Survival / Period		1997–2001	(95% CI)	2002–2006	(95% CI)	2007–2011	(95% CI)	2012–2016	(95% CI)
Observed	1-year	88.9	87.3–90.6	89.8	88.3–91.4	91.8	90.4–93.2	90.5	89.1–91.9
	3-year	78.4	76.3–80.6	78.1	76.1–80.3	79.4	77.4–81.5	79.6	77.7–81.5
	5-year	72.5	70.2–74.9	72.1	69.9–74.4	72.8	70.6–75.1	72.7	70.5–75.0
Net	1-year	90.6	88.9–92.4	91.8	90.2–93.4	93.7	92.3–95.2	92.2	90.8–93.7
	3-year	82.8	80.5–85.2	83.6	81.3–86.0	83.8	81.5–86.2	84.3	82.2–86.4
	5-year	79.8	77.1–82.6	81.2	78.5–84.0	80.1	77.5–82.8	80.6	78.0–83.3

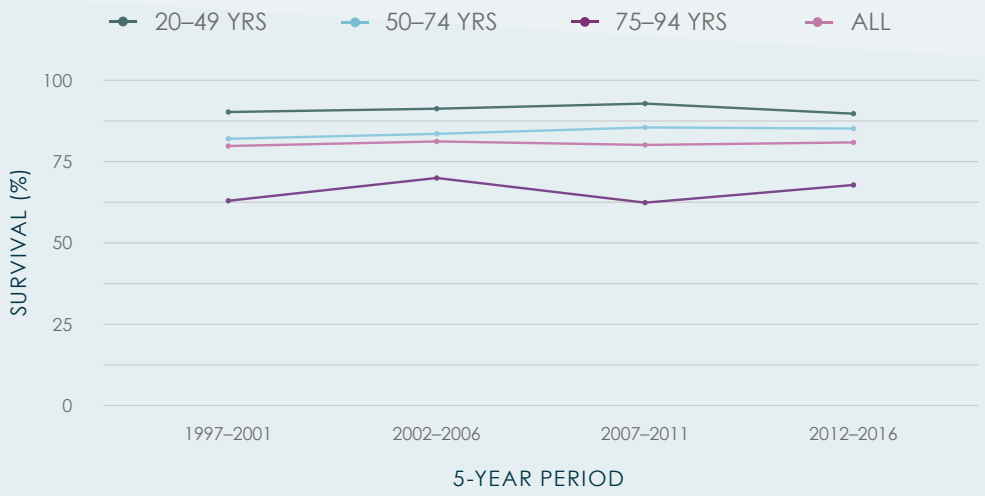
In Slovenia, compared to other selected cancers, cancer of the corpus uteri ranks 5th in women by five-year net survival.

Figure 3 shows the impact of age on the survival of patients with cancer of the corpus uteri. Five-year net survival is lowest in patients aged 75–94. Net survival of patients aged 50–74 at diagnosis ranges from 82–86% over the entire 20 years under review, and from 89–93% for those younger than 50 years.

The importance of stage at diagnosis is shown in Figure 4. Five-year net survival of patients with localized disease exceeded 93% in the last five-year period. Five-year net survival of patients with regional-stage disease was almost 55%, whereas in patients with distant disease at diagnosis, it was only slightly above 14%.

FIGURE 3

Five-year net survival of women with corpus uteri cancer by age group in Slovenia in 1997–2016.



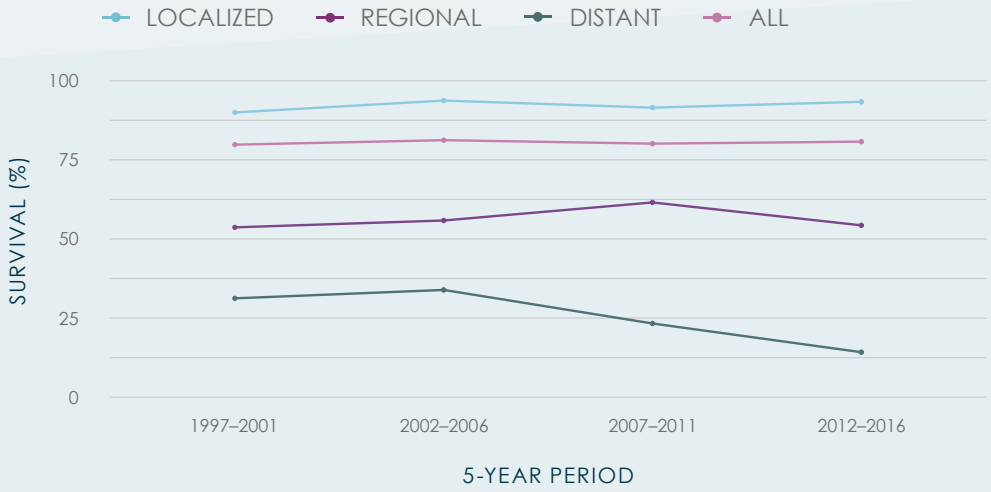


FIGURE 4

Five-year net survival of women with corpus uteri cancer by stage in Slovenia in 1997–2016.

CLINICAL COMMENTARY

Borut Kobal

Most cases of endometrial cancer are diagnosed in the first stage (stage FIGO IA-IIA), when treatment is usually surgical, including the removal of the uterus, its appendages and, if necessary, the lymph nodes in the pelvis. Data on incidence, mortality and overall survival did not change significantly in the reviewed 20-year period.

In accordance with ESGO, ESTRO and ESMO guidelines from 2015, we preoperatively identify groups of patients with different risks based on histopathological type, degree of differentiation and depth of myometrial invasion. Notwithstanding recent, mainly molecular differences within type I, stages IA (no invasion or invading less than half of myometrium) and IB (invading one half or more of myometrium) are classified between low- and medium-risk endometrial cancer according to the latest FIGO classification with G1 and G2 differentiation. Preoperative classification of patients with type I in risk groups is thus based on the histological sample and on non-invasive diagnostic imaging methods. The first choice is magnetic resonance imaging with contrast, and transvaginal ultrasound with the possibility of three-dimensional display is also increasingly used.

Since 2008, classical open surgery has been gradually replaced by a combined laparoscopic and vaginal approach (laparoscopically assisted vaginal hysterectomy with adnexectomy or a complete laparoscopic approach; total laparoscopic hysterectomy with adnexectomy). A minimally invasive approach is also the first choice of the ESGO, ESMO, and ESTRO guidelines for patients with low- or moderate-risk endometrial cancer. The laparoscopic approach allows simultaneous pelvic and para-aortic lymphadenectomy when indicated. Its advantages are mainly: reduction of postoperative complications associated with laparotomy, faster recovery and earlier initiation of additional treatment when indicated, while this approach does not affect the oncological outcome of treatment. It is also more favourable for patients aged 75–94, which is reflected in improved survival in this age group.

Surgical staging in endometrial cancer is based on removal of the pelvic lymph nodes. This procedure is not recommended in patients whose preoperative assessments indicate low- or medium-risk, but there is a possibility of incorrect risk assessment. In unclear cases of classification into risk groups, it is appropriate to perform a complete pelvic lymphadenectomy up to its anatomical limits or to follow the sentinel lymph node algorithm, which was introduced in 2015.

In prognostically unfavourable types of endometrial cancer, histologically classified as type II, surgical staging follows the principles of ovarian cancer surgery; the same applies to locally advanced endometrial cancer, in which we try to achieve optimal cytoreduction. Since 2015, in adjuvant treatment

for this type of endometrial cancer, radiotherapy has followed systemic treatment with chemotherapy. Given the short follow-up time, the success of this treatment strategy is not yet measurable.

Today, a minimally invasive surgical approach is the cornerstone of surgical treatment of endometrial cancer with unchanged oncological treatment results.

Helena Barbara Zobec Logar

In 2009, the new FIGO classification for cancer of the corpus uteri came into force. According to the new classification, stage Ia covers the following stages according to the 1988 FIGO classification: IA, IB, IIA and IIIA (positive peritoneal cytology) with invasion of less than half of myometrium. Stage Ib corresponds to the following stages according to the 1988 FIGO classification: stages Ic, IIa and IIIa (positive peritoneal cytology) with invasion of one half or more of myometrium. In the 2009 FIGO stages Ia and Ib G1 and G2 without lymphovascular invasion, adjuvant radiotherapy is not required, in contrast to stages Ia G3, Ib G3 and Ib G1, G2 with lymphovascular invasion in endometrioid carcinoma and in all non-endometrioid carcinomas that receive adjuvant radiotherapy with intravaginal brachyradiotherapy or teleradiotherapy. As the classification method for cancer of the corpus uteri and indications for postoperative radiotherapy changed, the number of patients who received postoperative radiotherapy between 2012–2016 decreased by 11 percentage points compared to the 2007–2011 period. As a result, the data are not completely comparable. Based on the current classification, stages Ia and Ib include a heterogeneous group of patients with different survival rates, as noted by other authors, so this may be the reason for minor differences in survival. At the same time, stage III no longer includes the prognostically favourable group IIIa with positive peritoneal cytology. Five-year survival in localized disease has improved slightly and is approximately 93%. Survival in regionally advanced disease, however, stabilized at 55%. Survival in metastatic disease has almost halved compared to 2007–2011, standing at 14%. The poorer survival of patients with metastatic disease cannot be explained by an increase in elderly patients or an increase in the number of untreated patients, because these percentages did not change significantly between 2012–2016 compared to 2007–2011. Five-year survival in the oldest age group of 75–94 years has even improved to 67%. Comorbidities could be a possible reason for the poorer survival of patients with metastatic disease.

Erik Škof

Cancer of the corpus uteri is the most common gynaecological cancer in Slovenia. Its incidence is on the rise as a result of population ageing. This disease is characterized by mostly occurring in older women (median age at diagnosis is more than 60 years). Although there is no effective prevention measure for this disease, uterine cancer has the best prognosis among gynaecological cancers. The reason is that symptoms usually appear early (menopausal gynaecological bleeding), when the disease is usually still limited to the lining of the uterus (endometrium). As a result, surgery may be less demanding in most patients: removal of the uterus with ovaries can usually be performed laparoscopically, which is increasingly performed in regional hospitals. Patients with a higher risk of recurrence of the disease—a higher stage of the disease and/or a histologically unfavourable (non-endometroid) type of cancer—are usually treated surgically in tertiary oncology centres, but they represent a minority. According to the latest recommendations, additional (adjuvant) treatment with chemotherapy and radiotherapy is recommended for these patients even when the disease is localized to the endometrium (stage I). This is why the proportion of patients receiving adjuvant chemotherapy is on the rise, mainly due to the higher proportion of non-endometroid-type corpus uteri cancer, which is diagnosed in about 20% of cases. Survival of women with cancer of the corpus uteri is the best among gynaecological cancers. In the 2012–2016 period, five-year net survival of all patients surpassed 80%, while five-year survival of patients with localized disease was as high as 93%. It is encouraging that it is improving in almost all age groups, especially in those aged 75–94, where incidence has almost doubled in the observed period.

References

Abu-Rustum NR, Zhou Q, Iasonos A, et al. The revised 2009 FIGO staging system for endometrial cancer: should the 1988 FIGO stages IA and IB be altered? Int J Gynecol Cancer 2011; 21: 511–6.

Benedetti Panici P, Basile S, Maneschi F, et al. Systematic pelvic lymphadenectomy vs. no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. J Natl Cancer Inst 2008; 100(23): 1307–16.

Creasman W. Revised FIGO staging for carcinoma of the endometrium. Int J Gynecol Obstet 2009; 105: 109.

Colombo N, Creutzberg C, Amant F, et al. ESMO-ESGO--ESTRO Consensus Conference on Endometrial Cancer: diagnosis, treatment and follow-up. Ann Oncol 2016; 27: 16–41.

Colombo N, Creutzberg C, Amant F, et al; ESGO-ESMO–ESGO–ESTRO Endometrial Consensus Conference Working Group. ESGO-ESMO-ESGO-ESTRO consensus conference on endometrial cancer: Diagnosis, treatment and follow-up. Radiother Oncol 2015; 113(3): 559–81.

Cormier B, Rozenholc AT, Gotlieb W, et al. Sentinel lymph node procedure in endometrial cancer: A systematic review and proposal for standardization of future research. Gynecol Oncol 2015; 138(2): 478–85.

Eriksson AGZ , Ducie J, Ali N, et al. Comparison of a sentinel lymph node and a selective lymphadenectomy algorithm in patients with endometrioid endometrial carcinoma and limited myometrial invasion. Gynecol Oncol 2016; 140: 394–9.

Humphrey MM, Apte SM. The use of minimally invasive surgery for endometrial cancer. Cancer Control 2009; 16(1): 30–7.

Mourits MJ, Bijen CB, Arts HJ, et al. Safety of laparoscopy versus laparotomy in early-stage endometrial cancer: a randomised trial. Lancet Oncol 2010; 11(8): 763–71.

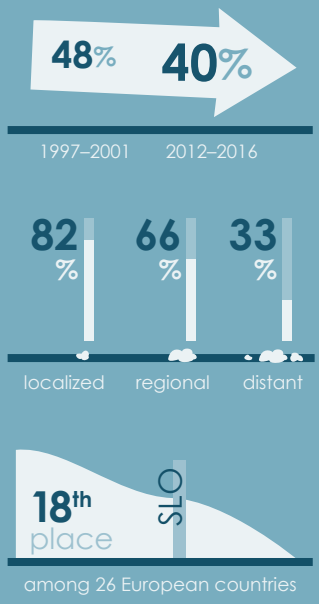
Šegedin B, Merlo S, Smrkolj Š, et al. Priporočila za obravnavo bolnic z rakom maternične telesa (Guidelines for treatment of corpus uteri cancer patients). Onkologija 2018; 22 (1): 96–114.

Tozzi R, Malur S, Koehler C, et al. Laparoscopy versus laparotomy in endometrial cancer: first analysis of survival of a randomized prospective study. J Minim Invasive Gynecol 2005; 12(2): 130–6.

Walker JL, Piedmonte MR, Spirtos NM, et al. Laparoscopy compared with laparotomy for comprehensive surgical staging of uterine cancer: Gynecologic Oncology Group Study LAP2. J Clin Oncol 2009; 27(32): 5331–6.

C56

OVARY



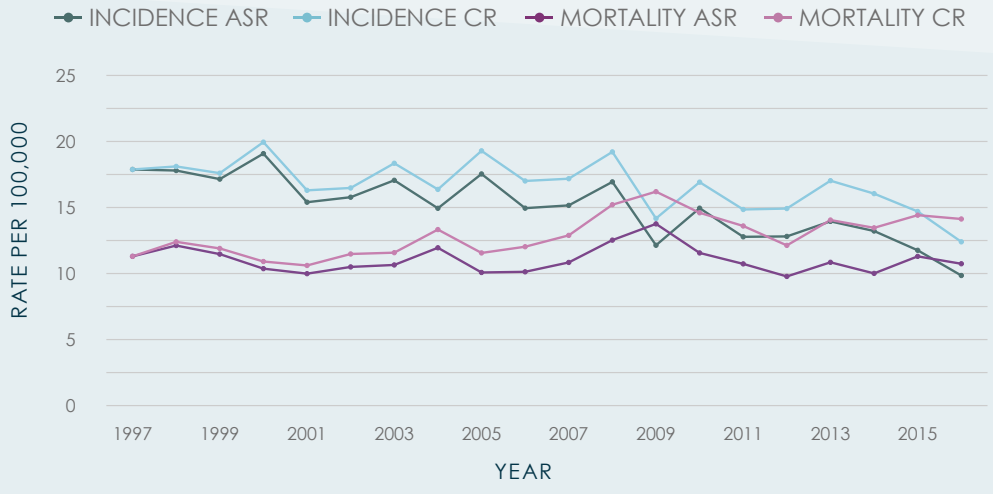
EPIDEMIOLOGY

In the last five-year period (2012–2016), on average 156 women were diagnosed with ovarian cancer in Slovenia each year, and 142 died. As shown Figure 1, the incidence rates of ovarian cancer are slowly declining. Between 2007 and 2016, the incidence rate of ovarian cancer decreased by 2.5% per year, a decrease that is not statistically significant. Ovarian cancer mortality rates did not change significantly. Between 2007 and 2016, the crude ovarian cancer mortality rate decreased by 0.4% per year. During this period, the crude and standardized mortality rates are close to or even exceed the crude and standardized incidence rates.

At the end of 2016, there were 1,587 women in Slovenia who had been diagnosed with ovarian cancer at some point in their lives. Of those, the diagnosis had been established less than one year ago in 107 women, one to four years ago in 330 women, and over ten years ago in 865 women.

FIGURE 1

The crude (CR) and age-standardized (ASR) incidence and mortality rates of ovarian cancer in Slovenia in 1997–2016.



The survival analysis included 3,353 cases of patients aged 20 to 94 years; 78 cases (2%) were excluded because they were diagnosed on the day of death or because they did not fulfil the age inclusion criteria.

Less than 5% of patients in each period did not have their disease confirmed microscopically. Among the microscopically confirmed cases, adenocarcinoma was most common (89%) in the last period, while other histological types were much less frequent, each occurring in less than 2% of cases. In 0.3% of cases, the histological type was not specified.

The largest proportion of women in all the observed periods were aged between 50 and 74 years at diagnosis. The disease was most commonly diagnosed at a distant stage (Table 1).

WOMEN		Age			Stage			Total
		20–49 yrs	50–74 yrs	75–94 yrs	Localized	Regional	Distant	
1997–2001		216	517	150	211	116	542	883
	%	24.5	58.6	17.0	23.9	13.1	61.4	
2002–2006		164	557	151	106	50	690	872
	%	18.8	63.9	17.3	12.2	5.7	79.1	
2007–2011		165	488	177	113	78	628	830
	%	19.9	58.8	21.3	13.6	9.4	75.7	
2012–2016		132	458	178	88	62	613	768
	%	17.2	59.6	23.2	11.5	8.1	79.8	

TABLE 1

Number and proportion of patients with ovarian cancer by age, stage and period of diagnosis in Slovenia in 1997–2016.

Regarding the specific primary treatment of ovarian cancer between 1997 and 2016, 61% of patients underwent surgery and concurrently received systemic therapy. Eighteen percent of patients were treated with surgery alone and 8% with systemic treatment alone. Across the entire observed period, a total of 11% of patients did not receive specific primary treatment, the proportion of which is slowly increasing over the years.

In all periods, ovarian cancer surgery was performed in at least 15 hospitals. In the last five year period, most operations were performed at the University Medical Centre Ljubljana (45%), the Institute of Oncology Ljubljana (24%), the University Medical Centre Maribor (18%) and the Celje General Hospital (7%), whereas in other hospitals 3% or fewer operations were performed. As part of their primary treatment, in the last five years, patients received systemic treatment at the Institute of Oncology Ljubljana (79%) and at the University Medical Centre Maribor (20%), as well as individual cases at the Nova Gorica General Hospital, Celje General Hospital and the Golnik University Clinic.

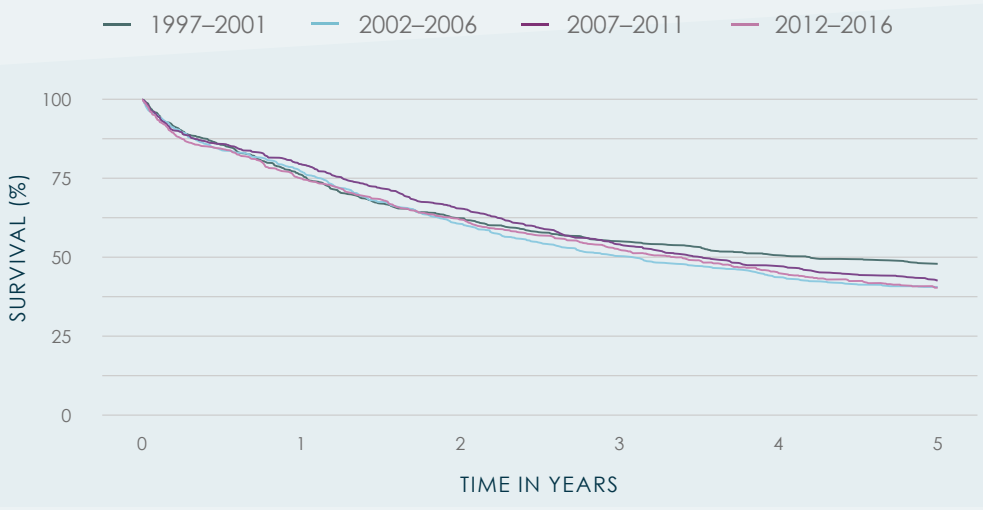


FIGURE 2

Net survival of patients with ovarian cancer by period of diagnosis in Slovenia in 1997–2016.

The survival of patients with ovarian cancer has not been increasing in relation to the year of diagnosis (Figure 2, Table 2). In the 20 years under review, the five-year net survival average around 43%.

TABLE 2

One-, three-, and five-year observed and net survival (with a 95% confidence interval–CI) of patients with ovarian cancer by period of diagnosis in Slovenia in 1997–2016.

WOMEN Survival / Period		1997–2001	(95% CI)	2002–2006	(95% CI)	2007–2011	(95% CI)	2012–2016	(95% CI)
Observed	1-year	75.1	72.3–78.0	76.0	73.3–78.9	78.4	75.7–81.3	74.1	71.1–77.3
	3-year	53.0	49.8–56.4	48.6	45.4–52.1	52.2	48.9–55.7	51.0	47.5–54.6
	5-year	44.6	41.5–48.0	38.3	35.2–41.7	40.2	37.0–43.7	38.5	35.0–42.3
Net	1-year	76.1	73.3–79.1	77.1	74.3–80.1	79.5	76.7–82.4	75.0	71.9–78.2
	3-year	55.1	51.7–58.6	50.3	46.9–53.9	54.1	50.6–57.8	52.5	48.9–56.3
	5-year	47.9	44.5–51.6	40.5	37.1–44.1	42.6	39.1–46.4	40.4	36.7–44.5

In Slovenia, compared to other selected cancers, ovarian cancer ranks 17th in women by five-year net survival.

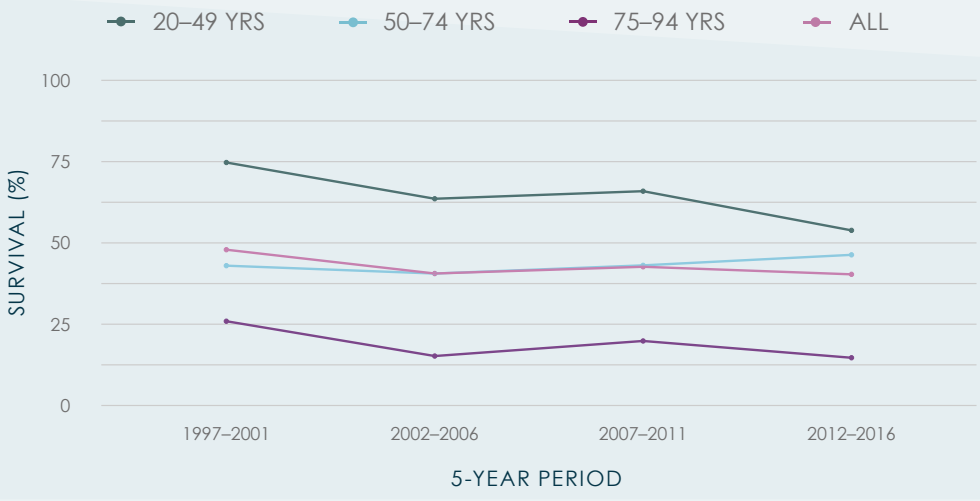
Figure 3 shows the impact of age on the survival of patients with ovarian cancer. The five-year net survival is lowest in patients aged 75–94. The survival of patients aged 50–74 years at diagnosis ranges from 40–46% across the observed periods, whereas the net survival of patients younger than 50 years is between 54–75%.

The importance of stage at diagnosis is shown in Figure 4. The five-year net survival of patients with the localized stage of the disease range from 79 to 95% over the entire observed period. The five-year net survival of patients in the regional stage reached almost 66% in the last period and in patients with the distant stage of the disease at diagnosis, it is about 33%.

The results of the world-wide CONCORD-3 study of patients diagnosed with cancer during the 15 years 2000–2014 in 71 countries and territories show that the five-year survival of Slovenian patients with ovarian cancer has slightly improved in the last five-year period compared to the previous period, but the improvement is not statistically significant (Figure 5). For patients diagnosed during

FIGURE 3

Five-year net survival of patients with ovarian cancer by age group in Slovenia in 1997–2016.



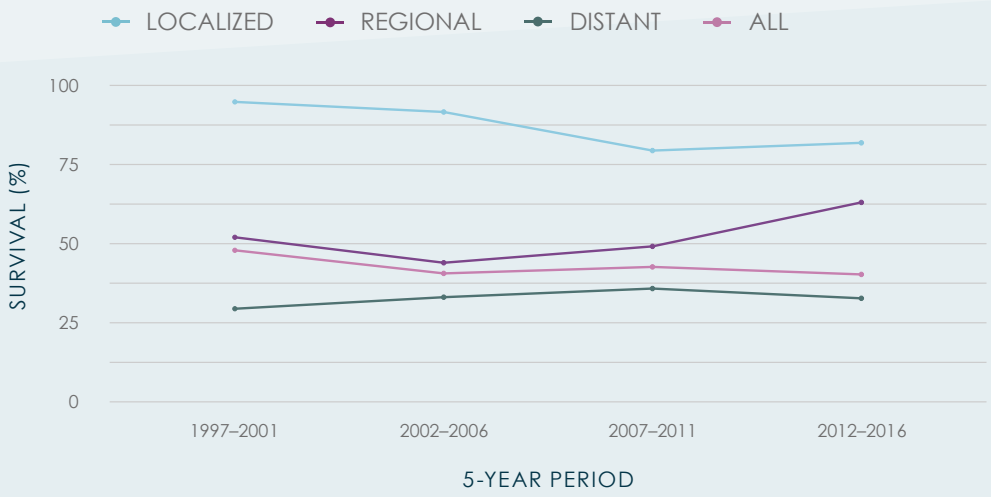


FIGURE 4

Five-year net survival of patients with ovarian cancer by stage in Slovenia in 1997–2016.

the most recent period (2010–2014), Slovenia ranked 18th among the 26 participating countries in Europe.

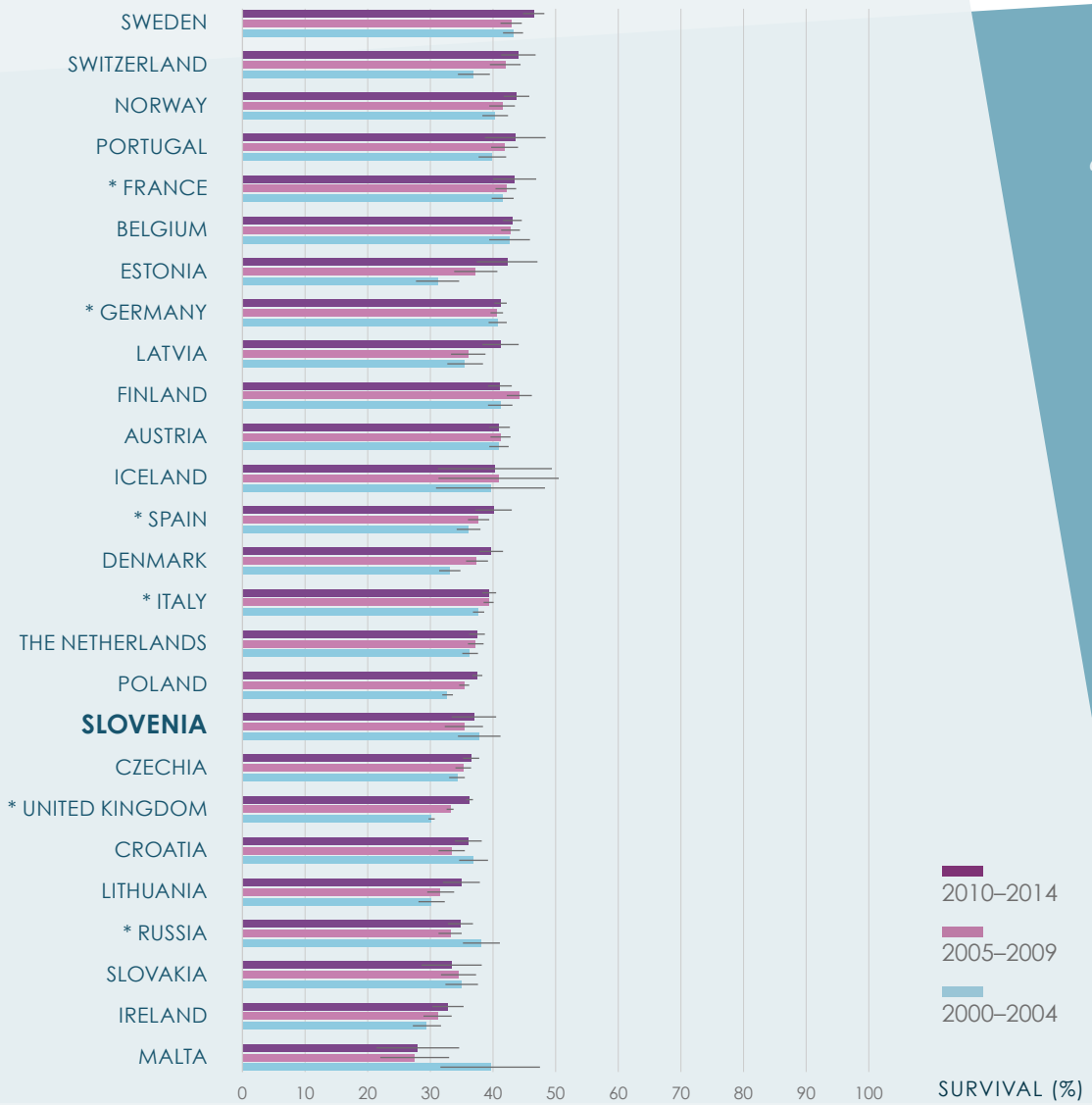


FIGURE 5

International comparison of age-standardized five-year net survival for ovarian cancer (with 95% confidence intervals) in patients diagnosed during 2000–2004, 2005–2009 and 2010–2014 (CONCORD-3)..

** Data doesn't cover a 100% of the country's population.*

CLINICAL COMMENTARY

Borut Kobal

Ovarian cancer has the worst prognosis among gynaecological cancers and the five-year survival rate for all stages of the disease is below 45%. Due to the late onset of symptoms and the lack of an effective screening method, as many as 75% of cases are diagnosed in the distant stages (FIGO III, IV), in which the five-year survival rate is even worse (about 30%). The standard initial treatment for ovarian cancer is optimal cytoreductive surgery along with cytotoxic chemotherapy. About a quarter of patients with the most common form of ovarian cancer, high-grade serous carcinoma, do not respond to treatment and die within one year of diagnosis. The remaining 70–80% of patients respond well to primary cytotoxic treatment, but they eventually develop chemoresistance, making a recurrent disease incurable. After 2007, in order to improve cytoreductive surgery, which aims to achieve the removal of the entire macroscopically visible tumour (complete cytoreduction), teams of surgeons were established in all three tertiary centres (University Medical Centre Ljubljana, University Medical Centre Maribor, Institute of Oncology Ljubljana), who are trained in both radical pelvic and upper abdominal surgery. Nevertheless, a significant proportion of patients remain for whom primary radical surgery is not possible due to comorbidities or age. There is also a proportion of patients for whom, despite the qualifications of the surgical team and the patients' relatively good general condition allowing for radical treatment, cytoreductive surgery is not possible due to the way the high-grade serous carcinoma has spread. These two groups of patients are currently treated with neoadjuvant chemotherapy followed by interval cytoreductive surgery. Between 2007 and 2016, in addition to imaging diagnostics, we began to introduce diagnostic laparoscopy for assessing the completeness of cytoreduction. Using a combination of these methods, we achieve a high rate of primary cytoreduction and offer patients the best chance of survival, while also enabling patients whose disease is inoperable to start chemotherapy early and receive interval cytoreductive surgery. The result of this strategy so far has been a longer disease recurrence-free interval with a better quality of life, though no improvement in survival has been observed.

Improvement in cytoreductive surgery through collaboration between gynaecological, oncological and visceral surgeons in tertiary centres is a major step forward in the surgical treatment of ovarian cancer, achieving a significant degree of cytoreduction and improved survival in a selected group of patients.

Erik Škof

Ovarian cancer is the second most common gynaecological cancer. It is a disease of older women (the median age of patients is 60 years). Significantly, there is no effective prevention or tools for early disease detection. As a result, in 75–80% of cases, the disease is diagnosed at a distant stage, which is the main reason why it has the worst prognosis among gynaecological cancers. In most patients, the cause of the disease is unknown. Research shows that the *BRCA 1/2* gene mutation (hereditary or somatic) is present in 20% of patients. According to our latest data, in Slovenia the *BRCA* mutation is found in more than 30% of patients with ovarian cancer. For this reason, since 2015, we have started recommending that all patients, when they are diagnosed with ovarian cancer, undergo genetic counselling and testing. Originally, for a long time, *BRCA* testing was used in breast and ovarian cancer prevention, but since 2016, it has also been used to identify patients with a high risk of the recurrence of ovarian cancer, who have a mutation in the *BRCA 1/2* gene, and would benefit from targeted drugs (PARP inhibitors). Ovarian cancer is usually treated with surgery and chemotherapy.

The incidence of ovarian cancer is slowly declining. The reason for this is not entirely known. More and more patients are being treated in tertiary oncology centres, which is in line with the recommendations, as this disease requires extensive surgery (often multivisceral resection) to ensure there is no macroscopic remnant of the tumour after the operation. This is the most important factor influencing disease prognosis. After surgery, patients are usually also treated with chemotherapy, i.e. platinum compounds and taxanes. Since 2013, those with highly advanced ovarian cancer (stage III, IV) also

receive bevacizumab, a biological drug classed as a VEGF inhibitor. Patients with a distant stage of the disease may start treatment with preoperative chemotherapy followed by delayed surgical treatment. The decision on the type of treatment and the manner in which it is to be implemented is made by a multidisciplinary council within a tertiary institution.

Despite intensive primary treatment, the survival of patients with ovarian cancer remains poor. The five-year survival of patients between 2012 and 2016 was only 40%, the worst so far. This is most likely due to an increase in the proportion of patients diagnosed with a distant stage of the disease (stage III, IV), as well as an increase in the proportion of older patients who usually have more comorbidities and are, therefore, unable to receive the aggressive treatment required to successfully manage this disease. Similarly, modest survival is recorded throughout the European Union, with the best reported in Scandinavia (around 45%), which is still far from good. We place high hopes in BRCA gene mutations testing and treatment with PARP inhibitors, which we started using in 2016 for patients with a recurrent disease, which were recently approved in the European Union for the primary treatment of BRCA-positive ovarian cancer.

References

Davidson B, Trope CG. Ovarian cancer: diagnostic, biological and prognostic aspects. Womens Health (Lond) 2014; 10: 519–33.

Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015; 136: 359–86.

Kobal B, Noventa M, Cvjetičanin B, et al. Primary debulking surgery versus primary neoadjuvant chemotherapy in high grade advanced stage ovarian cancer: comparison of survivals. Radiol Oncol 2018; 52(3): 307–319.

Sant M, ChirlaqueLopez MD, Agresti R, et al. Survival of women with cancers of breast and genital organs in Europe 1999-2007: results of the EUROCARE-5 study. Eur J Cancer 2015; 51: 2191–205.

Smrkolj Š, Logar Zobec HB, Šešek M. Rak jajčnikov: zbornik. Šola o ginekološkem raku (Ovarian cancer: the proceedings of School of gynecological cancers). Ljubljana: Association of Radiation and Oncology, Slovene Medical Association; 2016.

Strojnik K, Blatnik A, Novaković S, et al. High germline BRCA mutation detection rate among epithelial ovarian, fallopian tube and primary peritoneal cancer patients in Slovenia. In: Writzl K, Teran N, Maver A. Next generation sequencing in clinical practice: book of abstracts. Ljubljana: Slovenian Medical Association, Slovenian Association of Medical Genetics; 2017. p. 12.

Tapia G, Diaz-Padilla I. Molecular Mechanisms of Platinum Resistance in Ovarian Cancer. In: Diaz-Padilla I, eds. Ovarian Cancer - A Clinical and Translational Update. Rijeka: InTech; 2013.

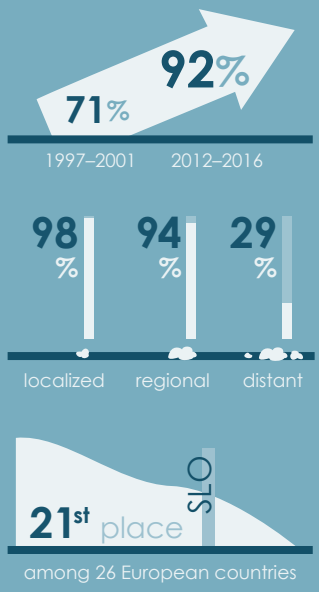
The Cancer Genome Atlas Research Network. Integrated genomic analysis of ovarian carcinoma. Nature 2011; 474: 609–15.

Zhang S, Royer R, Li S, et al. Frequencies of BRCA1 and BRCA2 mutations among 1,342 unselected patients with invasive ovarian cancer. Gynecol Oncol 2011; 121(2): 353.

Zobec Logar HB, Smrkolj Š, Merlo S, et al. Smernice za obravnavo bolnic z rakom jajčnikov, jajcevodov in s primarnim peritonealnim seroznim rakom (Guidelines for treatment of patients with cancer of the ovaries, fallopian tubes and primary peritoneal serous carcinoma). 2nd ed. Ljubljana: Association of Radiotherapy and Oncology, Slovene Medical Association, Institute of Oncology Ljubljana; 2016.

C61

PROSTATE

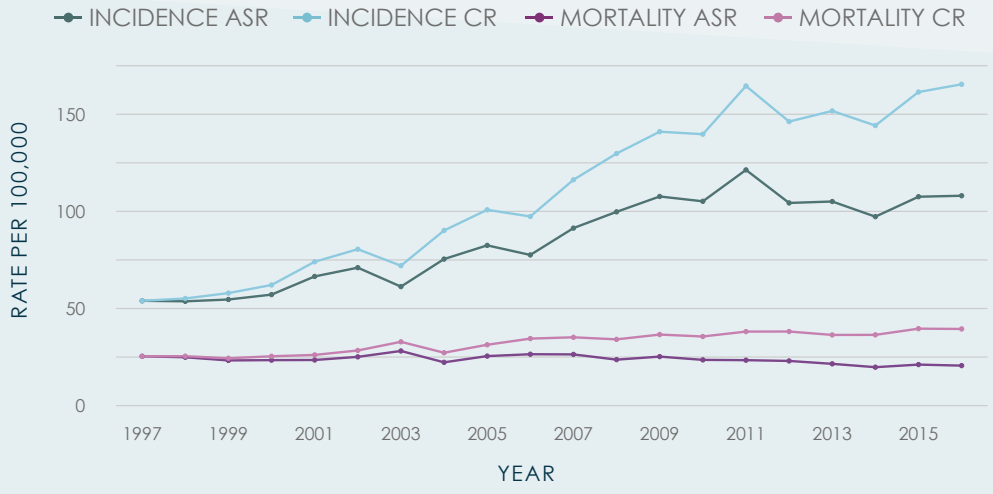


EPIDEMIOLOGY

In the last five-year period (2012–2016), 1,567 men on average were diagnosed with prostate cancer in Slovenia each year, and 388 died. As shown in Figure 1, the incidence rates of prostate cancer increased rapidly throughout the observed period. Between 2007 and 2016, the incidence rate of prostate cancer increased by 3% per year and the increase was statistically significant. About half of the increase can be attributed to the ageing of the population. The crude mortality rate of prostate cancer increased in a statistically significant way by 1.3% per year during this period. The dramatic increase in the incidence of prostate cancer is mainly due to the increasing use of the prostate-specific antigen (PSA) test in healthy men and therefore the detection of a large number of cancers that would never have led to symptomatic disease or death and would have otherwise remained undetected for life. Cancer mortality rates do not follow the same trends as the incidence rates, which also points to the overdiagnosis of prostate cancer as the cause behind the increased incidence. Data for recent years indicates that we have already reached the peak incidence of prostate cancer.

FIGURE 1

The crude (CR) and age-standardized (ASR) incidence and mortality rates of prostate cancer in Slovenia in 1997–2016.



At the end of 2016, there were 13,274 men in Slovenia who had been diagnosed with prostate cancer at some point in their lives. Of those, the diagnosis had been established less than one year ago in 1,607 men, one to four years ago in 5,103 men, and over ten years ago in 2,110 men.

The survival analysis included 21,473 cases of patients aged 20 to 94 years; 573 cases (3%) were excluded because they were diagnosed on the day of death or because they did not fulfil the age inclusion criteria.

Depending on the specific observation period, between 3–11% of patients did not have their disease confirmed microscopically; this proportion decreases with the increasing year of diagnosis. Among the microscopically confirmed cases, adenocarcinoma was the most common histological type, occurring in over 99% of cases in the last five-year period.

MEN		Age			Stage			Total
		20–49 yrs	50–74 yrs	75–94 yrs	Localized	Regional	Distant	
1997–2001		21	1918	859	1603	398	372	2798
	%	0.8	68.6	30.7	57.3	14.2	13.3	
2002–2006		32	2956	1211	2707	766	392	4199
	%	0.8	70.4	28.8	64.5	18.2	9.3	
2007–2011		79	5013	1735	4599	1550	440	6827
	%	1.2	73.4	25.4	67.4	22.7	6.4	
2012–2016		66	5592	1991	5236	1811	516	7649
	%	0.9	73.1	26.0	68.5	23.7	6.8	

TABLE 1

Number and proportion of patients with prostate cancer by age, stage and period of diagnosis in Slovenia in 1997–2016.

In all observed periods, about two-thirds of prostate cancer patients were aged 50–74 years at diagnosis and one-third were aged 75–94. Only about 1% of patients were aged 20–49 at diagnosis. The disease was most commonly diagnosed in the localized stage. Throughout the observed period, an increase in cancers diagnosed in the localized stage was observed (Table 1).

Regarding the specific primary treatment of prostate cancer between 1997 and 2016, 39% of patients were treated with surgery alone and 28% received systemic treatment alone. Eight percent of patients received surgery and systemic therapy, 6% were treated with radiotherapy and systemic therapy, while 3% received surgery, radiotherapy and systemic therapy. Throughout the five-year periods, the proportion of patients treated with surgery alone has increased (1997–2001: 25%; 2012–2016: 47%) and the proportion of patients who received systemic treatment has fallen (1997–2001: 39%; 2012–2016:

FIGURE 2

Net survival of patients with prostate cancer by period of diagnosis in Slovenia in 1997–2016.

18%). Throughout the observed period, 15% of patients did not receive specific primary treatment, the proportion of which is slowly increasing over the years (1997–2001: 10%; 2012–2016: 22%).

TABLE 2

One-, three-, and five-year observed and net survival (with a 95% confidence interval–CI) of patients with prostate cancer by period of diagnosis in 1997–2016.

MEN Survival / Period		1997–2001	(95% CI)	2002–2006	(95% CI)	2007–2011	(95% CI)	2012–2016	(95% CI)
Observed	1-year	84.8	83.5–86.1	88.1	87.1–89.1	92.4	91.8–93.0	93.8	93.2–94.3
	3-year	64.4	62.7–66.2	72.2	70.9–73.6	81.8	80.9–82.7	84.7	83.9–85.5
	5-year	52.9	51.1–54.8	62.7	61.2–64.2	73.4	72.3–74.4	77.3	76.3–78.3
Net	1-year	89.7	88.3–91.2	92.5	91.5–93.6	96.1	95.4–96.8	96.9	96.3–97.4
	3-year	76.6	74.4–78.8	84.2	82.5–85.8	91.8	90.7–92.9	93.6	92.6–94.5
	5-year	71.1	68.4–73.8	82.1	80.0–84.2	89.0	87.6–90.4	92.3	91.0–93.7

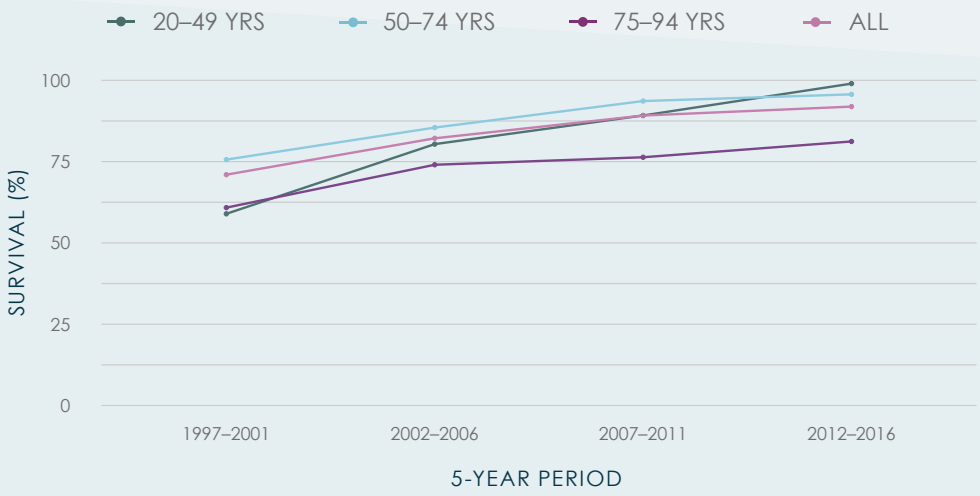
In all periods, prostate cancer surgery was performed in at least nine hospitals. In the last five-year period, most operations were performed at the Slovenj Gradec General Hospital (29%), the University Medical Centre Ljubljana (21%), the Celje General Hospital (20%), the University Medical Centre Maribor (12%), and the Nova Gorica General Hospital (6%); about 5% or fewer operations were performed at the Murska Sobota General Hospital, Novo Mesto General Hospital and Izola General Hospital. In the last five-year period, as part of their primary treatment, patients received systemic therapy in at least 12 health care institutions: most often at the Institute of Oncology Ljubljana (31%), the University Medical Centre Ljubljana (18%), and the University Medical Centre Maribor (11%); as well as 5–8% at private practices, Slovenj Gradec General Hospital, Murska Sobota General Hospital, Celje General Hospital, Novo Mesto General Hospital and Nova Gorica General Hospital; and in less than 3% at Izola General Hospital, Jesenice General Hospital, and the Golnik University Clinic.

The net survival of patients with prostate cancer has been gradually improving with an increasing year of diagnosis (Figure 2, Table 2). In the 20 years under review, the five-year net survival increased by 21 percentage points.

In Slovenia, compared to other selected cancers, prostate cancer ranks 2nd in men by five-year net survival.

FIGURE 3

Five-year net survival of patients with prostate cancer by age group in Slovenia in 1997–2016.



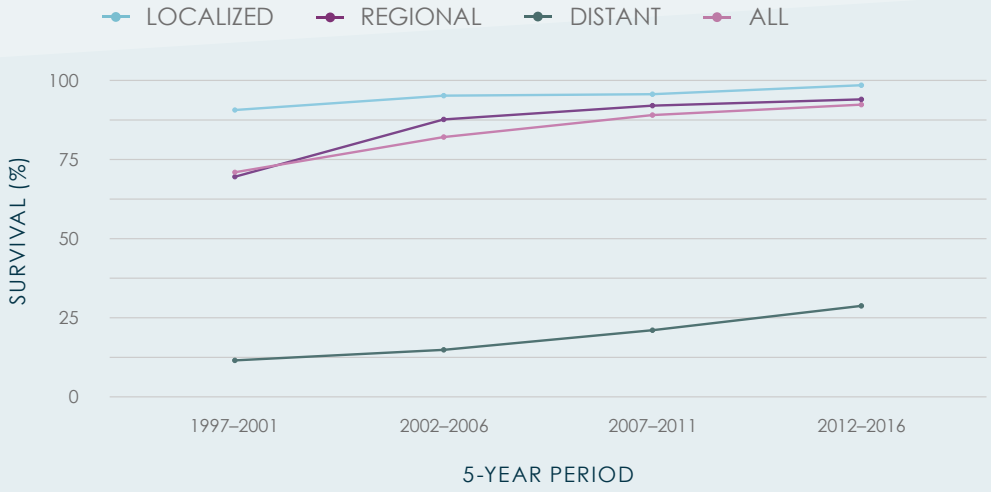


FIGURE 4

Five-year net survival of patients with prostate cancer by stage in Slovenia in 1997–2016.

Figure 3 shows the impact of age on the survival of patients with prostate cancer. In the last three observed periods, the five-year net survival was lowest in men aged 75–94 years. Over the 20-year period observed, survival improved in all age groups, most markedly in the 20–49 age group, which had the lowest survival in the 1997–2001 period with 59% and the highest in the 2012–2016 period with 99%.

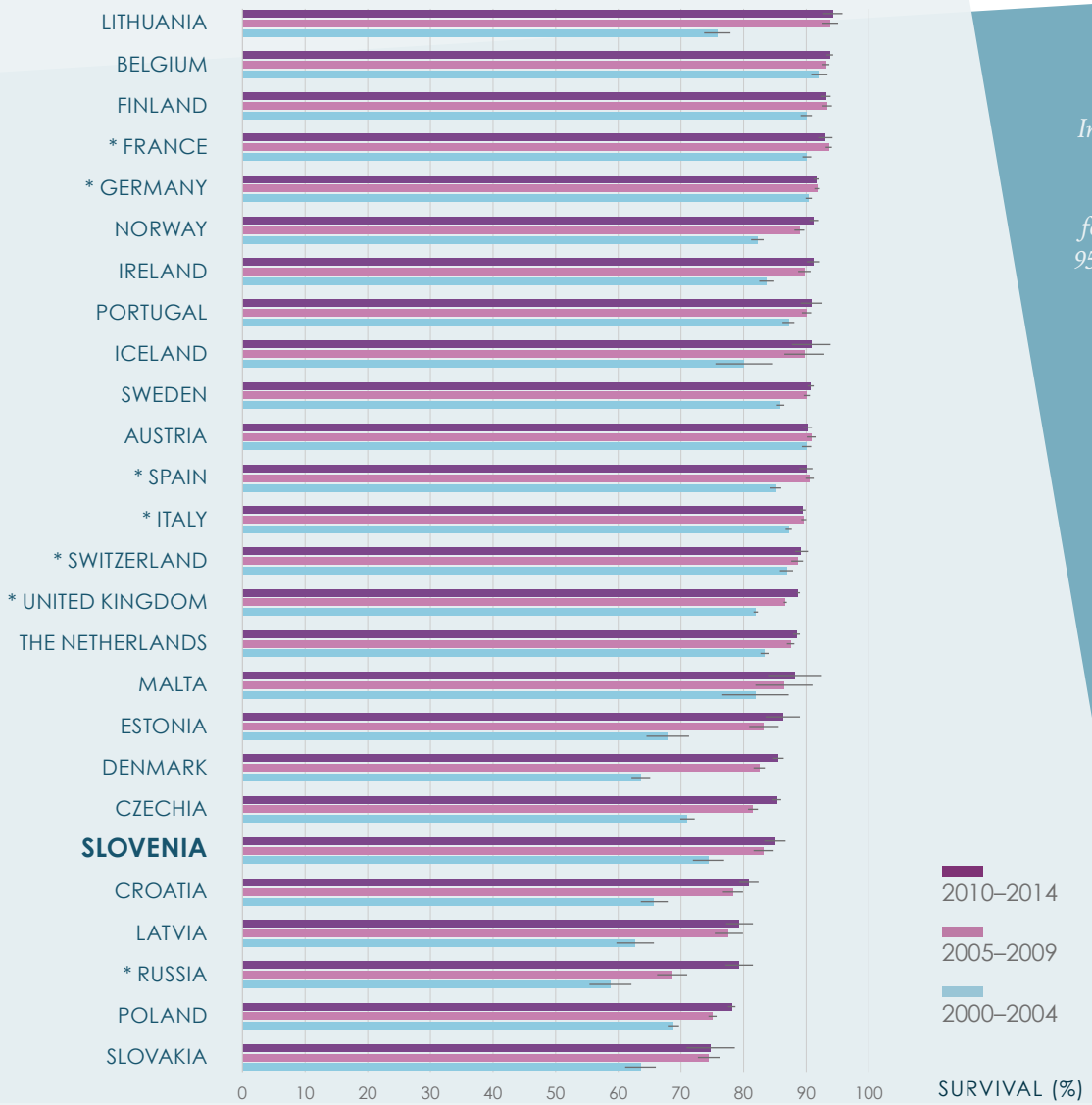


FIGURE 5

International comparison of age-standardized five-year net survival for prostate cancer (with 95% confidence intervals) in patients diagnosed during 2000–2004, 2005–2009 and 2010–2014 (CONCORD-3).

** Data doesn't cover a 100% of the country's population.*

The importance of the stage at diagnosis is shown in Figure 4. In all the observed periods, the five-year net survival of patients with the localized stage of the disease exceeded 90% and was slightly more than 98% in the last observed period. The five-year net survival of patients with the regional stage reached 94% in the last period, while it was 29% in patients with the distant stage of the disease at diagnosis. Between 1997 and 2016, the five-year net survival of prostate cancer patients has improved for all stages of the disease, most notably the regional stage.

The results of the world-wide CONCORD-3 study of patients diagnosed with cancer during the 15 years 2000–2014 in 71 countries and territories show that the five-year net survival of Slovenian prostate cancer patients has been improving (Figure 5). For patients diagnosed during the most recent period (2010–2014), Slovenia ranked 21st among the 26 participating countries in Europe.

CLINICAL COMMENTARY

Tomaž Smrkolj

In Slovenia, initial and in most cases follow-up diagnostics of prostate cancer are performed by urologists. The number of treated patients and microscopically confirmed cases of prostate cancer almost tripled between 1997–2001 and 2012–2016, due to several factors. The PSA tumour marker has been introduced into clinical practice and alerts physicians to pathological processes in the prostate, though it is not prostate cancer specific; rather, it can be an indicator for a wide range of prostatic diseases. PSA is a widely available and low-cost test, so its use is on the rise. Another factor is greater awareness on the part of the general population, which has increased through regular educational events for medical staff and laypeople. There is also a growing understanding that a significant proportion of prostate cancer has a hereditary component, which is why healthy relatives of cancer patients are increasingly undergoing preventive prostate examinations.

The proportion of prostate cancer patients who received surgery has almost doubled in the 20-year period, to almost half of all patients. This is due to the cancer being detected at an earlier stage (T1-T2) when surgery is feasible, as well as due to significant improvements in the psychophysical condition of prostate cancer patients aged over 75 years, which used to be the age limit for receiving surgical treatment 10 years ago. In the last five-year period, there have been changes in clinical practice regarding the stage of the disease when surgical treatment is still appropriate, so that surgical treatment is now increasingly performed in patients with stage T3 and even T4 disease, as well as high-risk patients with PSA levels above 20 ng/ml and a Gleason score of 8 or higher. Furthermore, radical prostate surgery is also increasingly utilized in metastatic patients in order to locally control the tumour and avoid later local complications (haematuria, hydronephrosis, urinary retention, infiltration into the rectum and pelvic floor).

The five-year survival of prostate cancer patients has increased significantly over the 20 years observed, with the largest increase (from 59% to 99%) being in the youngest age group (20 to 49 years), who also have the fewest comorbidities on average and are therefore most suitable for primary local radical (curative) treatment. The more widespread use of PSA in all groups of patients resulted in a shift in the stage at diagnosis towards the localized disease, which can be successfully managed with local treatment. This has led to the increased five-year survival in other age groups as well.

Janka Čarman

A more proactive approach for prostate cancer detection is reflected in an increase in the proportion of microscopically confirmed disease and contributes to the increasing incidence.

In recent years, the treatment of locally and/or regionally advanced prostate cancer and even metastatic prostate cancer has become increasingly aggressive. Since the advanced disease is life-threatening, we expect improvements in treatment success to be reflected in improved survival. That said, the

treatment of localized prostate cancer has no statistically significant effect on the 10-year survival of patients.

In Slovenia, the proportion of patients who, as part of their primary treatment, receive radiotherapy or a combination of radiotherapy and systemic therapy (hormone therapy) is still small. Despite modern radiotherapy techniques and excellent treatment results, the use of radiotherapy in the primary treatment of prostate cancer patients in Slovenia is much lower compared to some other European countries. One of the main reasons is that not all patients are managed by a multidisciplinary team before treatment is determined. The data shows that patients managed in this way are more likely to choose indiscriminately between the different treatment options; thus, among the patients opting for active treatment, the proportion of patients treated surgically and with radiotherapy is comparable. On the other hand, patients presented with treatment options by only one type of specialist (most often a urologist) more often opt for surgery. The treatment of prostate cancer with surgery and radiotherapy is comparable in terms of long-term survival and quality of life. Patients should be adequately informed about the treatment options, expected benefits and potential complications, and play an active role in the decision.

The proportion of patients primarily treated with systemic therapy is still (too) high in relation to the proportion of those with a primary advanced (metastatic) disease. For a localized disease, systemic treatment is not indicated.

The five-year survival of patients with prostate cancer in Slovenia is slightly lower than in some European countries. However, it is encouraging that Slovenia has improved by more than 20 percentage points over a 20-year period in terms of age-standardized five-year survival.

On average, patients with prostate cancer live long lives. Each type of treatment has possible side effects that can affect the quality of life of patients after treatment. Prostate cancer is often not life-threatening for patients, so their quality of life is extremely important. We expect that new molecular or genetic markers will allow the appropriate selection of those in need of active treatment in the first place, as well as those who need more aggressive treatment.

Boštjan Šeruga

The number of new prostate cancer cases has almost tripled in the last 20 years. Although both the crude and age-standardized incidence rates have increased markedly over time, a consistent trend is observed in the decline in the age-standardized mortality rate. The age structure of the cancer patients did not change significantly, only the proportion of patients in the age group from 50 to 74 years increased (for 5 percentage points), while at the same time, the proportion of patients in the 75 to 94 age group decreased (by 5 percentage points). Significantly, the proportion of patients with a distant stage of the disease at diagnosis decreased (13% : 7%), while the proportion of patients with a locoregional disease increased (71% : 92%), which may to some extent be the result of opportunistic screening for prostate cancer, which is certainly present in Slovenia.

According to the European Network of Cancer Registries (ENCR) in 2012, both the age-standardized incidence rate and the age-standardized mortality rate for Slovenia were higher than the EU-27 average. However, according to the results of the CONCORD-3 study, the five-year net survival of Slovenian prostate cancer patients diagnosed between 2010 and 2014 was approximately 85%, thus approaching the survival rate in Western European countries. According to the present analysis, the five-year net survival of all patients in the 2012–2016 period is 92%. Favourable trends in survival in all groups of patients are observed despite the increase in the proportion of patients who did not receive primary treatment at all (10% : 22%).

The substantially and statistically significant improved survival of patients with a distant (and regional) stage of the disease is mainly due to access to effective systemic treatments, which have been available in Slovenia in recent years. We are constantly striving for improved multidisciplinary cooperation between urologists and internist oncologists, though of course, such cooperation between urologists and oncologists can still be improved. The improved survival of patients with localized

prostate cancer may be due, at least in part, to opportunistic screening (lead-time bias) and in part to improvements in radical treatment (relating entirely to surgery), which is being provided to more patients (25% : 47%). The proportion of patients treated with radical radiotherapy was very small and did not change significantly during the period under review. With the further optimization of the radical treatment of localized prostate cancer, which primarily requires the coordinated cooperation of radiotherapists and urologists, a further improvement in the outcome of prostate cancer patients is expected. In the future, it is important that a higher proportion of patients with a locoregionally advanced disease receive multimodal treatment, which includes surgery, radiotherapy and systemic treatment.

Literatura

Allemani C, Matsuda T, Di Carlo V, et al. Global surveillance of trends in cancer survival: analysis of individual records for 37,513,025 patients diagnosed with one of 18 cancers during 2000–2014 from 322 population-based registries in 71 countries (CONCORD-3). Lancet 2018; 391: 1023–75.

European Network of Cancer Registries. Prostate cancer factsheet 2014. European Network of Cancer Registries; 2014. Available from: https://www.encr.eu/sites/default/files/factsheets/ENCR_Factsheet_Prostate_2014.pdf

Hamdy FC, Donovan JL, Athene JA, et al. 10-Year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. N Engl J Med 2016; 375: 1415–24.

Mottet N, van den Bergh VCN, Briers E, et al. EAU–ESTRO–ESUR–SIOG Guidelines on Prostate Cancer. European Association of Urology; 2019. Available from: https://uroweb.org/guideline/prostate-cancer/.

Sciarra A, Gentile V, Panebianco V. Multidisciplinary management of Prostate Cancer: how and why. Am J Clin Exp Urol 2013; 1(1): 12–7.

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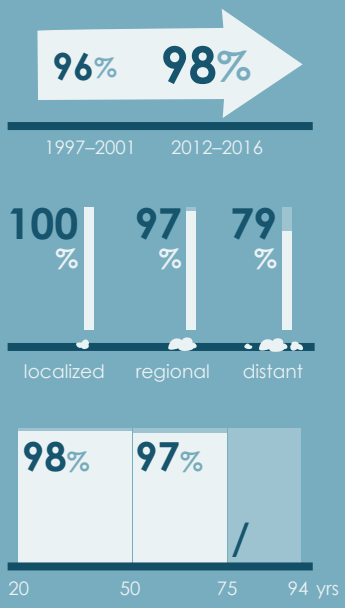
TESTIS



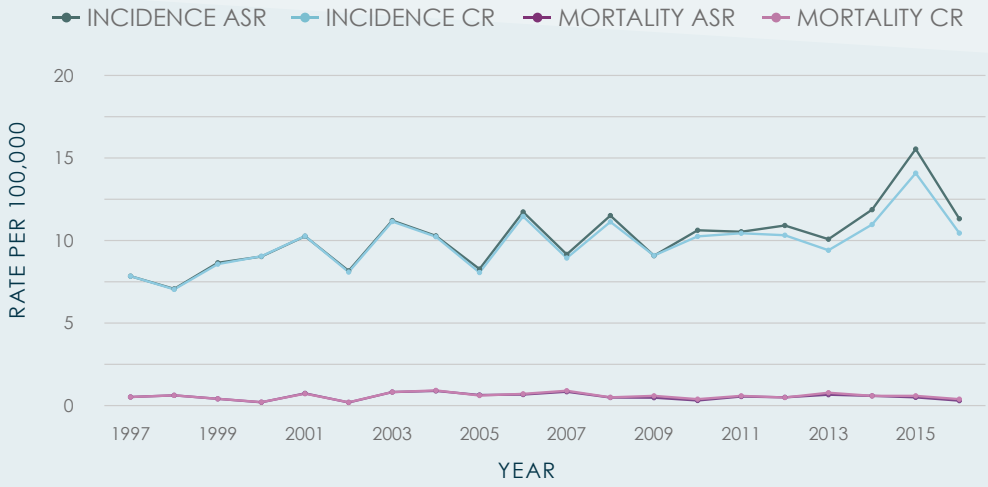
EPIDEMIOLOGY

In the last five-year period (2012–2016), 113 men on average were diagnosed with testicular cancer in Slovenia each year and 6 died. As shown in Figure 1, the incidence rates of testicular cancer increased but fluctuated considerably throughout the observed period. Between 2007–2016, the crude incidence rate of testicular cancer increased by 2.4% per year and the increase was not statistically significant. Testicular cancer mortality rates decreased during the observed period. Between 2007–2016, the crude mortality rate of testicular cancer decreased by 2.5% per year; however, the decrease was not statistically significant. Since most men get sick before the age of 50, the age-standardized rate was higher than the crude rate.

At the end of 2016, there were 2,424 men living in Slovenia who had been diagnosed with testicular cancer at some point in their lives. Of those, the diagnosis had been established less than one year ago in 108 men, one to four years ago in 445 men, and over ten years ago in 1,392 men.

FIGURE 1

The crude (CR) and age-standardized (ASR) incidence and mortality rates of testicular cancer in Slovenia in 1997–2016.



The survival analysis included 1,885 cases of patients aged 20–94; 69 cases (3.5%) were excluded because they were diagnosed on the day of death or because they did not fulfil the age inclusion criteria.

Depending on the specific observation period, the proportion of unspecified cases of testicular cancer (C62.9) increased; in the last five-year period (2012–2016), the site was unspecified in more than 97% of cases.

Only two patients did not have microscopically confirmed disease during the entire observation period. In the last five-year period, 63% of microscopically confirmed cases were seminomas, 32% were mixed germ cell tumours, and about 5% were malignant trophoblastic tumours. The proportion of seminomas increased throughout the observed period.

MEN		Age			Stage			Total
		20–49 yrs	50–74 yrs	75–94 yrs	Localized	Regional	Distant	
1997–2001		363	26	0	231	106	52	389
	%	93.3	6.7	0.0	59.4	27.3	13.4	
2002–2006		439	26	0	284	139	41	465
	%	94.4	5.6	0.0	61.1	29.9	8.8	
2007–2011		435	48	4	332	118	35	487
	%	89.3	9.9	0.8	68.2	24.2	7.2	
2012–2016		474	68	2	405	91	47	544
	%	87.1	12.5	0.4	74.5	16.7	8.6	

TABLE 1

Number and proportion of patients with testicular cancer by age, stage and period of diagnosis in Slovenia in 1997–2016.

In all observed periods, most men were diagnosed with testicular cancer between the ages of 20–49. There were only six patients aged 75–95 in the entire observed period. The disease was most commonly diagnosed in the localized stage. Throughout the 20 years under review, there was an increase in cancers diagnosed in the localized stage, as well as an increase in the number of cases in the 50–74 age group (Table 1).

Regarding the specific primary treatment of testicular cancer between 1997 and 2016, 65% of patients were treated with surgery and systemic treatment and 34% were treated with surgery alone. During the observed period, the proportion of patients who were treated with surgery alone as their primary treatment increased (1997–2001: 20%; 2012–2016: 43%), and the proportion of patients treated with a combination of surgery and systemic therapy declined. Only 0.4% of patients were without specific primary treatment across the entire period under review.

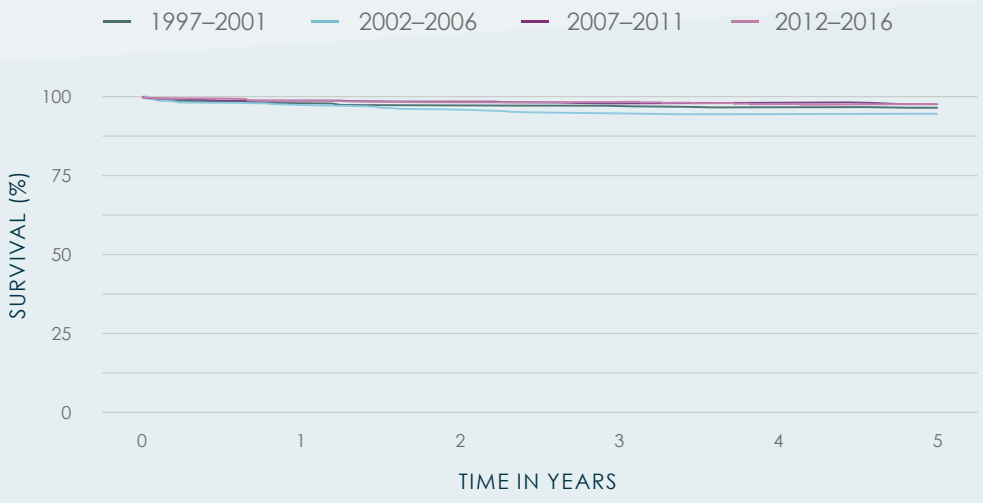


FIGURE 2

Net survival of patients with testicular cancer by period of diagnosis in Slovenia in 1997–2016.

In all periods, testicular cancer surgery was performed in at least nine hospitals. In the last five-year period, most procedures were performed at the University Medical Centre Ljubljana (50%), University Medical Centre Maribor (13%), the Celje General Hospital (11%), the Novo Mesto General Hospital (8%), the Slovenj Gradec General Hospital (7%), and about 5% or less procedures were performed in other hospitals. In the last five-year period, as part of their primary treatment, patients mostly received systemic therapy at the Institute of Oncology Ljubljana (99%).

TABLE 2

One-, three- and five-year observed and net survival (with a 95% confidence interval–CI) of patients with testicular cancer by period of diagnosis in Slovenia in 1997–2016.

MEN Survival / Period		1997–2001	(95% CI)	2002–2006	(95% CI)	2007–2011	(95% CI)	2012–2016	(95% CI)
Observed	1-year	97.7	96.2–99.2	97.2	95.7–98.7	98.6	97.5–99.6	98.5	97.5–99.6
	3-year	96.1	94.3–98.1	94.0	91.8–96.2	96.9	95.4–98.5	97.6	96.3–98.9
	5-year	94.9	92.7–97.1	93.3	91.1–95.6	96.3	94.6–98.0	96.3	94.6–97.9
Net	1-year	97.9	96.5–99.5	97.4	95.9–98.9	98.7	97.7–99.8	98.7	97.7–99.7
	3-year	97.1	95.2–99.0	94.7	92.5–96.9	97.8	96.3–99.4	98.3	97.0–99.6
	5-year	96.4	94.2–98.7	94.5	92.2–96.9	97.6	95.7–99.6	97.6	95.9–99.3

The net survival of patients with testicular cancer was consistently high in relation to the year of diagnosis (Figure 2, Table 2). In the 20 years under review, five-year net survival did not change significantly and, with the exception of the period from 2002–2006, was more than 95% (Table 2).

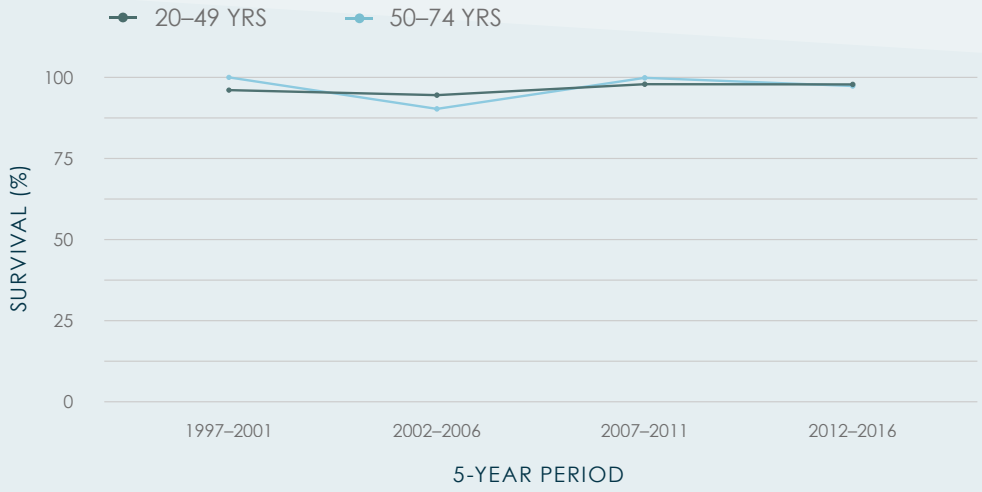
In Slovenia, compared to other selected cancers, testicular cancer ranks 1st in men by five-year net survival.

Figure 3 shows the impact of age on the survival of patients with testicular cancer. In testicular cancer age at diagnosis did not play a significant role, as the five-year net survival in both the 20–49 and 50–74 age groups was over 90% in the whole period under review, and in the last five-year period over 97% in both age groups.

The importance of stage at diagnosis is shown in Figure 4. In all observed periods, five-year net survival of patients with localized disease was more than 99%, the survival of patients with regional disease

FIGURE 3

Five-year net survival of patients with testicular cancer by age group in Slovenia in 1997–2016.



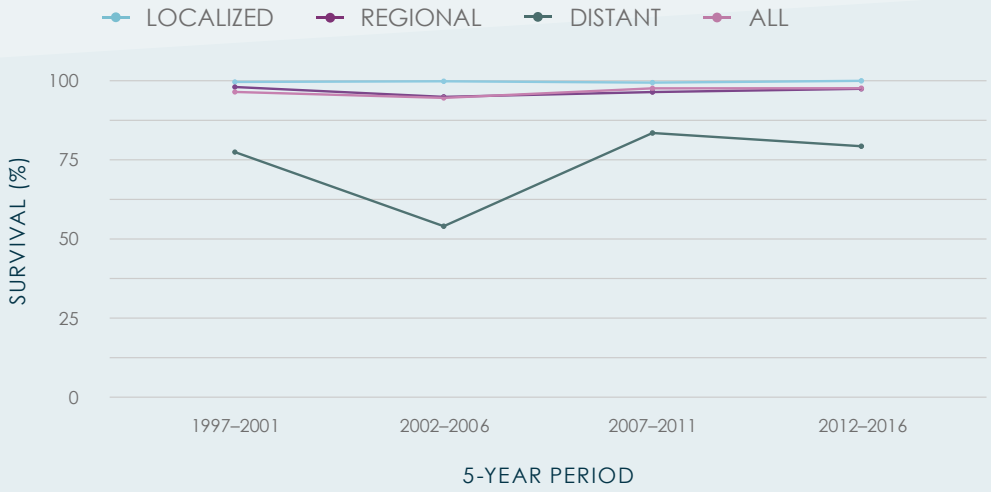


FIGURE 4

Five-year net survival of patients with testicular cancer by stage in Slovenia in 1997–2016.

was more than 95%, and in patients with distant disease at diagnosis, five-year net survival was 54–83%. The five-year net survival of patients with disseminated testicular cancer between 1997–2016 shows greater variability mainly due to the lower number of cases, while the survival trend in the localized and regional stages was relatively constant.

CLINICAL COMMENTARY

Tomaž Smrkolj

Over the 20-year period under review, the number of patients with newly diagnosed testicular cancer increased by almost 40%. The testicle is an organ that is well accessible to clinical examination, and men themselves notice pathology in the testicle, from which we conclude that the increase in the total number of patients with established testicular cancer cannot be attributed to increased awareness and promotion of self-examination. It is true, however, that men's awareness and testicular self-examination allow diagnosis in a lower stage when treatment outcomes are better. The epidemiological factors for the development of testicular cancer occur as part of testicular dysgenesis syndrome (cryptorchidism, hypospadias, decreased fertility) and are probably environmental.

The primary treatment for testicular cancer is always surgery by removing the diseased testicle for the purpose of diagnostics and to remove the primary tumour, as reflected by the data. In the entire 20-year period, only 1% of patients had non-surgical primary treatment.

It should be noted that the number of patients who undergo surgical removal of retroperitoneal lymph nodes after the completion of systemic treatment has fallen significantly in the last 15 years due to a change in doctrine.

The proportion of patients with localized disease increased from 59% to 74% over the 20-year period, resulting in a decrease in regionally advanced and metastatic disease, due to awareness-raising of the younger male population at school, in the media and by family physicians. The availability and quality of ultrasound imaging of the scrotum, which is the primary imaging examination for testicular cancer, has also significantly improved.

The extremely high five-year survival of patients with localized and regional testicular cancer has not changed over the 20-year period, reaching 95–100%. The improvement in survival in metastatic disease from 77% to 79% can be attributed to improved systemic treatment, and possibly also to more aggressive surgical treatment of metastatic deposits detected by modern imaging methods.

In the developed Western world, the incidence of testicular cancer has been on a steep rise since the Second World War, and although the growth trend has been slowing down in the last 20 years, we are still seeing constant growth. The incidence time trends of testicular cancer in Slovenia are completely comparable to other countries in the West.

Data on the specific primary treatment for patients with testicular cancer reflect the advances or changes in treatment of patients with clinical stage I, who until 2005 mostly received adjuvant treatment. Patients with seminoma received chemotherapy (carboplatin) and patients with non-seminomatous germ cell tumours were treated surgically with retroperitoneal lymphadenectomy. After the introduction of an active surveillance programme, the number of retroperitoneal lymphadenectomies decreased significantly, whereas the percentage of patients with seminoma treated with adjuvant chemotherapy (carboplatin) decreased to a lesser extent. The reason for this is that we did not have and still do not have good predictive factors for the course of the disease to decide on adjuvant treatment with carboplatin, and furthermore, adjuvant chemotherapy with carboplatin is short-term (1 outpatient administration) and is not associated with any significant adverse effects. As a rule, patients need a maximum of one month of sick leave following such treatment.

A minimal percentage of patients treated with systemic treatment alone could be attributed to primary mediastinal dysgerminomas with a good response to systemic treatment that did not require additional surgery.

The large percentage of patients who were treated with surgery and systemic treatment reflects the sum of treatments with surgical removal of testicles and adjuvant chemotherapy and the treatment of locoregionally advanced and metastatic disease, often involving a combination of surgical removal of testicles, adjuvant chemotherapy and surgery for residual lesions. The percentage of patients treated with surgery and systemic therapy decreased after 2005 due to a decrease in combination treatments in patients with clinical stage I germ cell tumours. As indicated, this is a smaller decline in treating patients with seminoma with adjuvant chemotherapy (carboplatin) and a greater decline in treating patients with non-seminomatous germ cell tumours with retroperitoneal lymphadenectomy. However, more recently, between 2012–2016, the number of patients treated with a combination of surgery and systemic therapy increased again on the account of patients with high-risk clinical stage I non-seminomatous germ cell tumours who were treated with adjuvant chemotherapy following the BEP regimen.

In the last 15 years, we have observed a trend of a slight shift in the incidence of testicular cancer towards a slightly older population. This trend is due to an increase in the incidence ratio of seminoma to non-seminomatous germ cell tumours in favour of seminoma, which usually occurs in the approximately 10 years older population of patients with testicular cancer in comparison to the patient population with non-seminomatous germ cell tumours. Above all, the proportion of patients with clinical stage I non-seminomatous germ cell tumours is increasing, which is a well-curable disease among older patients too. This is also reflected in a completely unchanged or overlapping curve of the age-standardized and crude mortality rates.

For decades, the survival of patients with non-seminomatous germ cell tumours in Slovenia has been the highest possible using existing treatment methods, as 2–3% of all patients with testicular cancer develop resistance to cisplatin chemotherapy and also die from testicular cancer. Such a high survival rate is possible because, as a small country of two million, we have had a well-established centralized approach to treatment for decades. According to the review of hospitals where primary treatment takes place, after the initial surgical treatment (orchiectomy), which takes place in urology units of nine Slovenian hospitals, all patients are referred for multidisciplinary treatment at the Institute of Oncology Ljubljana, where most of them either remain in the active surveillance programme (clinical stage I) or undergo metastatic disease treatment and surveillance through a post-treatment follow-up programme. The slight drop in survival in the 2001–2006 period, especially in patients with metastatic testicular cancer, was partly due to poorly planned and premature staff changes made in the non-seminomatous germ cell tumours treatment team at the Institute of Oncology. This is reaffirmed by the well-known fact that testicular cancer is a well-curable disease, but only if managed by a permanent and experienced multidisciplinary team specializing in the treatment of patients with testicular cancer.

References

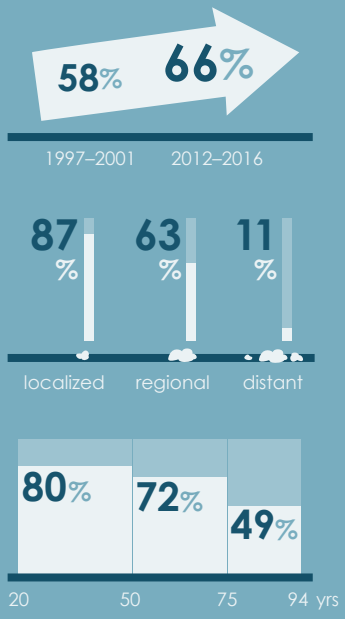
Laguna MP, Albers P, Albrecht W, et al. EAU guidelines on testicular cancer. European Association of Urology; 2019. Available from: https://uroweb.org/guideline/testicular-cancer/.

Znaor A, Lortet-Tieulent J, Jemal A, et al. International variations and trends in testicular cancer incidence and mortality. Eur Urol 2014; (6): 1095–106.

Znaor A, Lortet-Tieulent J, Jemal A, et al. International testicular cancer incidence trends: generational transitions in 38 countries 1900–1990. Cancer Causes Control 2015 (26): 151–8.

C64–C65

KIDNEY



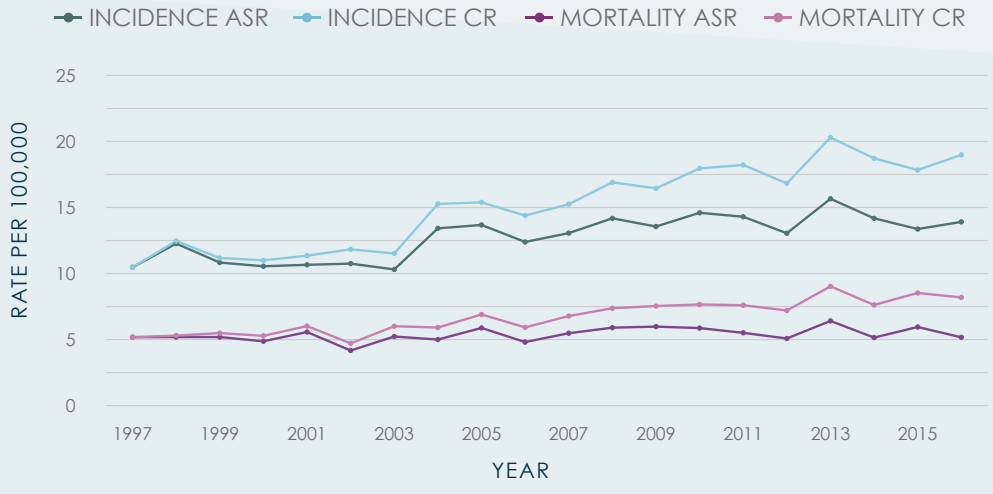
EPIDEMIOLOGY

In the last five-year period (2012–2016), 382 people on average per year were diagnosed with renal cancer in Slovenia, 247 men and 135 women, and 167 people died, 109 men and 58 women. As shown in Figure 1, renal cancer incidence rates increased throughout the observed period. Between 2007–2016, the crude incidence rate of renal cancer increased by 2% per year, by 1.6% in men and 2.6% in women. The increase is statistically significant in both sexes together as well as separately. Over half of the increase in incidence in the observed period can be attributed to population ageing. Renal cancer mortality rates are also increasing. Between 2007–2016, the crude renal cancer mortality rate increased by 1.9% per year, by 2.3% in men and by 1.1% in women. The increase is statistically significant in both sexes together.

At the end of 2016, there were 3,173 people living in Slovenia who had been diagnosed with renal cancer at some point in their lives. Of those, the diagnosis had been established less than one year ago in 320 people, one to four years ago in 937 people, and over ten years ago in 1,059 people.

FIGURE 1

The crude (CR) and age-standardized (ASR) incidence and mortality rates of renal cancer in Slovenia in 1997–2016.



The survival analysis included 5,786 cases of patients aged 20–94; 338 cases (5.5%) were excluded because they were diagnosed on the day of death, or because they did not fulfil the age inclusion criteria.

In specific observation periods, in 5–11% of cases, the disease occurred in the renal pelvis (C65), and the remaining cases of disease occurred in the kidney (C64).

Depending on the specific observation period, more than 86% of patients had microscopically confirmed disease; between 2012–2016 this was 90%. Among all microscopically confirmed cases, adenocarcinoma, which occurred in 90% of cases in the last five-year period, was the most common histological type, followed by carcinoma of the transitional epithelium (8%). In approximately 1% of cases, the carcinoma was not histologically specified.

	Sex		Age			Stage			Total
	Men	Women	20–49 yrs	50–74 yrs	75–94 yrs	Localized	Regional	Distant	
1997–2001	664	388	151	724	177	615	180	193	1052
	% 63.1	36.9	14.4	68.8	16.8	58.5	17.1	18.4	
2002–2006	841	465	157	868	281	719	251	271	1306
	% 64.4	35.6	12.0	66.5	21.5	55.1	19.2	20.8	
2007–2011	1074	548	170	1086	366	990	295	319	1622
	% 66.2	33.8	10.5	67.0	22.6	61.0	18.2	19.7	
2012–2016	1166	640	132	1150	524	1043	388	360	1806
	% 64.6	35.4	7.3	63.7	29.0	57.8	21.5	19.9	

TABLE 1

Number and proportion of patients with renal cancer by sex, age, stage and period of diagnosis in Slovenia in 1997–2016.

Throughout the 20 years under review, more men than women were diagnosed with renal cancer, the majority of patients was aged 50–74 years. Over the years, an increase in the proportion of patients aged 75–94 has been observed. The disease was most commonly diagnosed in the localized stage (Table 1).

Regarding the specific primary treatment of renal cancer in 1997–2016, over 75% of patients were treated with surgery alone, and around 3% received systemic therapy in addition to surgery. The proportion of patients without specific primary treatment was in the 11–16% range in the observed five-year periods, without a clear trend.

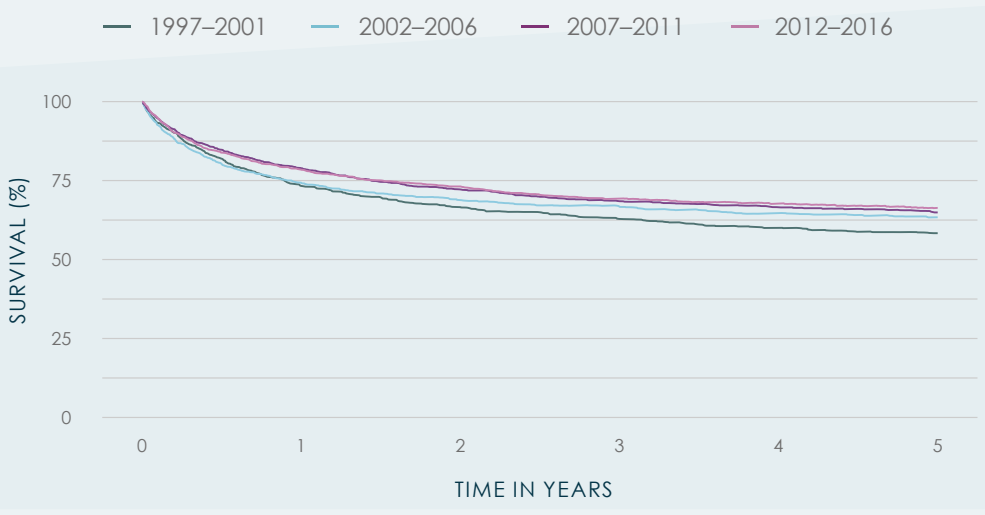


FIGURE 2

Net survival of patients with renal cancer by period of diagnosis in Slovenia in 1997–2016.

Throughout the observed period, renal cancer surgery was performed in at least nine hospitals. Most procedures were performed at the University Medical Centre Ljubljana (43%), the University Medical Centre Maribor (16%), the Slovenj Gradec General Hospital (10%), Novo Mesto General Hospital (9%), and Celje General Hospital (7%). As part of their primary treatment in the last five-year period, patients mostly received systemic treatment at the Institute of Oncology Ljubljana (over 95%).

The net survival of patients with renal cancer by year of diagnosis has been gradually increasing (Figure 2, Table 2). In the 20 years under review, five-year net survival increased by slightly less than 8 percentage points. Throughout the observed period, no major differences were observed between the sexes in the five-year net survival of patients with renal cancer (Table 2).

TABLE 2

One-, three- and five-year observed and net survival (with a 95% confidence interval–CI) of patients with renal cancer by sex and period of diagnosis in Slovenia in 1997–2016.

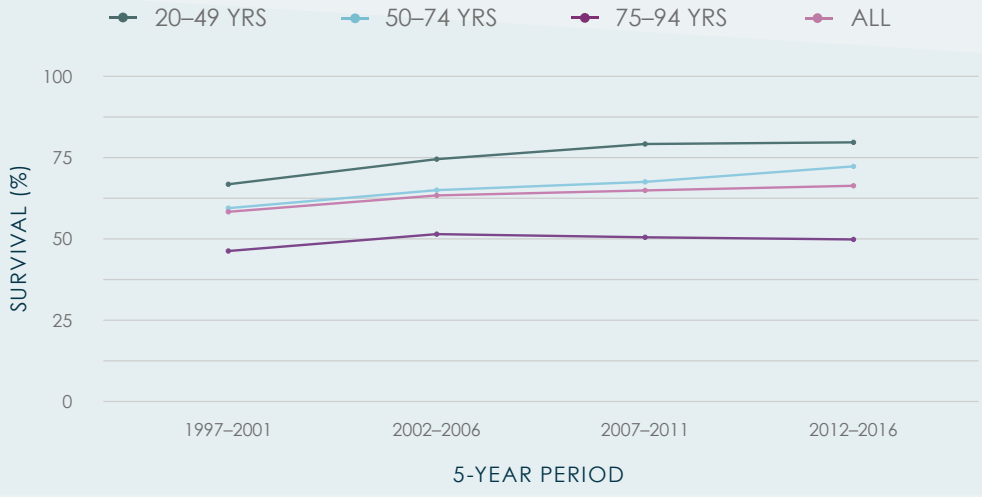
Survival / Period			1997–2001	(95% CI)	2002–2006	(95% CI)	2007–2011	(95% CI)	2012–2016	(95% CI)
Observed	1-year	all	71.4	68.7–74.2	72.3	69.9–74.7	77.0	75.0–79.1	76.5	74.6–78.5
		men	70.3	66.9–73.9	71.9	68.9–75.0	79.3	76.9–81.8	76.5	74.1–79.0
		women	73.2	68.9–77.7	72.9	69.0–77.1	72.5	68.8–76.3	76.5	73.3–79.9
	3-year	all	57.9	55.0–60.9	61.1	58.5–63.8	63.8	61.5–66.2	64.4	62.2–66.7
		men	56.1	52.5–60.0	60.1	56.9–63.5	65.9	63.1–68.8	63.4	60.7–66.3
		women	60.8	56.2–65.9	62.8	58.6–67.4	59.7	55.7–63.9	66.2	62.6–70.0
	5-year	all	50.6	47.7–53.7	54.4	51.8–57.2	57.4	55.0–59.8	58.0	55.7–60.5
		men	48.1	44.5–52.1	53.5	50.2–56.9	58.8	55.9–61.8	56.2	53.3–59.3
		women	54.9	50.2–60.1	56.1	51.8–60.8	54.6	50.6–58.9	61.4	57.6–65.4
Net	1-year	all	73.4	70.6–76.2	74.3	71.8–76.9	78.9	76.8–81.0	78.5	76.5–80.5
		men	72.5	69.0–76.2	74.2	71.1–77.4	81.4	78.9–83.9	78.5	76.1–81.1
		women	74.8	70.4–79.5	74.4	70.4–78.7	74.0	70.2–77.9	78.3	75.0–81.8
	3-year	all	62.9	59.7–66.3	66.8	63.9–69.8	68.5	66.0–71.1	69.3	66.9–71.8
		men	61.7	57.6–66.0	66.3	62.7–70.1	71.0	68.0–74.2	68.6	65.6–71.7
		women	64.9	59.8–70.3	67.5	62.9–72.5	63.5	59.2–68.1	70.7	66.7–74.9
	5-year	all	58.4	54.9–62.1	63.4	60.2–66.8	64.8	62.0–67.7	66.2	63.4–69.2
		men	56.5	52.1–61.3	63.0	58.9–67.3	66.9	63.5–70.4	64.6	61.1–68.3
		women	61.4	56.0–67.4	64.0	58.9–69.6	60.6	56.0–65.7	69.3	64.8–74.1

In Slovenia, compared to other selected cancers, renal cancer is ranked 8th in men and 6th in women by five-year net survival.

Figure 3 shows the impact of age on the survival of patients with renal cancer. Five-year net survival was highest in all observed periods in people aged 20–49 at diagnosis and lowest in people aged

FIGURE 3

Five-year net survival of patients with renal cancer by age group in Slovenia in 1997–2016.



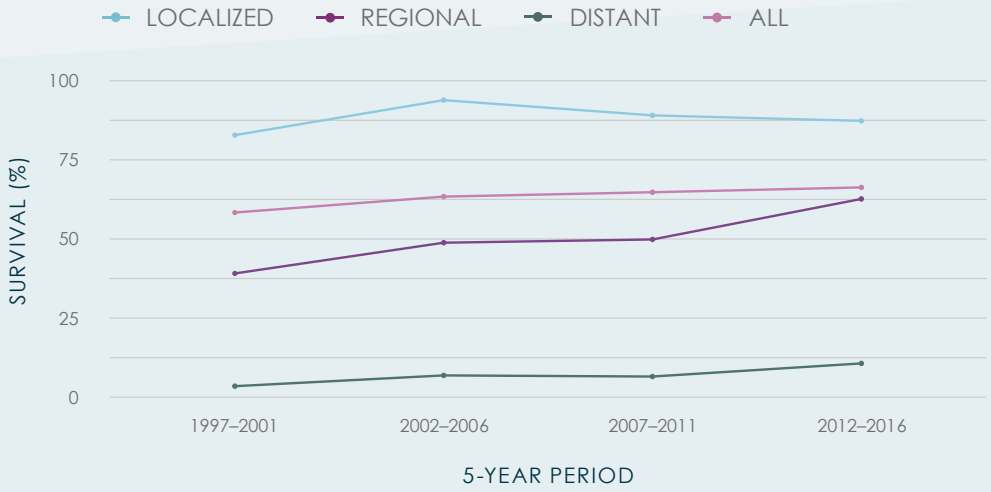


FIGURE 4

Five-year net survival of patients with renal cancer by stage in Slovenia in 1997–2016.

75–94. Over the period under review, five-year net survival improved in the 20–49 and 50–74 age groups. In the 50–74 age group, the difference between the first observed period (1997–2001) and the last (2012–2016) was almost 13 percentage points and is statistically significant (Figure 3).

The importance of stage at diagnosis is shown in Figure 4. The five-year net survival of patients with localized disease was 87% in the last five-year period, but stagnated in the 20 years under review. In the observed period, the survival of patients with regional disease improved the most. Even in patients with distant disease, an improvement in net survival is seen in the observed period, but this is still relatively low, amounting to just over 10% in the last five-year period.

CLINICAL COMMENTARY

Tomaž Smrkolj

The gender ratio of patients with renal cancer remained the same throughout the 20-year period, at around 1.8 male to 1 female, with the gap attributed to risk factors, namely smoking, hypertension, excessive alcohol consumption and being overweight.

The number of renal cancer patients has increased by about 70% in 20 years, which is due to longer life expectancy of population together with much greater availability of abdominal imaging, the most important types of which are ultrasound and computerized tomography of the abdomen. More than half of new cases of renal cancer are found by chance in imaging examinations of the abdominal organs performed on the patient on suspicion of other diseases of the abdomen or due to non-specific problems. Renal tumours are thus detected at an earlier stage and are smaller. The classic triad of characteristic symptoms (haematuria, lumbar pain, and palpable tumour) is uncommon and is found only in 6–10% of patients at diagnosis.

Unfortunately, the earlier detection of renal cancer is not currently reflected in lower mortality, as the age-standardized mortality rate has not changed in 20 years, neither in Slovenia nor in the European Union. In some countries of the European Union, mortality is even rising slightly.

Overall five-year survival increased slightly in the 20 years under review (from 58% to 66%), which nevertheless indicates improved effectiveness of treatment, both earlier surgery and the introduction of modern systemic therapy.

Depending on the stage of the disease at the time of diagnosis, five-year survival in regional disease increased markedly (from 39% to 63%), indicating a synergistic effect of radical surgical treatment of advanced stages with lymph node removal and systemic therapy. Five-year survival in localized renal

cancer is high (87%), but it increased much less in 20 years under review, namely by 4 percentage points. Five-year survival is much higher in younger patients (80%), while patients aged 75–94 achieve a 49% five-year survival. This can be attributed to impaired renal function due to age, and to other comorbidities in which serious complications occur earlier as part of renal failure.

Janka Čarman

The role of radiotherapy in renal cancer is limited to advanced disease. With modern stereotactic techniques, we are able to achieve excellent local control (especially of brain or bone metastases), reduce problems and improve quality of life, but without a significant effect on survival.

Boštjan Šeruga

The number of new cases of renal cancer has increased by 70% in the last 20 years, largely as a result of population ageing, but also in part due to improvements in diagnostics and changing prevalence of risk factors associated with the development of renal cancer. While the age-standardized incidence rate increased slightly during this time, the age-standardized mortality rate in Slovenia remained stable. Over the period under review, the proportion of patients aged 75–94 increased more markedly, and the proportion of younger patients with renal cancer decreased slightly. In the observed period, the proportion of patients with regional and distant disease at the time of diagnosis was 17–21% and 18–21%, respectively. Older people with renal and also other cancers, who will represent the majority of all cancer patients in Slovenia in the future, require special treatment considerations, which is why geriatric oncology should be systematically introduced into the National Cancer Control Programme.

The proportion of patients treated with surgery in Slovenia is higher (80%) than in the United Kingdom (56%), therefore, other factors that could be leading to a worse outcome of the disease should be considered, such as inadequate or delayed appropriate diagnostic procedures or initiation of treatment. Primary prevention of renal cancer should remain one of the priorities in Slovenia. The five-year net survival of all patients with renal cancer improved gradually but significantly over the period under review (from 58% to 66%), most markedly in patients with regional and distant disease, which may reflect the effect of better surgical treatment and systemic treatment with targeted therapy.

In the overall patient population, five-year net survival improved most markedly in patients in the 20–74 age group, but not in patients aged 75–94. For a more accurate interpretation, treatments and outcomes in older patients with renal cancer would need to be analysed in more detail. In the future, immunotherapy, which we recently introduced into practice, will also have an important impact on the outcomes of renal cancer treatment.

References

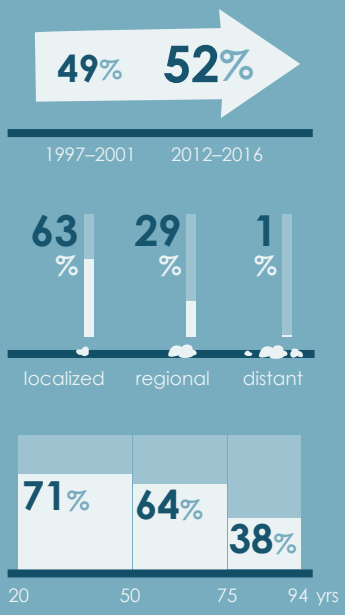
Cancer Research UK. Kidney cancer. London: Cancer Research UK; 2019. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/kidney-cancer

European Network of Cancer Registries. Kidney cancer factsheet. European Network of Cancer Registries; 2017. Available from: https://www.encr.eu/sites/default/files/factsheets/ENCR_Factsheet_Kidney_2017.pdf

Ljungberg B, Albiges L, Bensalah K, et al. EAU Guidelines on renal cell carcinoma. European Association of Urology; 2019. Available from: https://uroweb.org/guideline/renal-cell-carcinoma/

C67

BLADDER



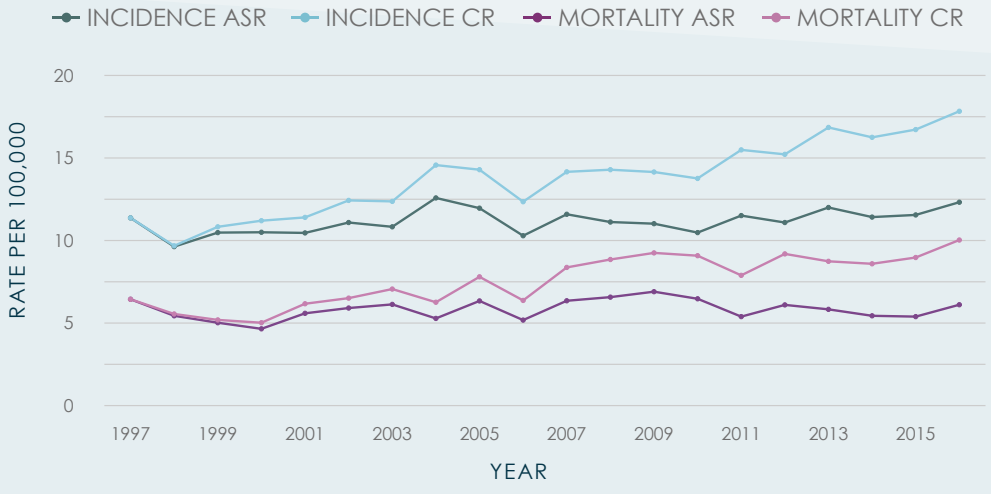
EPIDEMIOLOGY

In the last five-year period (2012–2016), 341 people per year on average were diagnosed with bladder cancer in Slovenia, 248 men and 93 women, and 188 people died, 131 men and 57 women. As shown in Figure 1, incidence of bladder cancer increased throughout the observed period. Between 2007–2016, the crude incidence rate of bladder cancer increased by 2.7% per year, by 2.6% in men and by 2.9% in women. The increase is statistically significant in both sexes combined and in each sex individually. The increase in the incidence rates can mostly be attributed to population ageing (over 80%). Bladder cancer mortality rates are also rising. Between 2007 and 2016, the crude mortality rate of bladder cancer increased by 0.8% per year, by 0.5% in men and by 2% in women. The increase is not statistically significant.

At the end of 2016, there were 2,013 people in Slovenia who had been diagnosed with bladder cancer at some point in their lives. Of those, the diagnosis had been established less than one year ago in 305 people, one to four years ago in 680 people, and over ten years ago in 549 people.

FIGURE 1

The crude (CR) and age-standardized (ASR) incidence and mortality rates of bladder cancer in Slovenia in 1997–2016.



The survival analysis included 5,429 cases of patients aged 20–94; 127 cases (2.3%) were excluded because they were diagnosed on the day of death, or because they did not fulfil the age inclusion criteria.

In the 20 years under review, 84–96% of cases did not have a specific site of onset reported (C67.9). The proportion of unspecified cases of bladder cancer increased by 13 percentage points in the last five-year period (2012–2016) compared to the 1997–2001 period.

Depending on the individual observation period, up to 5% of patients did not have microscopically confirmed disease. Of all microscopically confirmed cases, carcinoma of the transitional epithelium, which occurred in 94% of cases in the last five-year period, was the most common histological type. In 3% of cases, the carcinoma was not histologically defined.

	Sex		Age			Stage			Total
	Men	Women	20–49 yrs	50–74 yrs	75–94 yrs	Localized	Regional	Distant	
1997–2001	797	243	54	679	307	755	190	55	1040
	% 76.6	23.4	5.2	65.3	29.5	72.6	18.3	5.3	
2002–2006	948	341	52	789	448	946	221	72	1289
	% 73.6	26.5	4.0	61.2	34.8	73.4	17.2	5.6	
2007–2011	1048	383	47	771	613	1041	253	105	1431
	% 73.2	26.8	3.3	53.9	42.8	72.8	17.7	7.3	
2012–2016	1218	451	51	864	754	1266	281	106	1669
	% 73.0	27.0	3.1	51.8	45.2	75.9	16.8	6.4	

TABLE 1

Number and proportion of patients with bladder cancer by sex, age, stage and period of diagnosis in Slovenia in 1997–2016.

Throughout the observed period, significantly more men (over 70%) than women were diagnosed with bladder cancer. The largest proportion of patients was aged from 50–74 at diagnosis. In the period under review, there was an increase in cases in older age; in the oldest age group (75–94 years) the proportion increased by 16 percentage points over the 20 years. The disease was most often diagnosed in the localized stage (Table 1).

Regarding the specific primary treatment of bladder cancer between 1997–2016, 71% of patients were treated with surgery alone, about 10% received systemic treatment in addition to surgery, and about 5% received radiotherapy in addition to surgery. Across the entire period under review, 8% of patients did not receive a specific primary treatment; the proportion of patients who did not receive a specific primary treatment slightly increased over the 20 years under review.

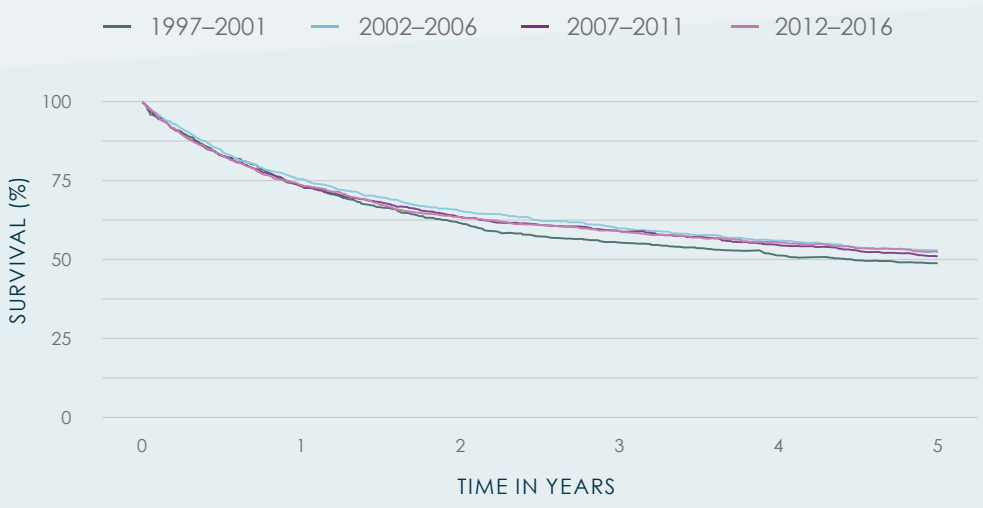


FIGURE 2

Net survival of patients with bladder cancer by period of diagnosis in Slovenia in 1997–2016.

In all periods, bladder cancer surgery was performed in at least eight hospitals. In the las five-year period, most procedures were performed at the University Medical Centre Ljubljana (51%), University Medical Centre Maribor (17%), Novo Mesto General Hospital (8%), Slovenj Gradec General Hospital and Celje General Hospital (7%) and less than 5% elsewhere. As part of primary treatment in the last five-year period, patients received systemic treatment at the Institute of Oncology Ljubljana (79%), at the University Medical Centre Ljubljana (9%), and approximately 5% at Murska Sobota General Hospital and Slovenj Gradec General Hospital.

TABLE 2

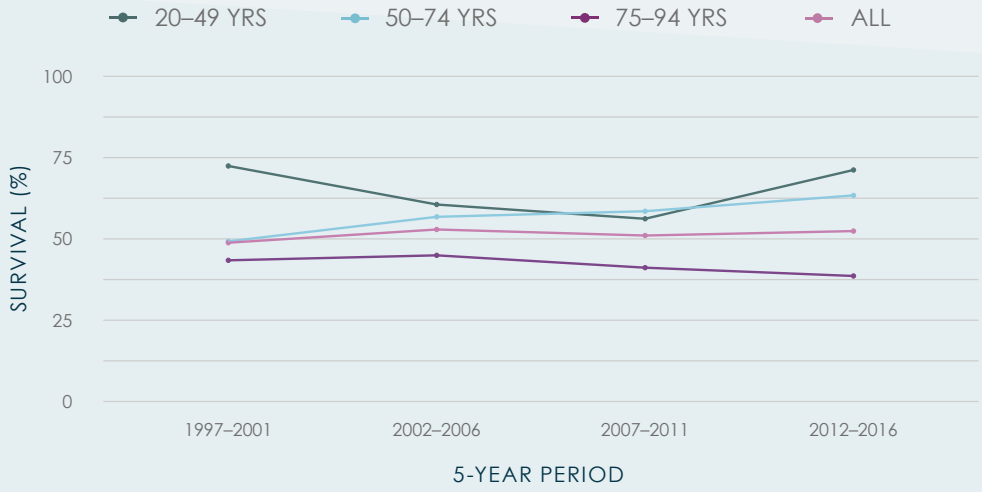
One-, three-, and five-year observed and net survival (with a 95% confidence interval – CI) of patients with bladder cancer by sex and period of diagnosis in Slovenia in 1997–2016.

Survival / Period			1997–2001	(95% CI)	2002–2006	(95% CI)	2007–2011	(95% CI)	2012–2016	(95% CI)
Observed	1-year	all	70.3	67.6–73.1	72.0	69.6–74.5	70.1	67.8–72.5	70.4	68.2–72.6
		men	70.4	67.3–73.6	73.4	70.7–76.3	73.0	70.4–75.7	71.5	69.0–74.1
		women	70.0	64.4–76.0	68.0	63.3–73.2	62.1	57.5–67.2	67.4	63.2–71.9
	3-year	all	48.5	45.6–51.7	51.8	49.1–54.6	51.4	48.9–54.1	51.7	49.4–54.2
		men	48.0	44.7–51.6	53.5	50.4–56.8	54.7	51.7–57.8	53.4	50.6–56.2
		women	50.2	44.3–56.9	46.9	41.9–52.5	42.6	37.9–47.8	47.4	43.0–52.2
	5-year	all	38.2	35.4–41.3	41.3	38.7–44.1	40.6	38.2–43.3	42.3	39.8–44.9
		men	37.2	34.0–40.7	42.2	39.2–45.5	43.4	40.5–46.5	44.2	41.3–47.3
		women	41.6	35.8–48.3	38.7	33.9–44.2	33.2	28.8–38.2	37.1	32.5–42.2
Net	1-year	all	73.7	70.8–76.7	75.4	72.9–78.0	73.4	70.9–75.9	73.4	71.1–75.8
		men	74.0	70.7–77.4	77.0	74.1–80.1	76.6	73.8–79.5	74.8	72.1–77.5
		women	72.8	67.0–79.0	70.9	65.9–76.3	64.5	59.6–69.8	69.8	65.4–74.5
	3-year	all	55.6	52.2–59.3	59.9	56.7–63.3	59.1	56.1–62.2	59.0	56.2–61.9
		men	55.4	51.4–59.7	62.3	58.6–66.3	63.4	59.9–67.1	61.3	58.1–64.7
		women	55.5	48.8–63.0	53.1	47.2–59.7	47.2	41.9–53.1	52.8	47.8–58.3
	5-year	all	49.0	45.2–53.1	52.9	49.2–56.9	51.0	47.7–54.6	52.4	49.0–56.0
		men	48.5	44.1–53.2	54.2	49.8–59.0	55.4	51.4–59.7	55.3	51.3–59.6
		women	50.5	42.9–59.4	49.1	42.5–56.7	39.1	33.6–45.4	44.4	38.4–51.3

The net survival of bladder cancer patients did not change significantly in relation to the year of diagnosis (Figure 2, Table 2). During the 20 years observed, five-year net survival was approximately 50%. Across the whole period under review, five-year net survival of bladder cancer improved in men and slightly worsened in women, but the changes were not statistically significant. Between 2012–2016, survival was 11 percentage points lower in women than in men, which was statistically significant (Table 2).

FIGURE 3

Five-year net survival of patients with bladder cancer by age group in Slovenia in 1997–2016.



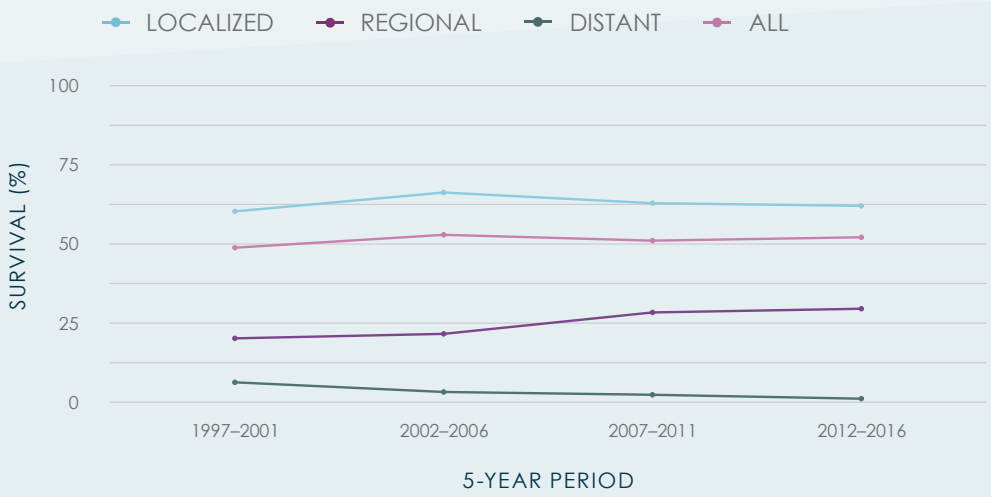


FIGURE 4

Five-year net survival of patients with bladder cancer by stage in Slovenia in 1997–2016.

In Slovenia, compared to other selected cancers, bladder cancer is ranked 12th in men and 15th in women by five-year net survival.

Figure 3 shows the impact of age on the survival of bladder cancer patients. In the whole period, net survival is lowest in people aged 75–94 (about 40%). Survival in this age group declined slightly, by 5 percentage points, over the 20-year period. Survival at diagnosis in people aged 20–49 decreased between 2002–2006 and 2007–2011, to the level of survival in the 50–74 age group (at approximately 58%). In the last five-year period, however, it rose again in the youngest age group and was the highest (71%). Due to the small number of cases between 1997–2016, the time trend of five-year net survival of patients aged 20–49 indicates higher variability between five-year periods, but the differences in survival were not statistically significant. Five-year net survival in the 50–74 age group improved constantly in the whole period under review and was a statistically significant 14 percentage points higher in the 2012–2016 period compared to the first five-year period.

The importance of stage at diagnosis is shown in Figure 4. The five-year net survival of patients in a localized stage did not change significantly across the observed period and was about 63%. The five--year net survival of patients with regional disease improved slightly, reaching 29% in the last five-ye-ar period, whereas in patients with distant disease at diagnosis, it deteriorated through the observed periods and was only about 1% in the last five-year period.

CLINICAL COMMENTARY

Tomaž Smrkolj

The age-standardized incidence rate of bladder cancer did not change between 1997–2016, which can be explained by the fact that, in addition to increased life expectancy, other factors (smoking, exposure to aromatic amines in the workplace) that affect the development of bladder cancer, in Slovenia did not change significantly.

The primary treatment for bladder cancer is transurethral resection of bladder tumour and is at the same time a diagnostic—for pathohistological determination of the tumour grade and stage—and a therapeutic method in non-muscle invasive bladder cancer. About 75% of all bladder tumours at di-agnosis fall into this category. Thus, the proportions of various specific primary treatment methods have changed only slightly in 20 years; in Slovenia, surgery was the primary treatment method in around 90% of cases.

The proportion of localized bladder cancer increased from 73% to 76% in the 20 years under review, the proportion of regional cancer decreased by two percentage points, and the proportion of metastatic cancer increased by one percentage point. However, this was not reflected in the overall five-year survival of patients, which ranged from 49–52%. A growth in five-year survival was observed in patients with regional disease, which is attributed to the use of systemic treatment and the introduction of extensive surgical removal of pelvic lymph nodes, whereas in localized bladder cancer five-year survival has not changed. Of concern is the fact that over the 20 years under review, the five-year survival rate of women with bladder cancer has decreased in absolute terms and compared to men, with a difference of more than five percentage points. How much of these results can be attributed to factors related to the organization of the Slovenian healthcare system? Results from the study "Early diagnosis of malignant neoplasms of the urinary tract in Slovenia – status report and proposal of future measures", which was carried out under the auspices of the Slovenian Cancer Registry, will further elucidate these issues.

Janka Čarman

Survival of bladder cancer patients has not changed significantly in the last 20 years, despite advances in treatments in all areas.

In urothelial bladder cancer, research suggests the importance of determining four different molecular types: basal and luminal type, each with two subtypes, showing different levels of sensitivity or resistance to chemotherapy. We expect that additional research will establish the role of various predictive and prognostic markers, which will allow for the selection of an appropriate treatment.

The proportion of Slovenian patients receiving conserving treatment (a combination of radiotherapy, surgery and systemic therapy) is small. We hope that, on the basis of molecular or genetic markers in the future, we will be able to more reliably select patients in whom we will be able to keep their bladder and thus provide a higher quality of life with the same treatment outcome. Today, radiotherapy is mostly used to treat patients who are not suitable for cystectomy.

Muscle invasive bladder cancer occurs less frequently in women than in men, but with more advanced stages and poorer survival than in men. Among the presumed reasons for this is the longer time lag from the onset of problems to the appropriate diagnosis in women (with a broader differential diagnosis); the impact of the differences between oestrogens and androgens between the sexes is also being studied.

Boštjan Šeruga

The number of new bladder cancer cases has increased by approximately 60% in the last 20 years. The age structure of bladder cancer patients has also changed significantly over that period. The proportion of patients aged 75–94 at diagnosis has gradually increased, reaching 45% in the last five-year period. Older people with bladder cancer, as well as those with other cancers, who will account for the majority of all cancer patients in Slovenia in the future, require special treatment. Therefore, geriatric oncology should be systematically introduced into the National Cancer Control Programme in Slovenia.

While according to the data of the European Network of Cancer Registries (ENCR) for 2012 the age-standardized incidence rate for Slovenia is lower than the average for the EU 27, but the age-standardized mortality of bladder cancer patients in Slovenia is higher than the European average. The distribution of patients by stages in Slovenia did not change significantly over the 20 years under review; the proportion of patients with regional and distant disease was 23–25%. According to Cancer Research UK, which, like the Slovenian Cancer Registry, manages and reports data for invasive bladder cancer (C67), the proportion of patients with metastases at diagnosis in the United Kingdom between 2012–2014 was 17–20%. In Slovenia, postponed or late diagnosis and treatment of bladder cancer could be the cause of a slightly higher proportion of patients with advanced bladder cancer at diagnosis and, consequently, a worse outcome of the disease. Five-year net survival for all patients improved only slightly over the observed period (from 49% to 52%), most notably on account of patients with regional disease.

The overall proportion of patients receiving chemotherapy after diagnosis was around 15% and is stable throughout the observed periods. It is not possible to determine exactly how many of these patients actually received perioperative chemotherapy, but this proportion is certainly lower than reported in the literature. An important reason for this is undoubtedly the marked increase in the proportion of older people with bladder cancer who are not suitable for this type of treatment. In any case, further efforts will be needed to upgrade interdisciplinary cooperation between oncologists and urologists in Slovenia. As expected, five-year net survival for patients with advanced bladder cancer did not improve, as no other, more effective systemic treatments were available for this disease during the analysed time periods other than chemotherapy.

References

Babjuk M, Burger M, Compérat E, et al. EAU Guidelines on non-muscle-invasive bladder cancer. European Association of Urology; 2019. Available from https://uroweb.org/guideline/non-muscle-invasive-bladder-cancer/

Cancer Research UK. Bladder cancer. Cancer Research UK; 2019. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bladder-cancer/incidence

Cohn JA, Vekhter B, Lyttle C, et al. Sex disparties in diagnosis of bladder cancer after initial presentation with hematuria: a nationwide claims-based investigation. Cancer 2014; 120 (4): 555–61.

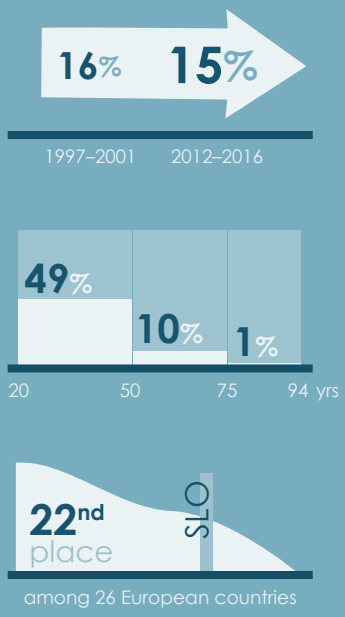
European Network of Cancer Registries. Bladder cancer factsheet 2016. European Network of Cancer Registries; 2016. Available from: https://www.encr.eu/sites/default/files/factsheets/ENCR_Factcheet_Bladder_Cancer_2016.pdf.

Macleod LC, Yabes JG, Yu M, et al. Trends and appropriateness of perioperative chemotherapy for muscle-invasive bladder cancer. Urol Oncol 2019; 37:462–9.

Witjes JA, Bruins M, Cathomas R, et al. EAU Guidelines on muscle-invasive and metastatic bladder cancer. European Association of Urology; 2019. https://uroweb.org/guideline/non-muscle-invasive-bladder-cancer-muscle-invasive-and-metastatic/.

C70–C72

BRAIN

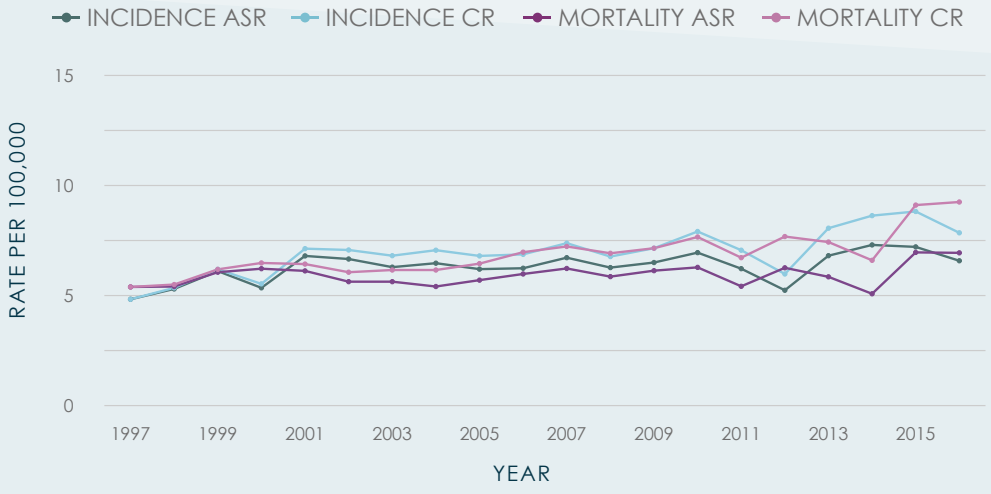


EPIDEMIOLOGY

In the last five-year period (2012–2016), 162 people per year on average were diagnosed with a malignant neoplasm of the brain (i.e. ICD-10 sections: Malignant neoplasms of meninges, brain, spinal cord, cranial nerves and other parts of central nervous system) in Slovenia,93 men and 69 women, and 165 people died, 86 men and 79 women. As shown in Figure 1, the incidence rate of this cancer did not change significantly during the observed period. Between 2007–2016, the crude incidence rate of malignant neoplasm of the brain increased by 2% per year; in men it increased by 2.8%, whereas in women it increased by 0.9% per year, but the increase was not statistically significant. The mortality rate of malignant neoplasm of brain shows more variability. For both sexes combined, the crude mortality rate increased by 2.4% per year between 2007–2016, but not statistically significantly. For men, a decrease of 3% per year was initially observed between 2007–2014, and a notable increase (31% per year) from 2014–2016, but none of the changes were statistically significant. In women, the crude mortality rate of malignant neoplasm of the brain increased by 3.3% per year between 2007–2016, which is a statistically significant increase.

FIGURE 1

The crude (CR) and age-standardized (ASR) incidence and mortality rates of malignant neoplasm of the brain in Slovenia in 1997–2016.



At the end of 2016, there were 759 people in Slovenia who had been diagnosed with a malignant neoplasm of the brain at some point in their lives. Of those, the diagnosis had been established less than one year ago in 108 people, one to four years ago in 173 people, and over ten years ago in 339 people.

The survival analysis included 2,560 cases of patients aged 20–94; 258 cases (9%) were excluded because they were diagnosed on the day of death, or because they did not fulfil the age inclusion criteria.

	Sex		Age			Stage			Total
	Men	Women	20–49 yrs	50–74 yrs	75–94 yrs	Localized	Regional	Distant	
1997–2001	290	224	165	307	42	502	6	2	514
1997–2001 %	56.4	43.6	32.1	59.7	8.2	97.7	1.2	0.4	
2002–2006	334	290	146	395	83	612	9	2	624
2002–2006 %	53.5	46.5	23.4	63.3	13.3	98.1	1.4	0.3	
2007–2011	380	296	184	395	97	672	3	1	676
2007–2011 %	56.2	43.8	27.2	58.4	14.4	99.4	0.4	0.2	
2012–2016	428	318	145	437	164	741	4	1	746
2012–2016 %	57.4	42.6	19.4	58.6	22.0	99.3	0.5	0.1	

TABLE 1

Number and proportion of patients with malignant neoplasms of the brain by sex, age, stage and period of diagnosis in Slovenia in 1997–2016.

In the whole period under review, 15–20% of cases did not have a specified site (C71.9 or C72.9). Among those with a specified site, most cases (16–32%) occurred as an overlapping lesion of the brain (C71.8), followed by the frontal lobe (C71.1) and temporal lobe (C71.2), where the disease occurred in 13–24% of cases. In the parietal lobe (C71.3), a malignant neoplasm occurred in about 7%, and in the occipital lobe (C71.4) in about 4% of cases. Over the last five-year period, the proportion of overlapping lesions of the brain decreased by 16 percentage points compared to 1997–2001.

Depending on the individual observation period, up to 17% of patients did not have microscopically confirmed disease. Among all microscopically confirmed cases, malignant glioma, which occurred in 97% of cases in the last five-year period, was the most common histological type. In less than 0.5% of cases, the histological type was not specified.

Throughout the whole observed period, more men than women were diagnosed with a malignant neoplasm of the brain. Among those the largest proportion was aged from 50–74. Over the 20-year period, an increase in cases was observed in the oldest age group. In almost all cases, the disease was diagnosed in the localized stage (Table 1).

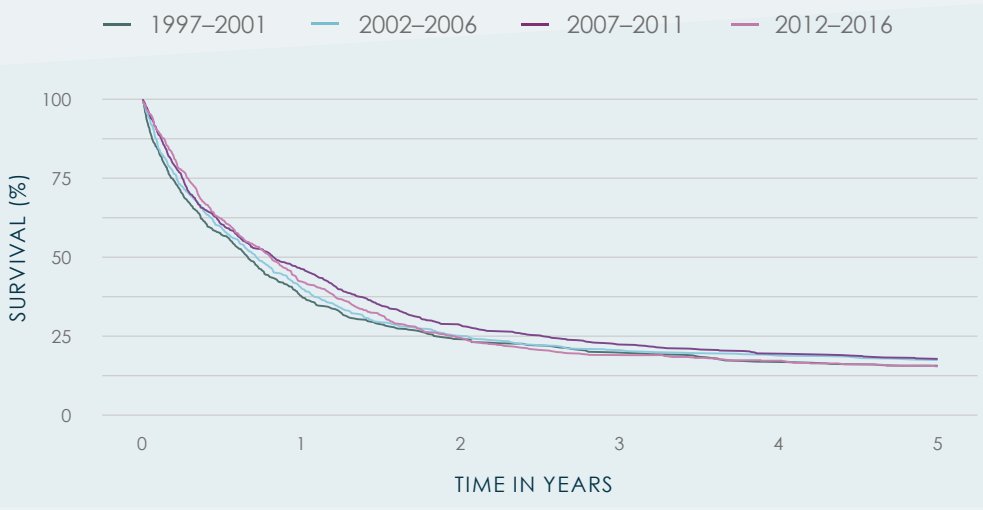


FIGURE 2

Net survival of patients with a malignant neoplasm of the brain by period of diagnosis in Slovenia in 1997–2016.

Regarding the specific primary treatment of malignant neoplasms of the brain between 1997– 2016, 26% of patients were treated with surgery alone, the same percentage received systemic therapy and radiotherapy in addition to surgery, and 22% were treated with surgery in combination with radiotherapy. Over the 20-year period, there was a marked increase in the combination of all three types of therapies as primary treatment (1997–2001: 4.5%; 2012–2016: 35.5%), whereas surgery alone decreased significantly. Just under a fifth (19%) of patients were without a specific primary treatment across the entire period; the proportion of this group of patients did not change significantly during the 20 years under review.

TABLE 2

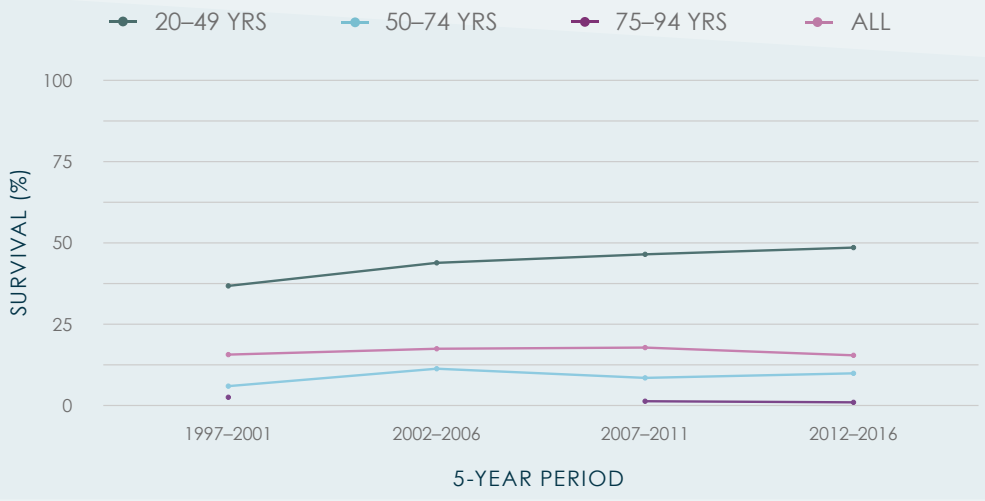
One-, three-, and five-year observed and net survival (with a 95% confidence interval – CI) of patients with malignant neoplasms of the brain by sex and period of diagnosis in Slovenia in 1997–2016.

Survival / Period			1997–2001	(95% CI)	2002–2006	(95% CI)	2007–2011	(95% CI)	2012–2016	(95% CI)
Observed	1-year	all	37.5	33.6–42.0	39.9	36.3–44.0	46.0	42.4–49.9	42.0	38.6–45.7
		men	36.5	31.4–42.5	40.5	35.5–46.1	50.0	45.2–55.3	44.4	39.9–49.4
		women	38.8	33.0–45.8	39.3	34.1–45.4	40.9	35.6–46.9	38.7	33.7–44.4
	3-year	all	19.6	16.4–23.3	20.3	17.4–23.7	22.0	19.1–25.4	18.8	16.2–21.8
		men	16.7	12.9–21.6	19.3	15.5–24.1	21.6	17.8–26.1	19.4	16.0–23.5
		women	23.2	18.3–29.5	21.4	17.2–26.7	22.6	18.3–27.9	17.9	14.2–22.7
	5-year	all	15.3	12.4–18.7	16.9	14.2–20.1	17.5	14.8–20.6	15.1	12.6–18.0
		men	12.9	9.5–17.4	14.5	11.2–18.8	16.8	13.5–21.1	15.3	12.1–19.3
		women	18.3	13.9–24.1	19.7	15.6–24.8	18.2	14.3–23.2	14.8	11.2–19.5
Net	1-year	all	37.8	33.8–42.3	40.3	36.6–44.4	46.4	42.8–50.4	42.4	38.9–46.1
		men	36.9	31.7–43.0	41.0	35.9–46.7	50.5	45.7–55.9	44.9	40.4–50.0
		women	39.0	33.1–46.0	39.6	34.3–45.7	41.1	35.9–47.2	38.9	33.9–44.7
	3-year	all	19.9	16.7–23.7	20.7	17.7–24.2	22.4	19.4–25.8	19.1	16.5–22.2
		men	17.0	13.2–22.1	19.8	15.9–24.7	22.0	18.1–26.6	19.9	16.4–24.1
		women	23.5	18.5–29.8	21.7	17.4–27.0	22.9	18.6–28.3	18.1	14.3–22.9
	5-year	all	15.7	12.8–19.2	17.5	14.6–20.8	17.8	15.1–21.0	15.4	12.9–18.5
		men	13.2	9.8–17.9	15.1	11.6–19.6	17.2	13.8–21.6	15.8	12.4–20.1
		women	18.7	14.2–24.7	20.1	15.9–25.4	18.5	14.6–23.6	15.0	11.4–19.7

In the whole period under review, surgery of malignant neoplasms of the brain was mostly performed in two hospitals. In the last five-year period, slightly more than 71% of operations were performed at the University Medical Centre Ljubljana, and 27% at the University Medical Centre Maribor. The proportion of surgical procedures at the Maribor institution is increasing. In the last five-year period, patients received systemic treatment at the Institute of Oncology Ljubljana (over 99%).

FIGURE 3

Five-year net survival of patients with malignant neoplasms of the brain by age group in Slovenia in 1997–2016.



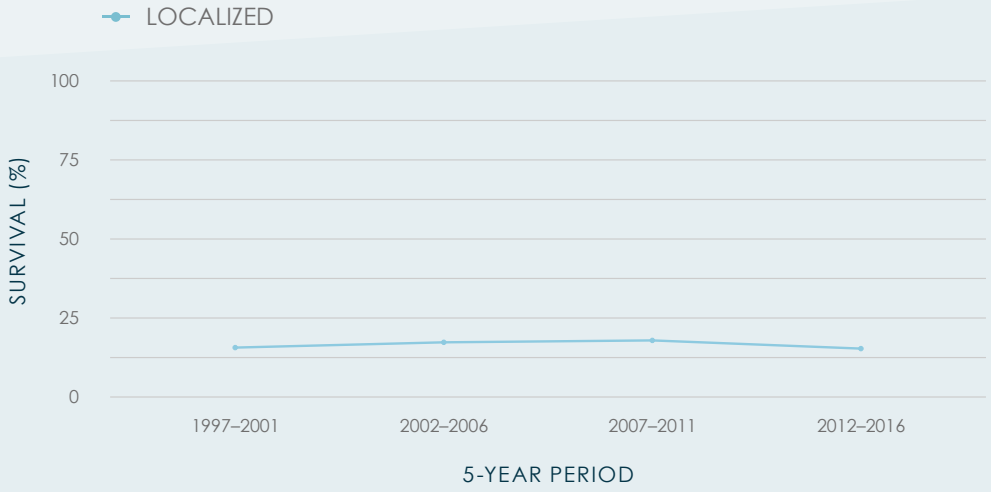


FIGURE 4

Five-year net survival of patients with malignant neoplasms of the brain in localized stage in Slovenia in 1997–2016.

The net survival of malignant neoplasms of the brain did not change significantly in relation to the year of diagnosis and ranged from 15–18% (Figure 2, Table 2). During the whole period under review, no major differences were observed between the sexes for five-year net survival of patients with malignant neoplasms of the brain (Table 2).

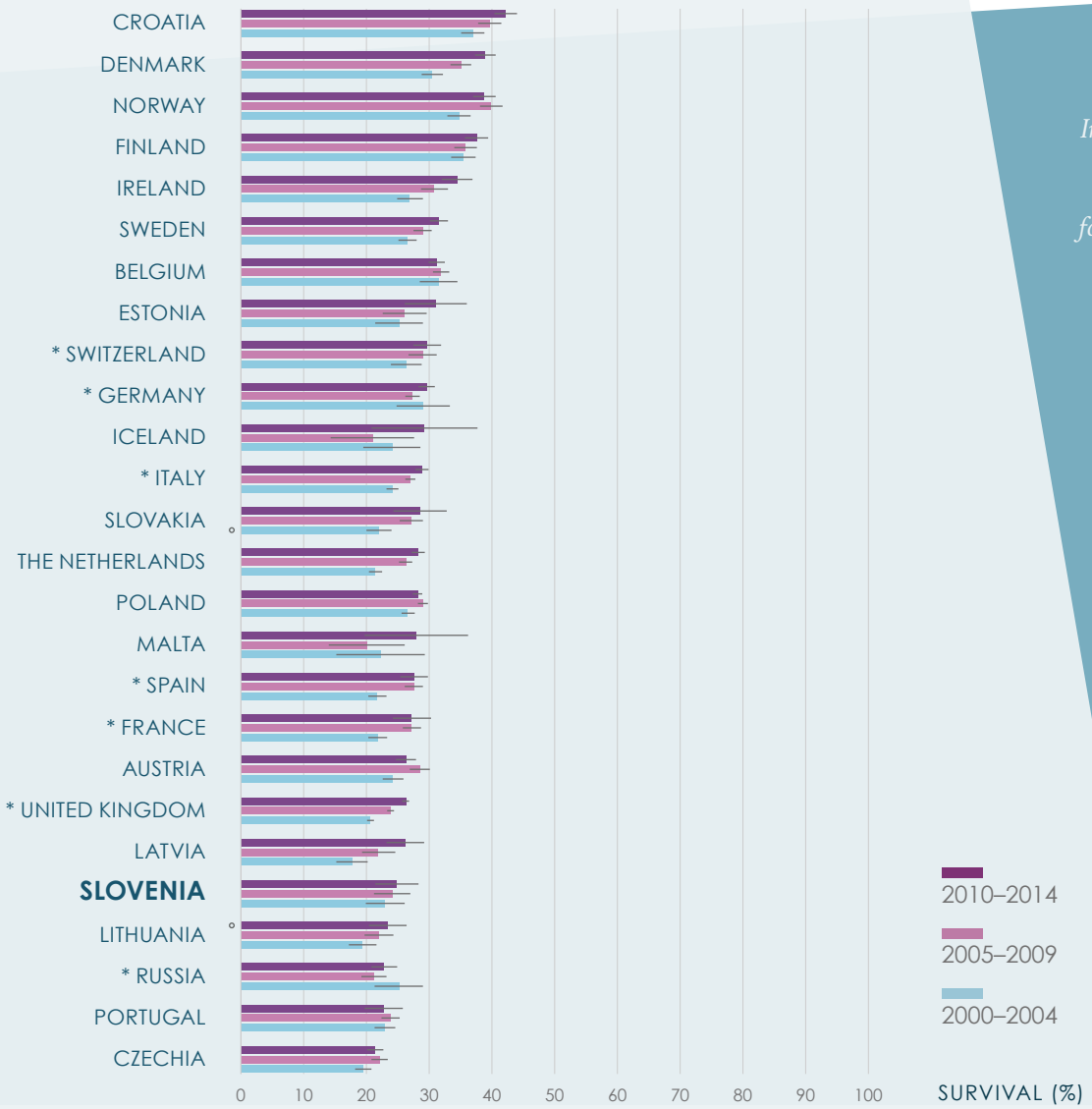


FIGURE 5

International comparison of age-standardized five-year net survival for malignant neoplasms of the brain (with 95% confidence intervals) in patients diagnosed during 2000–2004, 2005–2009 and 2010–2014 (CONCORD-3).

** Data doesn't cover a 100% of the country's population.*

° Survival estimate is less reliable.

In Slovenia, compared to other selected cancers, malignant neoplasm of the brain ranks 17th in men and 20th in women by five-year net survival.

Figure 3 shows the impact of age on the survival of patients with malignant neoplasms of brain. Five-year net survival was highest in the whole period in patients aged 20–49 at diagnosis and lowest in patients aged 75–94. Over the 20-year period, the five-year net survival of patients aged 20–49 at the time of diagnosis improved by just over 13 percentage points, and by 4 percentage points in the 50–74 age group; among patients aged 75–94, however, it decreased by more than 1 percentage point compared to the first five-year period.

Due to the very small number of cases (up to ten in a five-year period) in the regional and distant stages at the time of diagnosis, presentation by stages is not appropriate. Five-year net survival of patients with localized disease did not change across the entire observed period and hovered around 16%.

The results of the world-wide CONCORD-3 study of patients diagnosed during 15 years (2000–2014) in 71 countries and territories show that five-year net survival of Slovenian patients with malignant neoplasms of the brain has been improving (Figure 4). For patients diagnosed during the most recent period (2010–2014), Slovenia ranked 22nd among the 26 participating countries in Europe.

CLINICAL COMMENTARY

Uroš Smrdel

With new data on the survival of patients with brain tumours, we can basically repeat the comments from the previous report. However, the new report does present some changes. The survival analysis, which covered the period up to 2006, shows an improvement in the five–year survival of patients who were diagnosed between 2002 and 2006. This trend continued until 2012, when survival began to decline. Above all, to understand the survival trend it is important to track changes in the age of patients at diagnosis over time. While the proportion of patients aged under 50 almost halved during the observation period, the proportion of patients aged 75–94 tripled.

In younger patients, where the effectiveness of combination therapy was demonstrated, survival was prolonged in all tumours except glioblastoma due to more aggressive treatment, while no changes were observed in older patients in any of the malignant brain tumours. Treatment of older patients is thus still only partially effective. The CONCORD-3 study shows that progress in brain tumour survival is largely stagnant, with no significant improvements in glioblastoma treatment since 2004, whereas with other much rarer brain tumours, the introduction of systemic treatment has prolonged survival.

In the treatment of brain tumours, there has been a gradual decline in the proportion of patients treated with surgery alone and an increase in the proportion of patients treated with combination therapy. There is still a relatively large proportion of patients who do not receive any specific primary treatment, and there has been a slight increase in the proportion of patients who, in accordance with the results of the NORDIC and NOA-08 trials, are treated systemically after surgery. Especially after 2015, routine testing of patients over the age of 70 for methylation of the *MGMT* gene promoter was operationalised, which reduced the burden on patients receiving palliative care. In a commentary in a previous report, I placed considerable hope on finding new molecular targets that could further improve patient survival. During this period, there were several studies that identified potential targets, and the prospect of immunotherapy emerged, but the value of these targets has not yet been confirmed. In addition to treatment optimization, optimization of supportive care is currently one of the more important priorities for the management of patients with malignant neoplasms of the brain, as the results of the CONCORD-3 study show that survival is better where there is more effective palliative care.

References

Allemani C, Matsuda T, Di Carlo V, et al. Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. Lancet 2018; 391: 1023–75.

Arvold ND, Reardon DA. Treatment options and outcomes for glioblastoma in the elderly patient. Clin Interv Aging 2014; 9: 357–67.

Berghoff AS, Kiesel B, Widhalm G, et al. Programmed death ligand 1 expression and tumor-infiltrating lymphocytes in glioblastoma. Neuro Oncol 2015; 17(8): 1064–75.

Lakin N, Rulach R, Nowicki S, et al. Current advances in checkpoint inhibitors: lessons from non-central nervous system cancers and potential for glioblastoma. Front Oncol 2017; 7: 141.

Malmström A, Grønberg BH, Marosi C, et al. Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial. Lancet Oncol 2012; 13(9): 916–26.

Shah N, Schroeder B, Cobbs C. MGMT methylation in glioblastoma: tale of the tail. Neuro Oncol 2015; 17(1): 167–8.

Tabatabai G, Stupp R, Wick W, et al. Malignant astrocytoma in elderly patients. Curr Opin Neurol 2013; 26(6): 693–700.

Weller M, van den Bent M, Tonn JC, et al. European Association for Neuro-Oncology (EANO) guideline on the diagnosis and treatment of adult astrocytic and oligodendroglial gliomas. Lancet Oncol 2017; 18(6): e315–29.

Wick W, Platten M, Meisner C, et al. Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: the NOA-08 randomised, phase 3 trial. Lancet Oncol 2012; 13(7): 707–15.

Wiestler B, Claus R, Hartlieb SA, et al. Malignant astrocytomas of elderly patients lack favorable molecular markers: an analysis of the NOA-08 study collective. Neuro Oncol 2013; 15(8): 1017–26.

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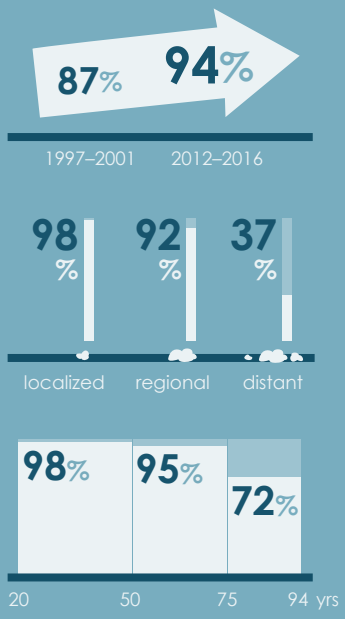
THYROID



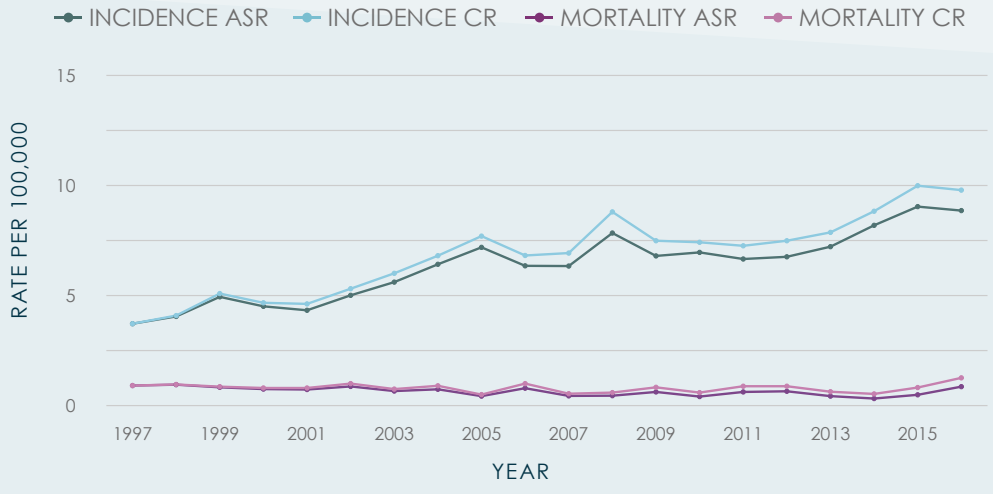
EPIDEMIOLOGY

In the last five-year period (2012–2016), 181 people per year on average were diagnosed with thyroid cancer in Slovenia, 43 men and 138 women, and 17 people died, 7 men and 10 women. As shown in Figure 1, the thyroid cancer incidence rate gradually increased throughout the observed period. Between 2007–2016, the crude incidence rate of thyroid cancer increased by 3.1% per year, by 3.6% in men and by 3% in women. The increase is statistically significant in both sexes combined. Population ageing did not significantly affect the increase in incidence. The increase can be largely attributed to the detection of a large number of cases that would not cause symptoms or death and would have remained hidden for life if they remained undiagnosed. The thyroid cancer mortality rate does not follow the rapid rise in incidence, which also indicates overdiagnosis of thyroid cancer.

At the end of 2016, there were 2,676 people in Slovenia who had been diagnosed with thyroid cancer at some point in their lives. Of those, the diagnosis had been established less than one year ago in 189 people, one to four years ago in 637 people, and over ten years ago in 1,183 people.

FIGURE 1

The crude (CR) and age-standardized (ASR) incidence and mortality rates of thyroid cancer in Slovenia in 1997–2016.



The survival analysis included 2,643 cases of patients aged 20–94; 129 cases (4.7%) were excluded because they were diagnosed on the day of death, or because they did not fulfil the age inclusion criteria.

During the entire observation period, only two patients did not have microscopically confirmed disease. In all periods, adenocarcinoma was the most common type of all microscopically confirmed cases, occurring in 96% of cases in the last five-year period. In 1% of cases, the histological type was not specified.

	Sex		Age			Stage			Total
	Men	Women	20–49 yrs	50–74 yrs	75–94 yrs	Localized	Regional	Distant	
1997–2001	105	305	176	188	46	236	131	38	410
1997–2001 %	25.6	74.4	42.9	45.9	11.2	57.6	32.0	9.3	
2002–2006	132	494	284	289	53	431	150	41	626
2002–2006 %	21.1	78.9	45.4	46.2	8.5	68.9	24.0	6.6	
2007–2011	175	565	316	354	70	572	134	33	740
2007–2011 %	23.7	76.4	42.7	47.8	9.5	77.3	18.1	4.5	
2012–2016	205	662	356	427	84	657	168	40	867
2012–2016 %	23.6	76.4	41.1	49.3	9.7	75.8	19.4	4.6	

TABLE 1

Number and proportion of patients with thyroid cancer by sex, age, stage and period of diagnosis in Slovenia in 1997–2016.

Thyroid cancer affected far more women (more than 75%) than men in all periods under review, with the largest proportion aged 50–74, followed by people aged 20–49. The disease was most commonly diagnosed in the localized stage (Table 1). Over the 20 years under review, there was a noticeable increase in cancers detected in the localized stage, the difference between the last and the first five-year period being 18 percentage points.

Regarding the specific primary thyroid cancer treatment between 1997–2016, over 65% of patients underwent surgery and received hormone replacement or suppression treatment and radiotherapy at the same time, and approximately one fifth of patients received systemic therapy in addition to surgery. In the 20-year period under review, the proportion of patients treated with specific surgery and systemic therapy as primary treatment increased compared to a combination of all three forms of treatment. Across the entire covered period, 2.5% of patients did not receive specific primary treatment.

In all periods, thyroid cancer surgery was performed in at least three hospitals. In the last five-year period, most surgery was performed at the Institute of Oncology Ljubljana (69%), followed by the University Medical Centre Ljubljana (18%) and University Medical Centre Maribor (5%), and less

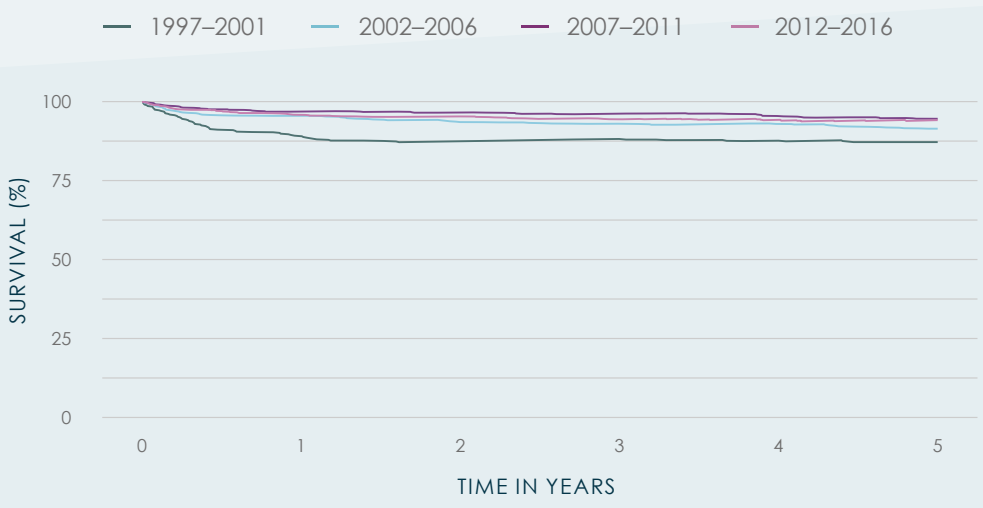


FIGURE 2

Net survival of patients with thyroid cancer by period of diagnosis in Slovenia in 1997–2016.

than 5% in other hospitals. As part of primary treatment, in the last five-year period, patients received hormone replacement or suppression treatment at the Institute of Oncology Ljubljana (75%), followed by the University Medical Centre Ljubljana (13%), and less than 5% in other hospitals.

The net survival of thyroid cancer patients gradually improved in relation to the year of diagnosis (Figure 2, Table 2). During the 20 years under review, five-year net survival improved by 7 percentage points. In the five-year net survival of thyroid cancer patients over the entire observation period, the gap between the sexes was in favour of women and amounted to 5–10 percentage points. This difference was statistically significant only in the period from 2007–2011 (Table 2).

TABLE 2

One-, three-, and five-year observed and net survival (with a 95% confidence interval – CI) of patients with thyroid cancer by sex and period of diagnosis in Slovenia in 1997–2016.

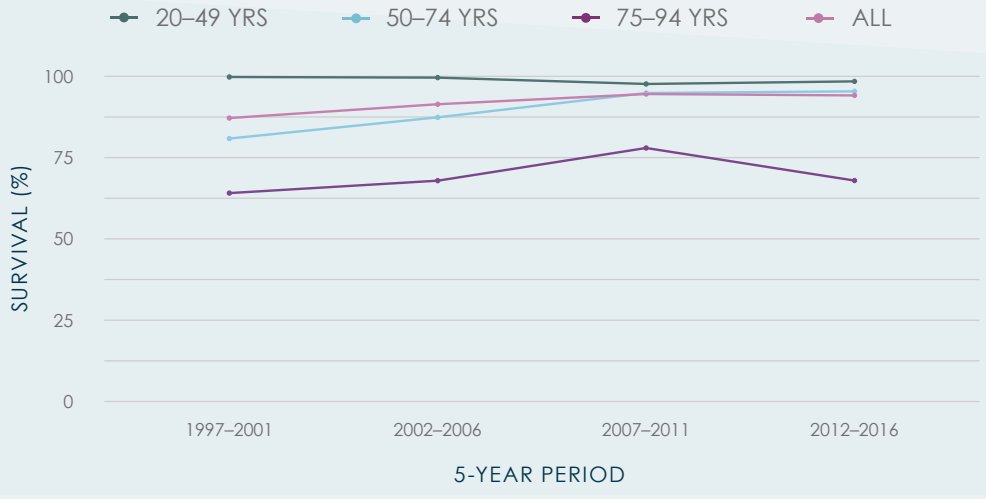
Survival / Period			1997–2001	(95% CI)	2002–2006	(95% CI)	2007–2011	(95% CI)	2012–2016	(95% CI)
Observed	1-year	all	88.1	85.0–91.3	94.7	93.0–96.5	96.0	94.5–97.4	95.0	93.6–96.5
		men	84.8	78.2–91.9	92.4	88.0–97.1	91.4	87.4–95.7	92.2	88.6–95.9
		women	89.2	85.8–92.7	95.3	93.5–97.2	97.4	96.0–98.7	95.9	94.4–97.4
	3-year	all	84.6	81.2–88.2	90.4	88.1–92.8	93.5	91.8–95.3	92.0	90.2–93.8
		men	79.1	71.6–87.2	85.6	79.8–91.8	85.7	80.7–91.1	87.2	82.8–91.9
		women	86.6	82.8–90.5	91.7	89.3–94.2	95.9	94.3–97.6	93.5	91.6–95.4
	5-year	all	81.7	78.1–85.5	86.9	84.3–89.6	90.0	87.9–92.2	89.7	87.6–91.8
		men	78.1	70.6–86.4	78.8	72.1–86.1	80.0	74.3–86.2	84.3	79.4–89.6
		women	83.0	78.8–87.3	89.1	86.4–91.9	93.1	91.0–95.2	91.4	89.1–93.7
Net	1-year	all	89.2	86.1–92.5	95.5	93.7–97.3	96.8	95.4–98.3	95.9	94.4–97.3
		men	86.8	80.0–94.2	93.6	89.1–98.3	92.9	88.8–97.2	93.3	89.6–97.2
		women	90.0	86.5–93.6	95.9	94.0–97.8	97.9	96.6–99.3	96.6	95.1–98.2
	3-year	all	88.2	84.5–92.0	93.0	90.6–95.5	96.0	94.1–97.9	94.5	92.6–96.4
		men	84.9	76.8–93.9	89.2	83.0–95.9	89.5	84.1–95.4	90.5	85.7–95.6
		women	88.4	84.5–92.5	93.9	91.4–96.5	97.7	96.0–99.4	95.7	93.7–97.7
	5-year	all	87.2	83.1–91.5	91.4	88.6–94.4	94.6	92.2–97.0	94.2	91.9–96.6
		men	88.1	79.5–97.7	85.8	78.3–93.9	86.6	80.1–93.7	90.6	85.1–96.4
		women	86.6	82.1–91.4	92.9	89.9–96.0	96.9	94.6–99.3	95.3	92.7–97.9

In Slovenia, compared to other selected cancers, thyroid cancer ranks 3rd in men and 1st in women by five-year net survival.

Figure 3 shows the impact of age on the survival of thyroid cancer patients. Five-year net survival was highest in all observation periods in subjects aged 20–49 at diagnosis and lowest in subjects aged 75–94. In the whole period under review, survival improved the most in the 50–74 age group—by 14

FIGURE 3

Five-year net survival of patients with thyroid cancer by age group in Slovenia in 1997–2016.



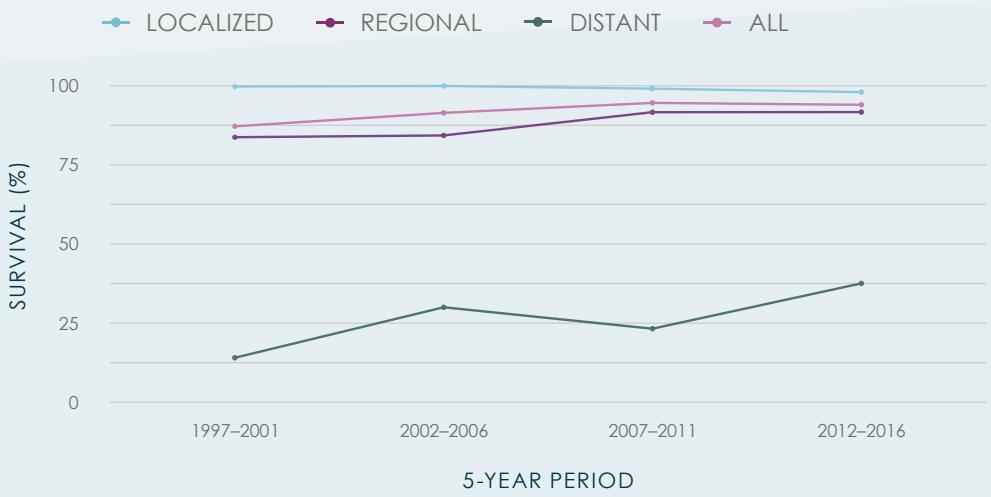


FIGURE 4

Five-year net survival of patients with thyroid cancer by stage in Slovenia in 1997–2016.

percentage points compared to the first five-year period—and thus almost caught up with survival in the youngest age group.

The importance of stage at diagnosis is shown in Figure 4. Five-year net survival of patients with localized disease surpassed 98% over the entire period. Five-year net survival of patients with regional disease reached 92% in the last observed period, and in patients with distant disease at diagnosis it was 37%. The time trend of five-year net survival of thyroid cancer patients between 1997–2016 shows an improvement in all stages, most notably in the regional stage (13 percentage points).

CLINICAL COMMENTARY

Nikola Bešić, Barbara Vidergar-Kralj, Marta Dremelj, Cvetka Grašič Kuhar

An increase in thyroid ultrasound examinations and better ultrasound equipment make it possible to diagnose very small changes in the thyroid gland that do not endanger the patient's life. The increased incidence of thyroid cancer in Slovenia can be attributed to papillary thyroid cancer, especially papillary microcarcinoma, i.e., papillary cancer of 10 mm or less, which has an excellent prognosis. The latest American and Slovenian guidelines for the diagnosis and treatment of thyroid cancer do not recommend cytological diagnosis of tumours smaller than 10 mm. Most patients with thyroid microcarcinoma are treated with surgery alone or are simply monitored by ultrasound, an option very few patients choose in Slovenia. Since 2015, patients with thyroid microcarcinoma no longer undergo total thyroidectomy, but merely lobectomy with thyroid istectomy. It is due to thyroid microcarcinoma patients that radioiodine treatment has been in decline since 2006. Patients with microcarcinoma are not treated by suppressing TSH using thyroid hormones, but take thyroid hormones in replacement doses. This improves their overall survival, as they are less likely to have cardiovascular disease and osteoporosis.

The good survival of thyroid cancer patients is also due to the fact that they are operated on only by surgeons experienced in thyroid surgery. Another reason is that treatment with radioiodine, radiotherapy, thyroid hormones and systemic therapy is performed by trained experts at the Institute of Oncology Ljubljana. Patients are also monitored and decisions regarding thyroid hormone suppression or replacement therapy are made solely at the Institute of Oncology.

During the observed period, the proportion of patients with regional and distant disease decreased, but the actual number of these patients hardly changed. Survival of these patients has improved due to earlier and better diagnostics, in which 18F-FDG PET-CT as well as computed tomography and

magnetic resonance imaging have been used in the last decade. Another reason why these patients live longer is that distant metastases are treated with radioiodine after administration of recombinant human TSH, which allows radioiodine treatment even in patients in whom hormonal withdrawal (hypothyroidism) is contraindicated. The third reason for the better survival of patients with metastases in the last decade is the use of targeted therapy, employed when treatment with radioiodine is no longer effective. Unfortunately, in most patients, drugs used in targeted therapy have only a transient effect.

It is gratifying that survival improved both in patients aged 50–74 and in those aged 75–94. Modern anaesthesia makes surgery safe even in patients who have many comorbidities. Male patients still have a poorer prognosis than women, mainly due to late diagnosis, as both patients and physicians, rarely think of thyroid disease in men.

References

Bešić N, Pilko G, Petrič R, et al. Papillary thyroid microcarcinoma: prognostic factors and treatment. J Surg Oncol 2008; 3: 221–5.

Bešić N, Schwartzbartl-Pevec, A, Klevišar Ivančič A, et al. Smernice diagnostike in zdravljenja diferenciranega raka ščitnice (Guidelines for diagnostics and treatment of differentiated thyroid cancer). Ljubljana: Institute of Oncology; 2017.

Grašič-Kuhar C. Sistemsko zdravljenje raka ščitnice (Systemic treatment of thyroid cancer). In: Novosti v sistemskem zdravljenju redkejših solidnih rakov. Dan internistične onkologije 2017. Ljubljana: Section of Medical Oncology, Slovene Medical Association, Medical Faculty of University of Ljubljana; 2017. p. 13–31.

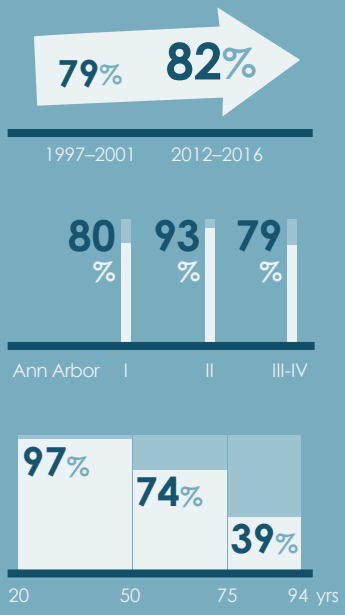
Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: The American Thyroid Association Guidelines Task Force on thyroid nodules and differentiated thyroid cancer. Thyroid 2016; 1:1–133.

Vaccarella S, Franceschi S, Bray F, et al. Worldwide thyroid cancer epidemic? The increasing impact of overdiagnosis. N Engl J Med 2016; 7: 614-7.

Žagar I, Schwarzbartl-Pevec AA, Vidergar-Kralj B, et al. Recombinant human thyrotropin-aided radioiodine therapy in patients with metastatic differentiated thyroid carcinoma. J Thyroid Res 2012; 2012: 670180.

C81

HODGKIN'S LYMPHOMA



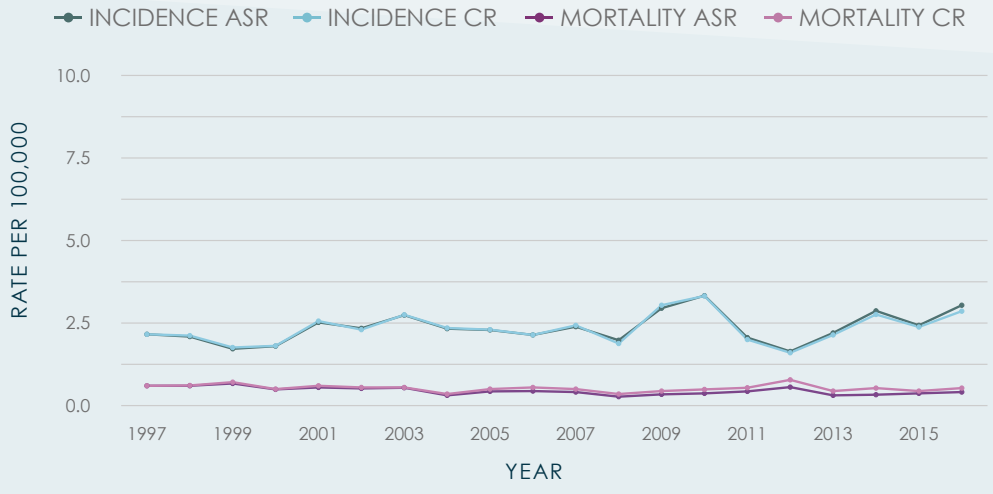
EPIDEMIOLOGY

In the last five-year period (2012–2016), 48 people per year on average were diagnosed with Hodgkin's lymphoma in Slovenia, 24 men and 24 women, and 11 people died, 4 men and 7 women. Figure 1 shows the time trend of Hodgkin's lymphoma incidence and mortality. Due to the small number of cases throughout the observed period, it is difficult to talk about a consistent trend. Over the last ten years, there has been an increase in the crude incidence rate by 0.9% per year; in men by 0.1% per year and in women by 1.6% per year. From 2007–2016, the crude mortality rate of Hodgkin's lymphoma increased by 0.6% per year in both sexes combined; it decreased by 6.6% per year in men and increased by 17.5% per year in women. No trend of the crude incidence and mortality rates is statistically significant.

At the end of 2016, there were 1,086 people in Slovenia who had been diagnosed with Hodgkin's lymphoma at some point in their lives. Of those, the diagnosis had been established less than one year ago in 56 people, one to four years ago in 161 people, and over ten years ago in 669 people.

FIGURE 1

The crude (CR) and age-standardized (ASR) incidence and mortality rates of Hodgkin's lymphoma in Slovenia in 1997–2016.



The survival analysis included 786 cases of patients aged 20–94; 157 cases (17%) were excluded because they were diagnosed on the day of death, or because they did not fulfil the age inclusion criteria.

In the whole observed period, most cases (40–47%) occurred in the form of nodular sclerosis (C81.1) and as mixed cellularity lymphoma (31–43%) (C81.2). In 3–6% of cases as nodular lymphocyte predominant lymphoma (C81.0), and in 1–3% of cases the disease occurred as lymphocyte depleted lymphoma (C81.3). Only two patients had other Hodgkin's lymphoma (C81.7). In 10–17% of cases, the form of the disease was not specified (C81.9).

	Sex		Age			Stage (Ann Arbor)			Total
	Men	Women	20–49 yrs	50–74 yrs	75–94 yrs	I	II	III+IV	
1997–2001	91	79	109	45	16	21	69	72	170
	% 53.5	46.5	64.1	26.5	9.4	12.4	40.6	42.4	
2002–2006	111	87	133	50	15	24	89	80	198
	% 56.1	43.9	67.2	25.3	7.6	12.1	45.0	40.4	
2007–2011	108	107	126	63	26	30	79	92	215
	% 50.2	49.8	58.6	29.3	12.1	14.0	36.7	42.8	
2012–2016	100	103	111	68	24	18	54	122	203
	% 49.3	50.7	54.7	33.5	11.8	8.9	26.6	60.1	

TABLE 1

Number and proportion of patients with Hodgkin's lymphoma by sex, age, stage and period of diagnosis in Slovenia in 1997–2016.

In the 20 years under review, the disease was microscopically confirmed in all cases. The majority of cases were unspecified nodular sclerosis Hodgkin's lymphomas (36% in the last five-year period) and mixed cellularity lymphomas (35% in the last five-year period). In 13% of cases in the last five-year period, the histological type of the Hodgkin's lymphoma was not specified.

In the first three five-year periods under review, slightly more men than women were diagnosed with Hodgkin's lymphoma, while in the last five-year period the two sexes were close to 50:50. Most people were diagnosed aged 20–49. In the first three periods the disease was detected in a similar proportion in the second, third and fourth stages, and in the last five-year period, it was most often detected in the third and fourth stages (Table 1).

Regarding the specific primary treatment of Hodgkin's lymphoma between 1997–2016, the largest proportion of patients (49%) received a combination of systemic treatment and radiotherapy or systemic treatment alone (39%). The proportion of patients without specific primary treatment throughout

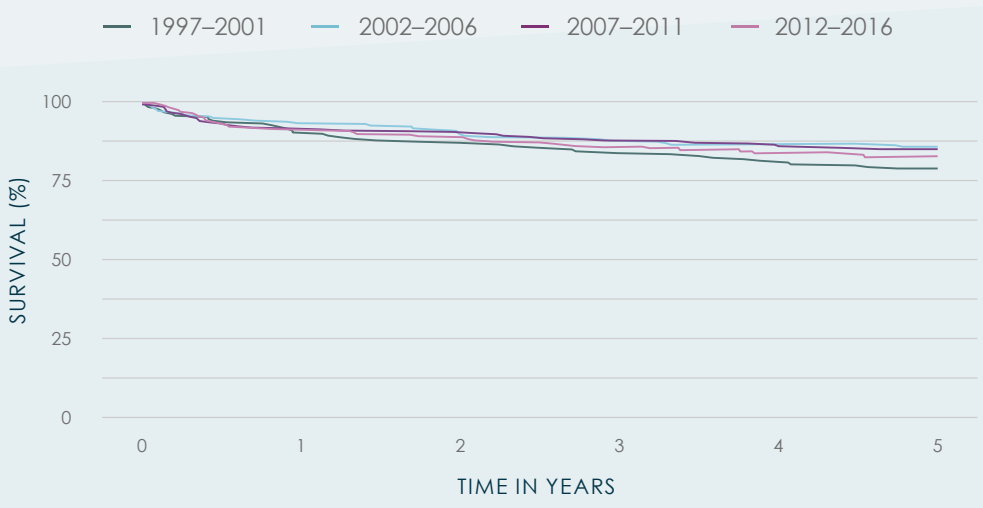


FIGURE 2

Net survival of patients with Hodgkin's lymphoma by period of diagnosis in Slovenia in 1997–2016.

the period under review was 6%; the proportion of this group did not change significantly during the observed five-year periods.

In the last five-year period, patients received systemic therapy as their primary treatment at the Institute of Oncology Ljubljana (99%).

TABLE 2

One-, three-, and five-year observed and net survival (with a 95% confidence interval – CI) of patients with Hodgkin's lymphoma by sex and period of diagnosis in Slovenia in 1997–2016.

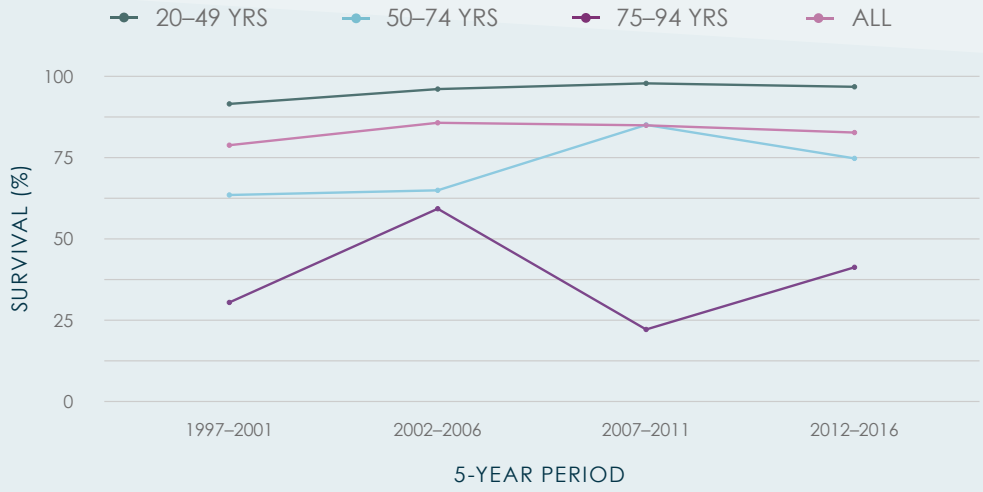
Survival / Period			1997–2001	(95% CI)	2002–2006	(95% CI)	2007–2011	(95% CI)	2012–2016	(95% CI)
Observed	1-year	all	89.4	84.8–94.1	92.4	88.8–96.2	91.2	87.5–95.0	90.6	86.7–94.7
		men	91.2	85.6–97.2	93.7	89.3–98.3	89.8	84.3–95.7	91.0	85.6–96.8
		women	87.2	80.2–95.0	90.8	84.9–97.1	92.5	87.7–97.6	90.3	84.8–96.2
	3-year	all	81.7	76.1–87.7	85.9	81.1–90.9	86.1	81.5–90.8	83.7	78.8–89.0
		men	81.3	73.7–89.7	83.8	77.2–90.9	85.2	78.7–92.2	81.0	73.6–89.0
		women	82.1	74.0–91.1	88.5	82.1–95.5	86.9	80.8–93.6	86.4	80.0–93.3
	5-year	all	75.8	69.6–82.5	82.8	77.7–88.3	82.8	77.9–88.0	79.6	74.0–85.7
		men	74.7	66.3–84.2	79.3	72.1–87.2	83.3	76.6–90.7	75.3	66.8–84.8
		women	77.0	68.2–86.9	87.4	80.6–94.6	82.2	75.3–89.8	83.7	76.6–91.5
Net	1-year	all	90.2	85.6–95.1	93.2	89.5–97.0	91.9	88.2–95.9	91.3	87.3–95.5
		men	92.1	86.4–98.2	94.2	89.7–98.9	90.6	85.0–96.5	91.3	85.8–97.2
		women	88.1	80.9–95.8	91.5	85.6–97.9	93.0	88.1–98.2	91.0	85.4–97.0
	3-year	all	83.7	77.7–90.2	87.6	82.7–92.9	88.1	83.3–93.1	85.6	80.3–91.2
		men	83.5	75.4–92.5	85.4	78.5–92.9	87.5	80.9–94.7	82.8	75.2–91.2
		women	83.5	74.9–93.0	89.7	83.1–97.0	88.6	82.0–95.7	88.2	81.1–95.9
	5-year	all	78.8	72.1–86.1	85.7	80.2–91.6	85.3	79.9–91.2	82.2	75.9–89.0
		men	78.3	69.3–88.5	81.5	73.8–90.1	86.5	79.4–94.2	78.3	69.2–88.5
		women	79.0	69.5–89.7	89.6	82.6–97.2	83.5	75.4–92.4	85.7	77.3–95.1

Net survival in Hodgkin's lymphoma varies according to the year of diagnosis, but the differences between the individual five-year periods are not statistically significant. Five-year net survival was highest (86%) between 2002–2006 and lowest (79%) between 1997–2001 (Figure 2, Table 2). During the overall observed period, there were no major differences between the sexes in the five-year net survival (Table 2).

In Slovenia, compared to other selected cancers, Hodgkin's lymphoma ranks 5th in men and 3rd in women by five-year net survival.

FIGURE 3

Five-year net survival of patients with Hodgkin's lymphoma by age group in Slovenia in 1997–2016.



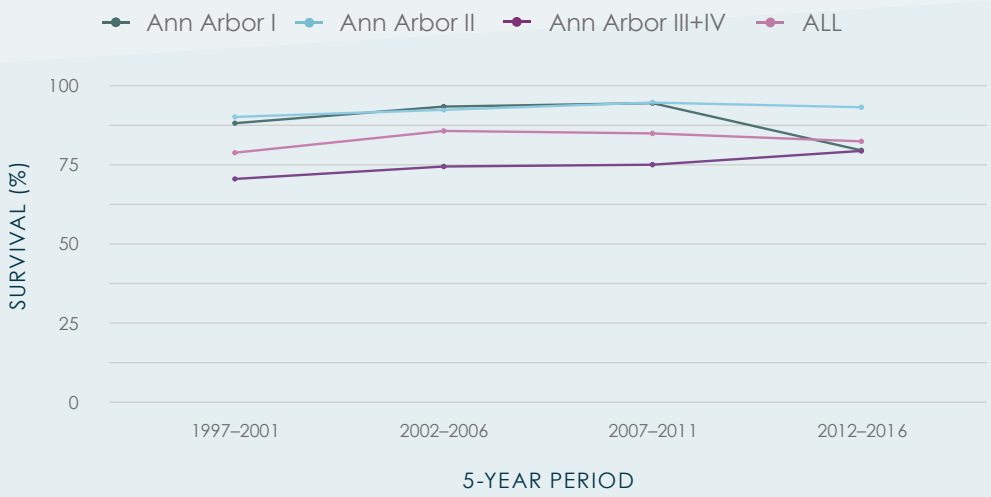


FIGURE 4

Five-year net survival of patients with Hodgkin's lymphoma by stage in Slovenia in 1997–2016.

Figure 3 shows the impact of age on the survival of patients with Hodgkin's lymphoma. The five-year net survival of patients aged 20–49 at diagnosis is the highest compared to other age groups, and ranges from 92–98% throughout the observed period. The five-year net survival of patients aged 75–94 is the lowest (23–59%). There is great variability in the five-year net survival throughout the observed period due to the small number of cases, but differences in survival by age are not statistically significant between periods (Figure 3).

The importance of stage at diagnosis is shown in Figure 4. The five-year net survival of patients with the disease detected in the first and second stages is similar and does not change significantly from period to period. In disease diagnosed in the first stage, it is slightly lower (80–95%) than in the second stage (90–95%). Due to the small number of cases, greater survival variability was observed in patients with early-stage disease, but the differences in survival between the periods and between the first and second stages are not statistically significant. The five-year net survival of patients with the disease detected in the third and fourth stages (71–79%) improves over the period under review.

The results of the world-wide CONCORD-3 study of patients diagnosed with cancer during the 15 years between 2000 and 2014 in 71 countries and territories include a whole group of lymphoid malignancies, including Hodgkin's lymphoma. An international comparison of survival for the whole group can be found in the chapter on non-Hodgkin's lymphomas (Figure 5). For patients diagnosed during the most recent period (2010–2014), Slovenia ranked 19th among the 26 participating countries in Europe.

CLINICAL COMMENTARY

Barbara Jezeršek Novaković

The age-standardized incidence of Hodgkin's lymphoma did not change significantly during the observed period. In terms of sex discrepancies, an equal proportion of men and women were diagnosed with Hodgkin's lymphoma in the last five-year period, whereas in the previous three five-year periods, men slightly predominated. The proportion of patients treated at the Institute of Oncology Ljubljana increased slightly over the period under review, while it decreased in other institutions. The proportion of patients treated with systemic therapy alone increased mainly in the last five-year observation period. This can most likely be attributed to the determination of remission with a PET/CT examination at the end of systemic treatment. This allows the safe cessation of radiotherapy when complete remission is achieved. Accordingly, the proportion of patients treated with a combination of systemic treatment and radiotherapy decreased during the same period. The proportion of patients treated with radiotherapy alone was negligible in all periods—only patients who were not eligible for

systemic therapy were treated in this way. Still, it is surprising that there was a large proportion of patients who did not receive a specific primary treatment at all; for the most part, these were those patients who were not suitable even for radiotherapy. However, it would be interesting to know how many patients in this group refused treatment.

Over the whole period under review, age-standardized mortality did not change significantly, and a decreasing trend was observed in the last two five-year periods. The best five-year net survival was in patients between 2002–2006, and the same was true for one- and ten-year survival. This was the period in which the disease was detected in the first or second stage in the largest proportion of patients and in the third and fourth stages in the lowest proportion. Among patients in whom disease was detected between 2012–2016, the proportion of those with regional disease increased by half compared to those diagnosed between 2002—2006. Despite improved methods of diagnosis and treatment, this may be one of the reasons for poorer survival in recent times. The deterioration in the five-year survival of patients with first-stage cancer in the last five-year period remains unexplained, as their survival was poorer both compared to second-stage cancer patients in the same period and to the first-stage patients in previous five-year periods. The only possible explanation would be that we underestimated the spread of the disease in patients classified as the first stage in the last five-year period. This, however, is unlikely given modern diagnostics, which includes the initial PET/CT examination. It would also be interesting to find out what proportion of these patients developed late effects from treatment, such as heart failure, lung damage, and secondary malignancies, and whether these may have affected survival. Otherwise, the survival of more recently diagnosed patients with advanced disease has improved with the introduction of more aggressive BEACOPP therapy at higher doses and the use of PET/CT examination to assess the spread of the disease and remission.

During the whole 20-year period, the proportion of patients under the age of 50 decreased slightly, while the proportion of those aged 50–74 as well as those aged 75–94 increased. Older patients are known to have more comorbidities and are less suitable for aggressive systemic treatment, which may also affect the slightly poorer five-year survival of all patients diagnosed in the last two five-year periods. The marked fluctuations in the five-year net survival of patients aged 75–94 are likely to reflect the proportion of these patients who were able to receive systemic therapy in individual five-year periods.

References

Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014; 32(27): 3059–68.

DeVita VT, Lawrence TS, Rosenberg SA, eds. DeVita, Hellman, and Rosenberg's Cancer: principles and practice of oncology (11th ed.). Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins; 2018.

Eichenauer DA, Aleman BMP, Andre M, et al. Hodgkin lymphoma: ESMO Clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018; 29 (Suppl4): iv19-iv29.

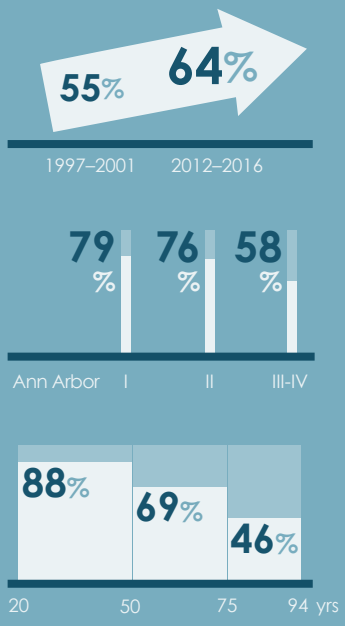
Jezeršek Novaković, B, Gašljević, G, Jagodic M, et al. Smernice za obravnavo bolnikov z malignimi limfomi (Guidelines for treatment of patients with lymphoid neoplasms). Ljubljana: Institute of Oncology; 2018.

Swerdlow SH, Campo E, Harris NL, et al, eds. WHO Classification of tumours of haematopoietic and lymphoid tissues (revised 4th ed.). Lyon, France: International Agency for Research on Cancer; 2017.

Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 2016; 127(20): 2375–90.

C82–C85

NON-HODGKIN'S LYMPHOMA



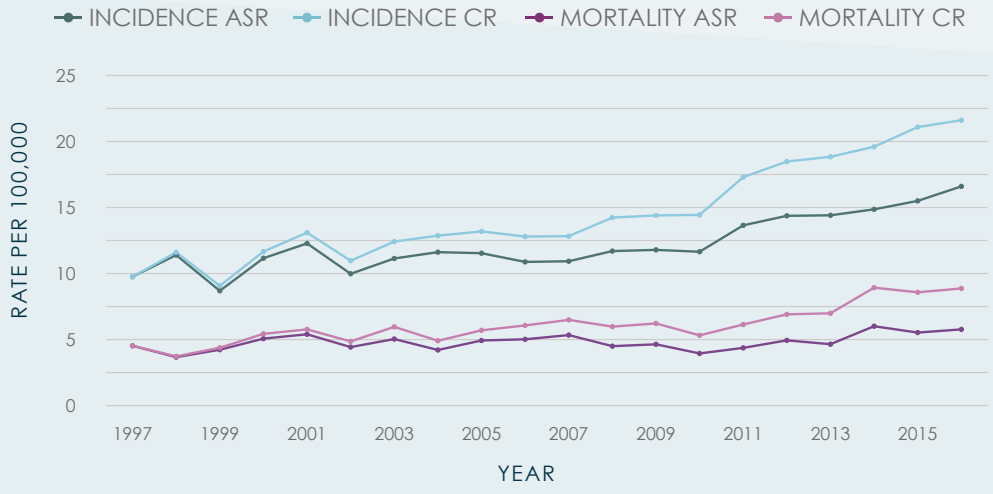
EPIDEMIOLOGY

In the last five-year period (2012–2016), 411 people per year on average were diagnosed with non-Hodgkin's lymphoma in Slovenia, 210 men and 201 women, and 166 people died, 82 men and 84 women. As shown in Figure 1, the non-Hodgkin's lymphoma incidence rate increased throughout the observed period. Over the last ten years, there has been a noticeable increase in the crude incidence rate by 6.2% per year, by 7.1% in men and by 5.2% in women. In slightly over 40%, the increase in incidence in the observed period can be attributed to population ageing. Between 2007 and 2016, the crude mortality rate of non-Hodgkin's lymphomas increased by 5.0% per year in both sexes combined, by 4.3% in men and by 5.8% in women. The increase is statistically significant in women and in both sexes combined.

At the end of 2016, there were 3,143 people in Slovenia who had been diagnosed with non-Hodgkin's lymphoma at some point in their lives. Of those, the diagnosis had been established less than one year ago in 369 people, one to four years ago in 968 people, and over ten years ago in 1,044 people.

FIGURE 1

The crude (CR) and age-standardized (ASR) incidence and mortality rates of non-Hodgkin's lymphoma in Slovenia in 1997–2016.



The survival analysis included 5,656 cases of patients aged 20–94; 216 cases (4%) were excluded because they were diagnosed on the day of death, or because they did not fulfil the age inclusion criteria.

In the whole 20-year period, most cases (47–62%) occurred in the form of non-follicular lymphoma (C83), in which the largest proportion (28–43%) was diffuse large B-cell lymphoma (C83.3) and 12–17% comprised other non-follicular lymphoma (C83.8). In 11–27% of patients, the disease occurred as follicular lymphoma (C82), in the largest proportion (5–14%) of which as other types of follicular lymphoma (C82.7), and in 1–6% as unspecified follicular lymphoma (C82.9). The disease occurred in the form of mature T/NK-cell lymphoma (C84) in about 9% of cases, with the largest proportion (about 4%) in the form of peripheral T-cell lymphoma, not elsewhere classified (C84.4), and other mature T/NK-cell lymphoma (C84.5). In other and unspecified types of non-Hodgkin's lymphoma (C85), the disease occurred in 5–35%; the proportion of unspecified types decreased over the period under review.

	Sex		Age			Stage (Ann Arbor)			Total
	Men	Women	20–49 yrs	50–74 yrs	75–94 yrs	I	II	III+IV	
1997–2001	485	547	197	585	250	318	210	363	1032
1997–2001 %	47.0	53.0	19.1	56.7	24.2	30.8	20.4	35.2	
2002–2006	551	642	201	655	337	336	213	461	1193
2002–2006 %	46.2	53.8	16.9	54.9	28.3	28.2	17.9	38.6	
2007–2011	724	716	208	773	459	326	205	671	1440
2007–2011 %	50.3	49.7	14.4	53.7	31.9	22.6	14.2	46.6	
2012–2016	1015	976	212	1121	658	397	240	1080	1991
2012–2016 %	51.0	49.0	10.7	56.3	33.1	19.9	12.1	54.2	

TABLE 1

Number and proportion of patients with non-Hodgkin's lymphoma by sex, age, stage and period of diagnosis in Slovenia in 1997–2016.

The disease was microscopically confirmed in all cases in the 20-year period under review. Most cases were diffuse large B-cell lymphoma (42% in the last five-year period) and marginal zone B-cell lymphoma (14% in the last five-year period). In 5% of cases in the last five-year period, the histological type of non-Hodgkin's lymphoma was not specified; the proportion of unspecified cases decreased with time.

In recent periods, the number of men and women with non-Hodgkin's lymphoma has been equalizing. Most people were diagnosed between the ages of 50–74. The disease was most commonly diagnosed in the third and fourth stages (Table 1).

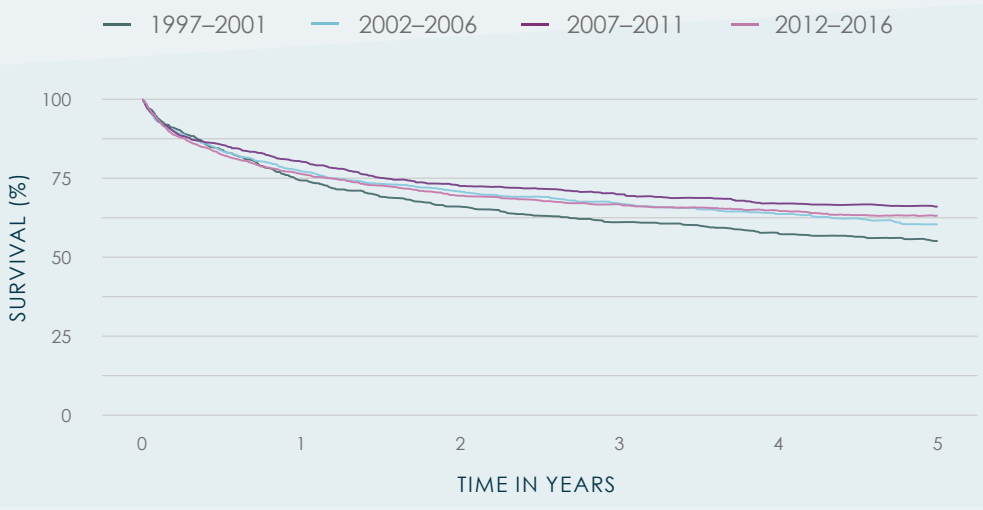


FIGURE 2

Net survival of patients with non-Hodgkin's lymphoma by period of diagnosis in Slovenia in 1997–2016.

Regarding the primary treatment of non-Hodgkin's lymphoma between 1997–2016, most patients (34%) received systemic therapy alone or a combination of systemic therapy and radiotherapy (19%). The proportion of patients who were treated with radiotherapy alone was 8%. Across the entire period under review, 22% of patients did not receive a specific primary treatment; the proportion of such patients gradually increased through the period under review.

TABLE 2

One-, three-, and five-year observed and net survival (with a 95% confidence interval–CI) of patients with non-Hodgkin's lymphoma by sex and period of diagnosis in Slovenia in 1997–2016.

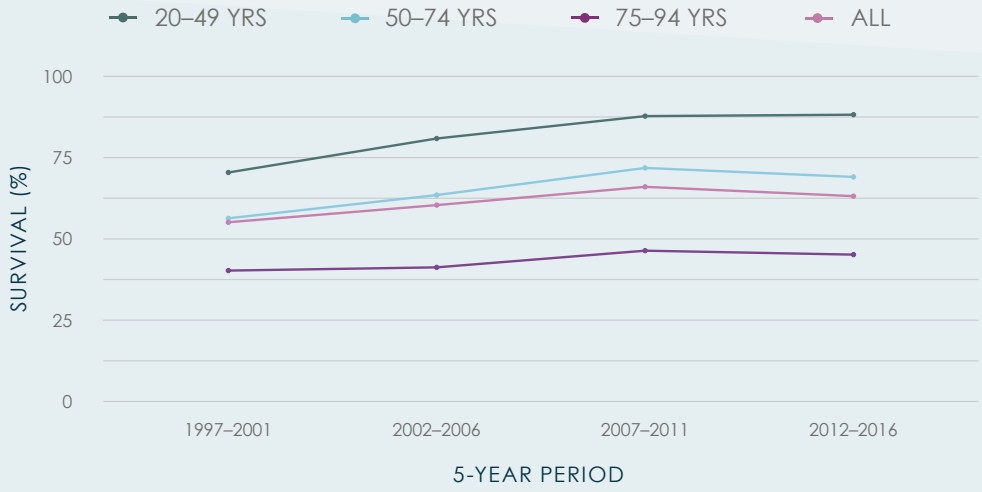
Survival / Period			1997–2001	(95% CI)	2002–2006	(95% CI)	2007–2011	(95% CI)	2012–2016	(95% CI)
Observed	1-year	all	72.2	69.5–75.0	74.9	72.4–77.4	77.8	75.7–80.0	74.4	72.5–76.4
		men	71.9	68.0–76.0	74.1	70.5–77.8	77.4	74.4–80.5	74.7	72.1–77.4
		women	72.4	68.7–76.2	75.6	72.3–78.9	78.2	75.3–81.3	74.2	71.5–77.0
	3-year	all	56.0	53.0–59.1	61.0	58.3–63.9	64.2	61.7–66.7	62.1	60.0–64.3
		men	56.0	51.8–60.6	59.4	55.4–63.6	62.4	59.0–66.1	62.6	59.7–65.7
		women	55.9	51.9–60.3	62.5	58.8–66.3	65.9	62.5–69.5	61.6	58.6–64.7
	5-year	all	47.1	44.2–50.3	52.6	49.8–55.5	57.7	55.2–60.3	55.3	53.0–57.7
		men	45.9	41.7–50.5	50.3	46.3–54.6	56.1	52.6–59.8	55.8	52.7–59.1
		women	48.3	44.3–52.6	54.5	50.8–58.5	59.4	55.9–63.1	54.8	51.6–58.2
Net	1-year	all	74.3	71.6–77.2	77.1	74.6–79.7	80.2	78.0–82.5	76.4	74.4–78.4
		men	74.4	70.4–78.7	76.6	72.9–80.6	80.0	76.8–83.2	76.9	74.2–79.7
		women	74.3	70.5–78.2	77.5	74.1–81.0	80.4	77.3–83.6	75.8	73.1–78.7
	3-year	all	61.0	57.7–64.5	67.0	63.9–70.2	69.9	67.1–72.7	67.0	64.7–69.4
		men	61.9	57.1–67.1	66.2	61.7–71.1	68.7	64.8–72.9	68.6	65.4–72.1
		women	60.1	55.7–64.9	67.5	63.5–71.8	70.9	67.1–74.9	65.3	62.1–68.7
	5-year	all	54.9	51.3–58.8	60.4	56.6–64.4	65.9	62.8–69.2	63.5	60.8–66.3
		men	55.1	49.8–60.9	58.6	52.7–65.1	65.3	60.9–70.1	65.7	61.9–69.8
		women	54.7	49.8–60.1	61.6	57.1–66.5	66.5	62.2–71.1	61.3	57.6–65.2

In the last five-year period, the majority of patients received systemic treatment as part of their primary treatment at the Institute of Oncology Ljubljana (88%), and to a lesser extent at the University Medical Centre Ljubljana (6%) and the University Medical Centre Maribor (2%). Some patients were also treated in other hospitals.

The net survival of non-Hodgkin's lymphoma patients in relation to the year of diagnosis has been gradually increasing (Figure 2, Table 2). During the 20 years under review, five-year net survival improved by 9 percentage points. During the whole 20-year period, no major differences were observed between the sexes for five-year net survival of non-Hodgkin's lymphoma patients (Table 2).

FIGURE 3

Five-year net survival of patients with non-Hodgkin's lymphoma by age group in Slovenia in 1997–2016.



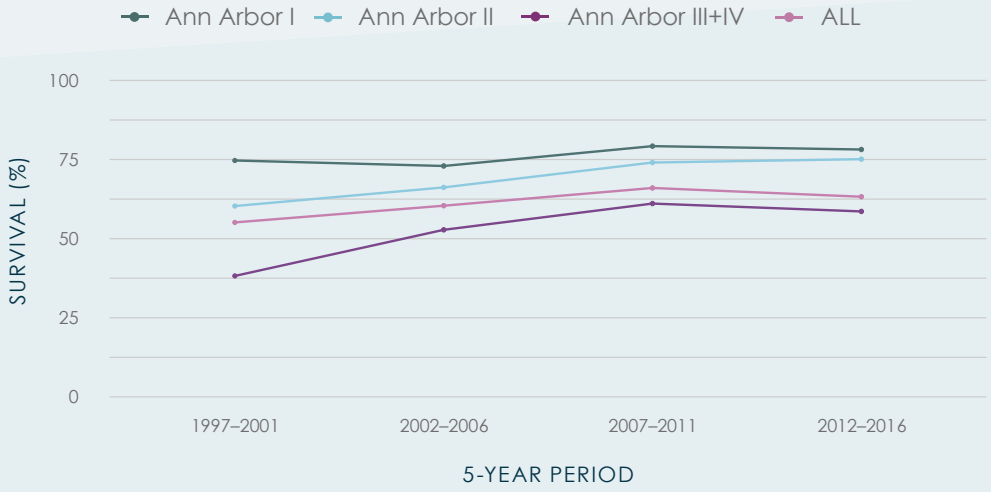


FIGURE 4

Five-year net survival of patients with non-Hodgkin's lymphoma by stage in Slovenia in 1997–2016.

In Slovenia, compared to other selected cancers, non-Hodgkin's lymphoma ranks 6th in men and 8th in women by five-year net survival.

Figure 3 shows the impact of age on the survival of non-Hodgkin's lymphoma patients. Five-year net survival was highest in all observed periods in those aged 20–49 at the time of diagnosis, and improved by 18 percentage points in the last five-year period, between 2012–2016, compared to the first period, between 1997–2001. The five-year net survival of patients aged 75–94 is the lowest at 40–46% (Figure 3).

The importance of stage at diagnosis is shown in Figure 4. Five-year net survival of patients diagnosed in the first stage surpassed 79% in the last five-year period. The five-year net survival of patients diagnosed in the second stage was 76%, approaching the first stage survival. Survival is poorest in patients diagnosed in the third and fourth stages (58% in the last five-year period), but improved by more than 20 percentage points in 2012–2016 compared to 1997–2001.

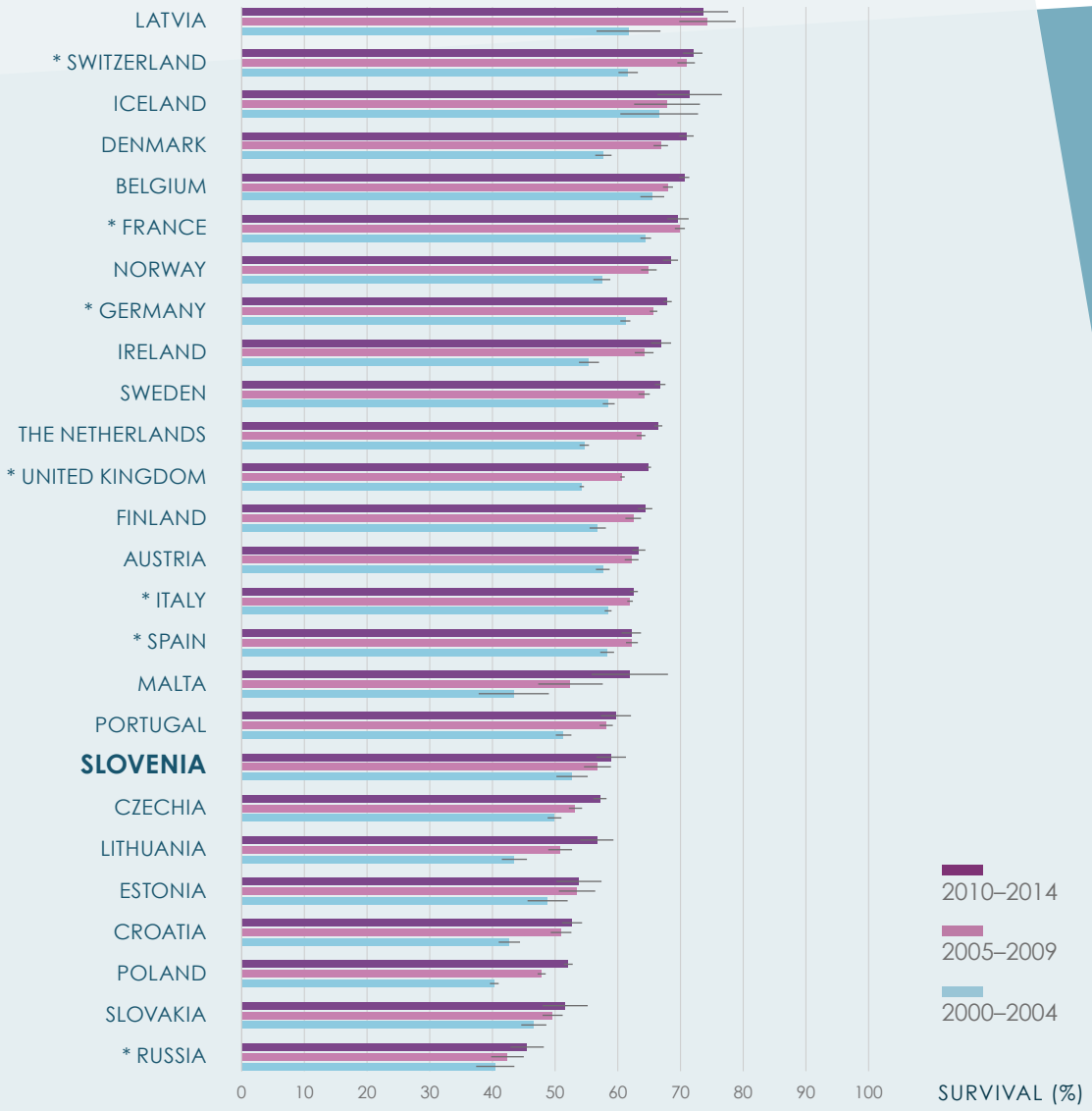


FIGURE 5

International comparison of age-standardized five-year net survival in lymphoid malignancies (with 95% confidence intervals) in patients diagnosed in 2000–2004, 2005–2009 and 2010–2014 (CONCORD-3).

** Data doesn't cover a 100% of the country's population.*

NOTE FOR FIGURE 5

Lymphoid malignancies were defined by HAEMACARE19 groups 1–19, incorporating morphology codes from the first revision of ICD-O-3: Lymphoma NOS (9590), NH Lymphoma NOS (9591,9597), Composite HL and NHL (9596), HL nodular lymphocyte predominance (9659), Classical HL (9650-9655, 9661-9665, 9667), CLL/SLL (9670, 9823), Immunoproliferative diseases (9671, 9760-9762), Mantle cell/centrocytic lymphoma (9673), Follicular B lymphoma (9690, 9691, 9695, 9698), Diffuse B lymphoma (9675, 9678-9680, 9684, 9688, 9712, 9735, 9737, 9738), Burkitt's leukaemia/lymphoma (9687, 9826), Marginal zone lymphoma (9689, 9699, 9764), T lymphoma cutaneous (9700, 9701, 9708, 9709, 9718, 9726), Other T-cell lymphoma (9702, 9705, 9714, 9716 9717, 9719, 9725, 9827, 9831, 9834, 9948), Lymphoblastic lymphoma/acute (precursor cell) lymphoblastic leukaemia (9727-9729, 9811-9818, 9835-9837), Plasma cell neoplasms (9731-9734), Mature B cell leukaemia (9833), Mature B-cell leukaemia, hairy cell (9940), Lymphatic leukaemia NOS (9820, 9832).

The results of the world-wide CONCORD-3 study of patients diagnosed during the 15 years between 2000 and 2014 in 71 countries and territories show that five-year net survival of Slovenian patients with lymphoid malignancies has been improving (Figure 5). The diagnoses that are included in the international comparison are listed below the figure and also include Hodgkin's lymphomas. For patients diagnosed during the most recent period (2010–2014), Slovenia ranked 19th among the 26 participating countries in Europe.

Barbara Jezeršek Novaković

During the 20-year period under review, the age-standardized incidence of non-Hodgkin's lymphomas increased quite sharply. In the last five-year period, almost twice as many patients were diagnosed than in the first five-year period. In terms of sex, women predominated in the first two five-year periods, while in the last two five-year periods the proportion of women and men is similar. The proportion of patients treated at the Institute of Oncology Ljubljana slightly increased, whereas at other institutions it decreased. The proportion of patients who received systemic therapy alone remained broadly unchanged during the observation period, whereas the proportion of patients receiving systemic therapy and radiotherapy decreased slightly in the last five-year period. Most likely, this can be attributed to the determination of remission with a PET/CT examination once systemic therapy is over. This allows a safe cessation of radiotherapy when complete remission is achieved. Surgical treatment is intended only for patients with indolent forms of first-stage lymphoma, where surgical biopsy of the affected lymph node is also the only treatment option. The high proportion of patients who did not receive specific primary treatment are mostly those with advanced indolent lymphoma who are only clinically monitored during the asymptomatic period, and to a lesser extent those who were not suitable for specific treatment.

Age-standardized mortality changed less than incidence in the period under review, and an upward trend was indicated in the most recent period. Patients had the best five-year net survival between 2007–2011, and the same goes for one-, three-, and ten-year survival. Between 2012 and 2016, one-, three- and five-year survival deteriorated slightly. The proportion of patients with localized disease (stages I and II) decreased, and the proportion of patients with distant disease increased accordingly. This can be explained, at least in part, by a more accurate diagnosis, which in most subtypes of non-Hodgkin's lymphomas involves a baseline PET/CT examination. The proportion of patients in whom the stage was not determined also remained relatively high. Survival of patients with localized disease (stages I and II) improved during the observed period; the same applies to the survival of patients with distant disease, except for patients diagnosed in the last five-year period, in whom survival deteriorated by 3 percentage points compared to the 2007–2011 period. The large proportion of patients diagnosed with distant disease also contributed to a slight deterioration in the five-year survival of all patients between 2012–2016.

The proportion of patients aged 75–94 at diagnosis increased during the period under review. Survival of patients aged 20–49 and those aged 75–94 improved throughout the observed period, while survival of patients aged 50–75 also improved, except between 2012–2016. The survival of all patients in the period from 2012–2016 was thus slightly lower than in the 2007–2011 period, most likely due to the predominant proportion of patients aged 50–75 and patients with distant disease.

References

Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014; 32(27): 3059–68.

DeVita VT, Lawrence TS, Rosenberg SA, eds. DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology (11th edition). Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins; 2018.

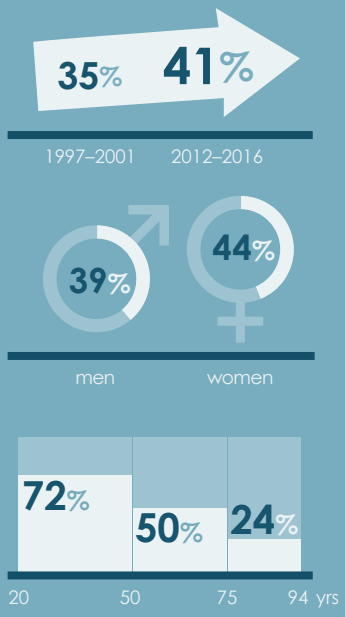
Jezeršek Novaković, B, Gašljević, G, Jagodic M, et al. Smernice za obravnavo bolnikov z malignimi limfomi (Guidelines for treatment of patients with lymphoid neoplasms). Ljubljana: Institute of Oncology; 2018.

Swerdlow SH, Campo E, Harris NL, et al., eds. WHO classification of tumours of haematopoietic and lymphoid tissues (Revised 4th Edition). Lyon: International Agency for Research on Cancer; 2017.

Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 2016; 127(20): 2375–90.

C90

PLASMACYTOMA



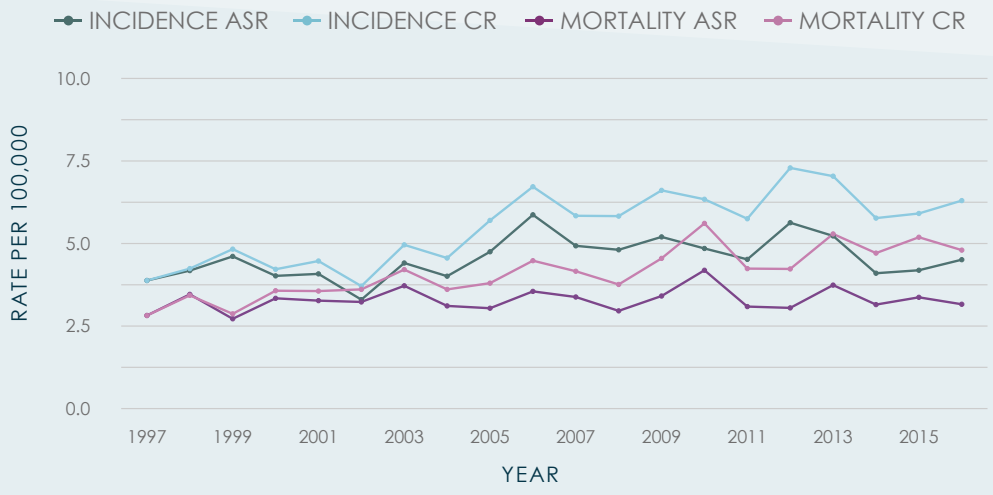
EPIDEMIOLOGY

In the last five-year period (2012–2016), 133 people per year on average were diagnosed with plasmacytoma (in ICD-10 chapter: Multiple myeloma and malignant plasma cell neoplasms) in Slovenia, 70 men and 63 women, and 100 people died, 50 men and 50 women. Figure 1 shows the time trend of plasmacytoma incidence and mortality rates. Due to the small number of cases throughout the observed period, it is difficult to talk about a consistent trend. Over the last ten years, the crude incidence rate increased by 0.5% per year in both sexes; it increased by 0.8% in men and decreased by 0.2% in women. Between 2007–2016, the crude mortality rate of plasmacytoma increased by 2% per year, by 2.9% in men and by 1.8% in women. The trend in the crude incidence and mortality rates is not statistically significant.

At the end of 2016, there were 618 people living in Slovenia who had been diagnosed with plasmacytoma at some point in their lives. Of those, the diagnosis had been established less than one year ago in 110 people, one to four years ago in 262 people, and over ten years ago in 93 people.

FIGURE 1

The crude (CR) and age-standardized (ASR) incidence and mortality rates of plasmacytoma in Slovenia in 1997–2016.



The survival analysis included 2,188 cases of patients aged 20–94; 34 cases (2%) were excluded because they were diagnosed on the day of death, or because they did not fulfil the age inclusion criteria.

Over the observed periods, most cases (88–94%) occurred as multiple myeloma (C90.0). The disease occurred in the form of extramedullary plasmacytoma (C90.2) in 5–12% of cases, and in the form of plasma cell leukaemia (C90.1) in 1% or less.

In all observed periods, the disease was confirmed microscopically in 99% of cases or more.

	Sex			Age			Total
	Men		Women	20–49 yrs	50–74 yrs	75–94 yrs	
1997–2001		181	236	26	281	110	417
	%	43.4	56.6	6.2	67.4	26.4	
2002–2006		239	260	39	314	146	499
	%	47.9	52.1	7.8	62.9	29.3	
2007–2011		322	289	44	350	217	611
	%	52.7	47.3	7.2	57.3	35.5	
2012–2016		349	312	34	371	256	661
	%	52.8	47.2	5.1	56.1	38.7	

TABLE 1

Number and proportion of patients with plasmacytoma by sex, age, and period of diagnosis in Slovenia in 1997–2016.

Plasmacytoma affected slightly more women than men in the first two five-year periods, from 1997–2006, and slightly more men than women in the last two five-year periods, from 2007–2016. The largest proportion of people were diagnosed between the ages of 50–74 (Table 1).

Regarding the specific primary treatment of plasmacytoma between 1997–2016, most patients (42%) received systemic treatment alone, followed by systemic treatment in combination with radiotherapy (16%). A total of 33% of patients were without specific primary treatment across the entire period under review; the proportion of patients who did not receive a specific primary treatment did not differ significantly between any of the observed periods.

As part of their primary treatment, patients were given systemic therapy in 11 hospitals. They most often received systemic therapy at the University Medical Centre Ljubljana (60%), less often at the University Medical Centre Maribor (13%), Celje General Hospital (10%), and Nova Gorica General Hospital (7%), and 5% or less in other hospitals.

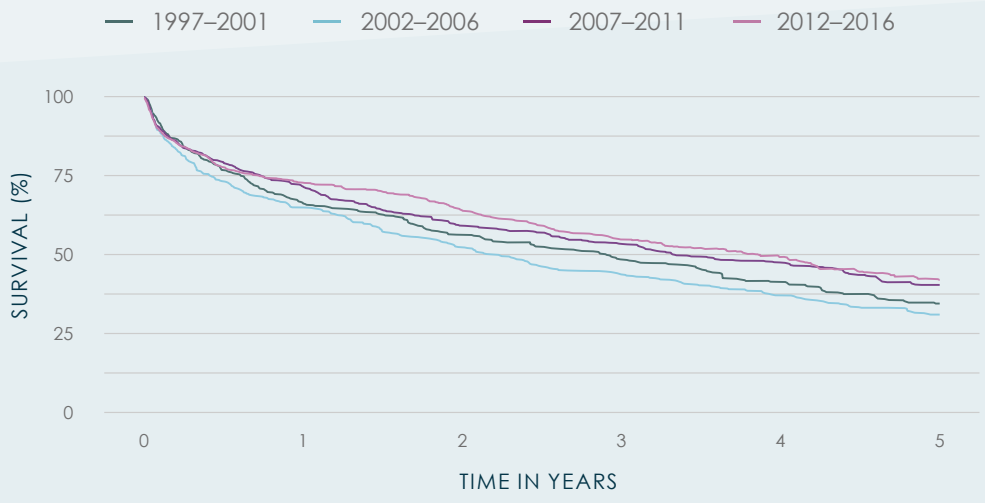


FIGURE 2

Net survival of patients with plasmacytoma by period of diagnosis in Slovenia in 1997–2016.

The net survival of patients with plasmacytoma has been gradually improving in relation to the year of diagnosis (Figure 2, Table 2). During the 20 years observed, five-year net survival improved by 6 percentage points, but the improvement is not statistically significant. During the whole 20 years under review, there were no major differences in five-year net survival observed between the sexes (Table 2).

TABLE 2

One-, three-, and five-year observed and net survival (with a 95% confidence interval – CI) of patients with plasmacytoma by sex and period of diagnosis in Slovenia in 1997–2016.

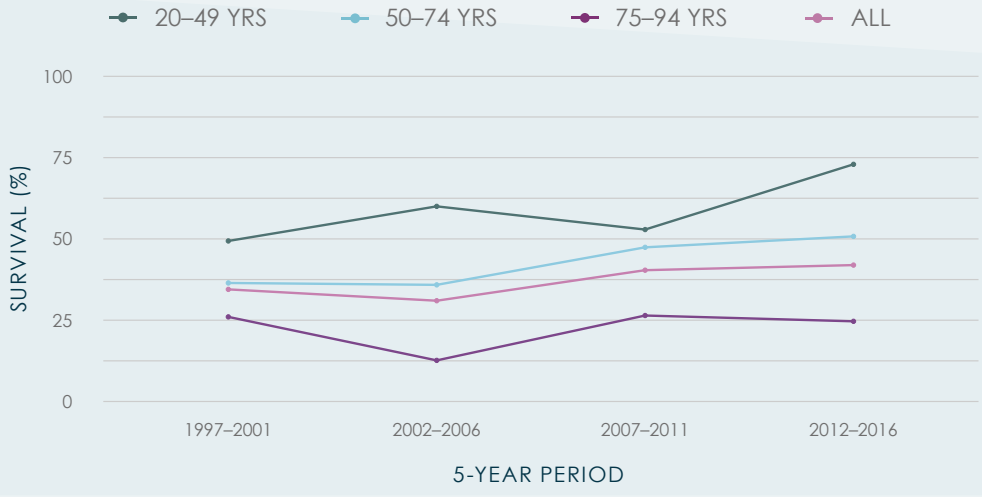
Survival / Period			1997–2001	(95% CI)	2002–2006	(95% CI)	2007–2011	(95% CI)	2012–2016	(95% CI)
Observed	1-year	all	63.9	59.4–68.7	63.1	59.0–67.5	69.2	65.7–73.0	70.5	67.1–74.1
		men	63.5	56.9–71.0	66.1	60.4–72.4	71.4	66.7–76.5	69.6	65.0–74.6
		women	64.1	58.3–70.6	60.4	54.7–66.6	66.8	61.6–72.4	71.5	66.6–76.7
	3-year	all	43.3	38.8–48.4	40.1	36.0–44.6	48.8	45.0–52.9	50.1	46.4–54.1
		men	45.8	39.0–53.6	42.7	36.9–49.4	49.4	44.2–55.2	50.7	45.7–56.2
		women	41.5	35.6–48.3	37.7	32.2–44.1	48.1	42.7–54.2	49.5	44.2–55.3
	5-year	all	28.8	24.8–33.5	27.3	23.6–31.5	35.2	31.6–39.2	36.5	32.7–40.7
		men	29.6	23.6–37.1	30.1	24.8–36.5	35.7	30.9–41.4	34.1	29.0–40.2
		women	28.2	23.0–34.6	24.6	19.9–30.5	34.6	29.5–40.6	38.9	33.6–45.1
Net	1-year	all	66.3	61.7–71.3	65.1	60.8–69.6	71.5	67.8–75.5	72.7	69.2–76.4
		men	66.5	59.6–74.2	68.4	62.5–75.0	74.3	69.3–79.6	72.1	67.2–77.3
		women	66.2	60.1–72.8	62.0	56.1–68.4	68.5	63.1–74.3	73.4	68.4–78.8
	3-year	all	48.7	43.5–54.4	43.8	39.2–48.9	53.4	49.1–58.1	54.6	50.4–59.1
		men	51.9	44.1–61.1	47.5	41.0–55.2	54.6	48.7–61.4	55.5	49.9–61.8
		women	46.2	39.6–53.8	40.3	34.3–47.4	52.1	46.2–58.8	53.5	47.6–60.1
	5-year	all	34.5	29.3–40.6	31.1	26.6–36.2	40.4	35.2–46.3	41.3	36.7–46.6
		men	36.8	28.9–46.9	35.6	28.9–43.9	41.2	33.4–50.8	38.9	32.6–46.4
		women	32.8	26.4–40.7	26.9	21.5–33.6	39.4	33.3–46.6	44.0	37.5–51.5

In Slovenia, compared to other selected cancers, plasmacytoma ranks 15th in men and 16th in women by five-year survival.

Figure 3 shows the impact of age on the survival of patients with plasmacytoma. Five-year net survival is highest in all observation periods in patients aged 20–49 at the time of diagnosis. It improved by 21 percentage points in the last five-year period (2012–2016) compared to the first five-year period (1997–2001). Five-year net survival is lowest (13–26%) in patients aged 75–94 years (Figure 3).

FIGURE 3

Five-year net survival of patients with plasmacytoma by age group in Slovenia in 1997–2016.



Samo Zver

Multiple myeloma is a common blood disease and results from monoclonal gammopathy of undetermined significance. Women and black people get sick more often. The incidence of the disease in Western Europe is five to ten people per 100,000 population. Between 2008–2011, the Clinical Department of Haematology at the University Medical Centre Ljubljana conducted a study on multiple myeloma incidence in Slovenian regions and found that it was highest in Ljubljana (75 cases per 10,000 population) and lowest in the Gorenjska and Koper regions (22 and 36 cases per 10,000 population, respectively). Our conclusion was that where there are no haematologists, the disease is not detected.

The number of newly diagnosed patients increased over the period under review, which shows that doctors are more aware of the disease and recognize it sooner. The incidence in the last two five-year periods (60 cases per 10,000 inhabitants) reflects the ongoing situation in Slovenia.

By far the largest number of patients received their first specific treatment at the Clinical Department of Haematology at the University Medical Centre Ljubljana. The number has increased in recent periods, and in the last five-year period, it amounted to as much as 50% of all patients in Slovenia, a concerningly high proportion of patients. At the University Medical Centre Maribor, the number of first-time patients has stagnated and is more than three times lower than at the University Medical Centre Ljubljana. The number of patients treated in Celje General Hospital is comparable to Maribor. This is not good, as Maribor should be Slovenia's second largest tertiary centre for the treatment of blood diseases, including multiple myeloma. In the whole period under review, about 30% of patients did not live long enough to receive primary treatment. These are the oldest patients (incidence of the disease increases with age), in whom the disease is very advanced, or even more commonly, patients with comorbidities for whom palliative treatment is the only suitable option.

Survival of treated patients improved with time (Figure 2). Survival improved most in the youngest group of patients. Those aged under 50 have a five-year survival rate of 72%, those aged 50–74 50% and those 75–94 24% (Figure 3). The significantly longer survival in patients younger than 70 is mainly due to consistent treatment with autologous haematopoietic stem cell transplantation, often in tandem, as well as due to the introduction of new drugs. In Slovenia, almost all the new drugs are available: proteasome inhibitors, immunomodulators, monoclonal antibodies, and histone deacetylase inhibitors. These drugs are used in combination with corticosteroids. However, combinations of new drugs have a number of side effects and therefore cannot be used in older patients as they are in younger ones. This is what clinical intelligence and experience dictate. The survival of multiple myeloma patients is expected to improve in the coming years.

References

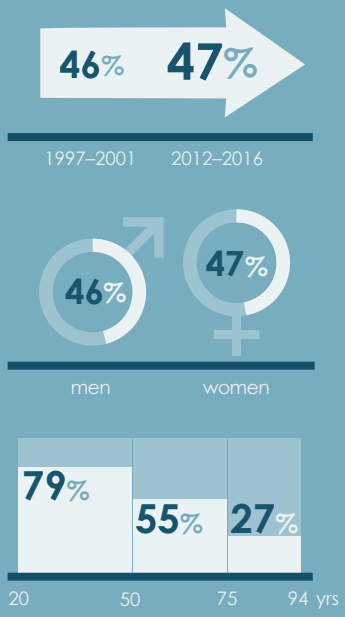
Mateos MV, Ludwig H, Bazarbachi A, et al. Insights on multiple myeloma treatment strategies. HemaSphere 2019; 3(1): e163.

Zver S, Melkič E, Radevska T. Zdravljenje diseminiranega plazmocitoma na Kliničnem oddelku za hematologijo UKC Ljubljana z avtologno presaditvijo krvotvornih matičnih celic v letih 2014 in 2015. Zdrav Vest 2016; 85(9): 467–75.

Zver S. Plazmacitne novotvorbe (Plasmocytoma). In: Košnik M, Štajer D, eds. Interna medicina. 5th ed. Ljubljana: Medical Faculty of University of Ljubljana, Slovene Medical Association, Buča; 2018. p. 1191–200.

C91–C95

LEUKAEMIAS



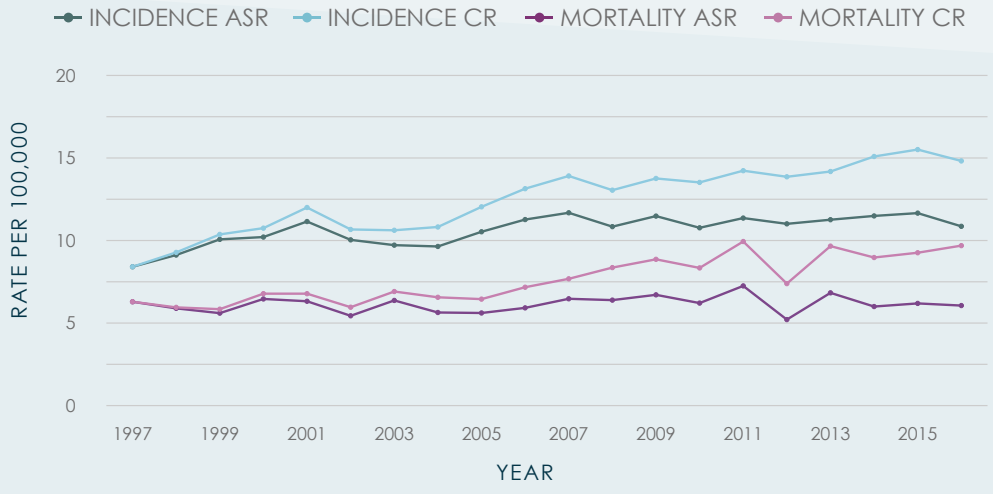
EPIDEMIOLOGY

In the last five-year period (2012–2016), 303 people per year on average were diagnosed with leukaemia in Slovenia, 172 men and 131 women, and 185 people died, 107 men and 78 women. Figure 1 shows the time trend of leukaemia incidence and mortality rates. Over the last ten years, the crude incidence rate increased by 1.4% per year, by 1.2% in men and 1.7% in women. The increase is statistically significant in both sexes combined and in women. Slightly over 60% of the increase in incidence rates in the observed period can be attributed to population ageing. Between 2007–2016, the leukaemia crude mortality rate increased by 1.9% per year, by 2.4% in men and by 1.3% in women. The increase is not statistically significant.

At the end of 2016, there were 2,029 people living in Slovenia who had been diagnosed with leukaemia at some point in their lives. Of those, the diagnosis had been established less than one year ago in 234 people, one to four years ago in 622 people, and over ten years ago in 720 people.

FIGURE 1

The crude (CR) and age-standardized (ASR) incidence and mortality rates of leukaemia in Slovenia in 1997–2016.



The survival analysis included 4,626 cases of patients aged 20–94; 436 cases (9%) were excluded because they were diagnosed on the day of death, or they did not fulfil the age inclusion criteria.

During the whole observed period, lymphoid leukaemias (C91) made up the highest (46–60%) proportion of leukaemias. Of lymphoid leukaemias, the highest proportion (39–51%) was chronic lymphocytic leukaemia of B-cell type (C91.1), followed by acute lymphoblastic leukaemia (C91.0) with about 5%, and hairy-cell leukaemia (C91.4) with about 2%. Myeloid leukaemia (C92) occurred in 30–41%, of which acute myeloiblastic leukaemia (C92.0) made up the highest proportion (14–25%), followed by chronic myeloid leukaemia (C92.1) with 5–9% and acute myelomonocytic leukaemia (C92.5) with 5%. Other leukaemias of specified cell type (C94) occurred in 5–10% and acute monocytic leukaemias (C93.0) in 2–3% of cases. Leukaemia of unspecified cell type (C95) occurred in 1–3%; in most cases, it was acute leukaemia of unspecified cell type (C95.0).

	Sex		Age			Total
	Men	Women	20–49 yrs	50–74 yrs	75–94 yrs	
1997–2001	507	387	133	523	238	894
1997–2001 %	56.7	43.3	14.9	58.5	26.6	
2002–2006	580	465	141	563	341	1045
2002–2006 %	55.5	44.5	13.5	53.9	32.6	
2007–2011	731	553	132	676	476	1284
2007–2011 %	56.9	43.1	10.3	52.7	37.1	
2012–2016	797	606	136	740	527	1403
2012–2016 %	56.8	43.2	9.7	52.7	37.6	

TABLE 1

Number and proportion of patients with leukaemia by sex, age, and period of diagnosis in Slovenia in 1997–2016.

Throughout the whole observed period, the disease was not microscopically confirmed in only one case. Most cases of microscopically confirmed disease were chronic lymphocytic leukaemia (39% in the last five-year period) and other leukaemias (51% in the last five-year period). 10% of cases were chronic myeloproliferative disease; there were no unspecified cases.

More men than women were diagnosed with leukaemia throughout the observed period. The largest proportion of people were diagnosed between the ages of 50–74 (Table 1).

Regarding the specific primary treatment of leukaemia between 1997–2016, the largest proportion of patients (33%) received systemic therapy alone, followed by systemic therapy in combination with radiotherapy in 2%. A total of 64% of patients were without specific primary treatment across the entire

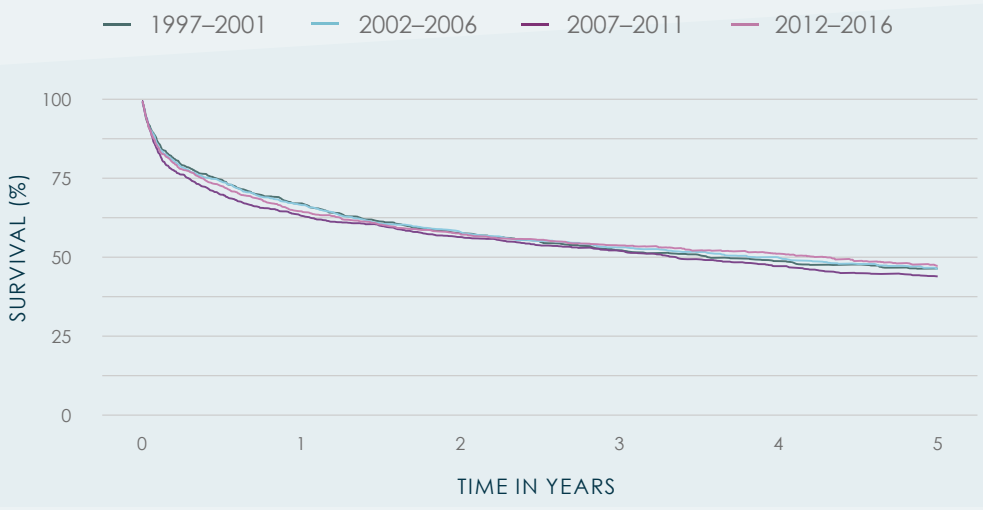


FIGURE 2

Net survival of patients with leukaemia by period of diagnosis in Slovenia in 1997–2016.

TABLE 2

One-, three-, and five-year observed and net survival (with a 95% confidence interval–CI) of patients with leukaemia by sex and period of diagnosis in Slovenia in 1997–2016.

Survival / Period			1997–2001	(95% CI)	2002–2006	(95% CI)	2007–2011	(95% CI)	2012–2016	(95% CI)
Observed	1-year	all	64.9	61.8–68.1	64.0	61.2–67.0	60.9	58.3–63.6	62.6	60.1–65.1
		men	67.3	63.3–71.5	65.2	61.4–69.2	62.9	59.5–66.5	61.1	57.8–64.6
		women	61.8	57.1–66.8	62.6	58.3–67.1	58.2	54.3–62.5	64.5	60.8–68.5
	3-year	all	47.0	43.8–50.4	47.2	44.3–50.3	46.7	44.0–49.5	49.3	46.8–52.0
		men	50.9	46.7–55.4	47.2	43.4–51.5	47.5	44.0–51.2	47.6	44.2–51.2
		women	41.9	37.2–47.1	47.1	42.8–51.9	45.6	41.6–49.9	51.6	47.8–55.8
	5-year	all	38.5	35.4–41.8	38.7	35.8–41.7	37.4	34.8–40.1	41.1	38.4–43.9
		men	41.2	37.2–45.7	38.5	34.7–42.6	39.4	36.0–43.1	39.5	36.1–43.3
		women	34.9	30.4–40.0	38.9	34.7–43.6	34.7	31.0–38.9	43.1	39.1–47.6
Net	1-year	all	67.0	63.8–70.3	66.4	63.5–69.5	63.1	60.4–65.9	64.4	61.9–67.1
		men	69.6	65.4–73.9	67.7	63.8–71.9	65.4	61.8–69.1	63.0	59.6–66.6
		women	63.6	58.8–68.8	64.8	60.4–69.5	60.1	56.0–64.5	66.3	62.5–70.3
	3-year	all	52.2	48.6–56.0	52.8	49.4–56.5	51.8	48.8–55.0	53.6	50.7–56.6
		men	56.7	52.0–61.8	52.6	48.1–57.5	52.7	48.7–57.0	52.0	48.3–56.1
		women	46.3	41.1–52.1	53.0	48.0–58.5	50.6	46.2–55.5	55.6	51.4–60.2
	5-year	all	46.4	42.6–50.5	46.0	42.3–50.0	43.6	40.4–47.1	46.6	43.2–50.2
		men	49.8	44.7–55.4	45.3	40.4–50.7	45.9	41.7–50.6	46.0	41.8–50.6
		women	41.6	36.2–47.9	46.7	41.1–53.0	40.5	35.8–46.0	47.2	41.9–53.0

period under review; the proportion of patients who did not receive a specific primary treatment did not significantly change through the observed five-year periods.

As part of their specific primary treatment in the last five-year period, patients received systemic therapy at 12 hospitals. They mostly received systemic treatment at the University Medical Centre Ljubljana (69%), less often at the University Medical Centre Maribor (12%) and General Hospital Celje (8%), and in other hospitals in 3% or less.

Regarding the year of diagnosis, the net survival of leukaemia patients has not been changing significantly (Figure 2, Table 2). During the 20 years observed, five-year net survival was similar in all five-year periods. During the overall observed period, no major differences were observed between the sexes for five-year net survival of leukaemia patients (Table 2).

In Slovenia, compared to other selected cancers, leukaemia ranks 13th in men and 14th in women by five-year net survival.

FIGURE 3

Five-year net survival of patients with leukaemia by age group in Slovenia in 1997–2016.

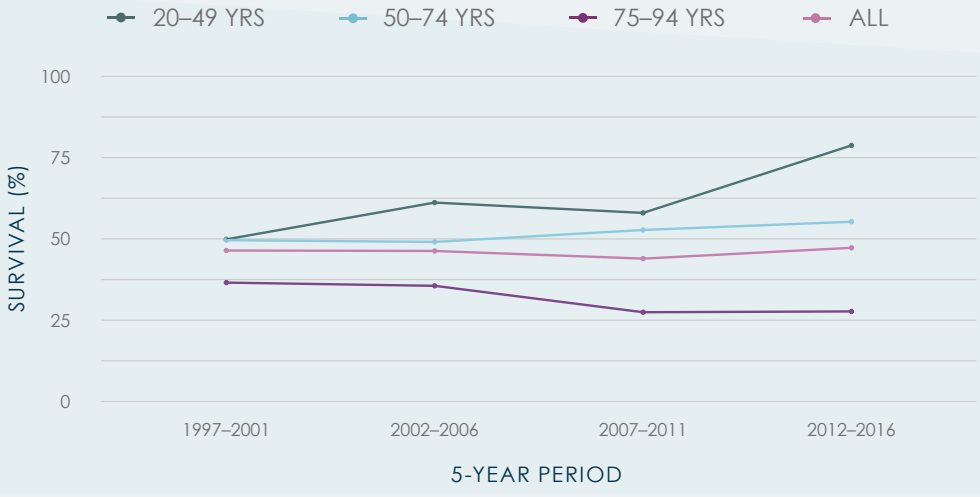


Figure 3 shows the impact of age on the survival of patients with leukaemia. In all observed periods five-year net survival is highest in patients aged 20–49 at the time of diagnosis, and improved by 29 percentage points comparing the last five-year period (2012–2016) to the first one (1997–2001). The five-year net survival is lowest (27–37%) in patients aged 75–94(Figure 3).

The results of the world-wide CONCORD-3 study of patients diagnosed with cancer during the 15 years between 2000 and 2014 in 71 countries and territories show that five-year net survival of Slovenian patients with myeloid malignancies is deteriorating with time, but the change is not statistically significant (Figure 5). The diagnoses included in the international comparison are listed below the figure. For patients diagnosed during the most recent period (2010–2014), Slovenia ranked 20th among the 26 participating countries in Europe.

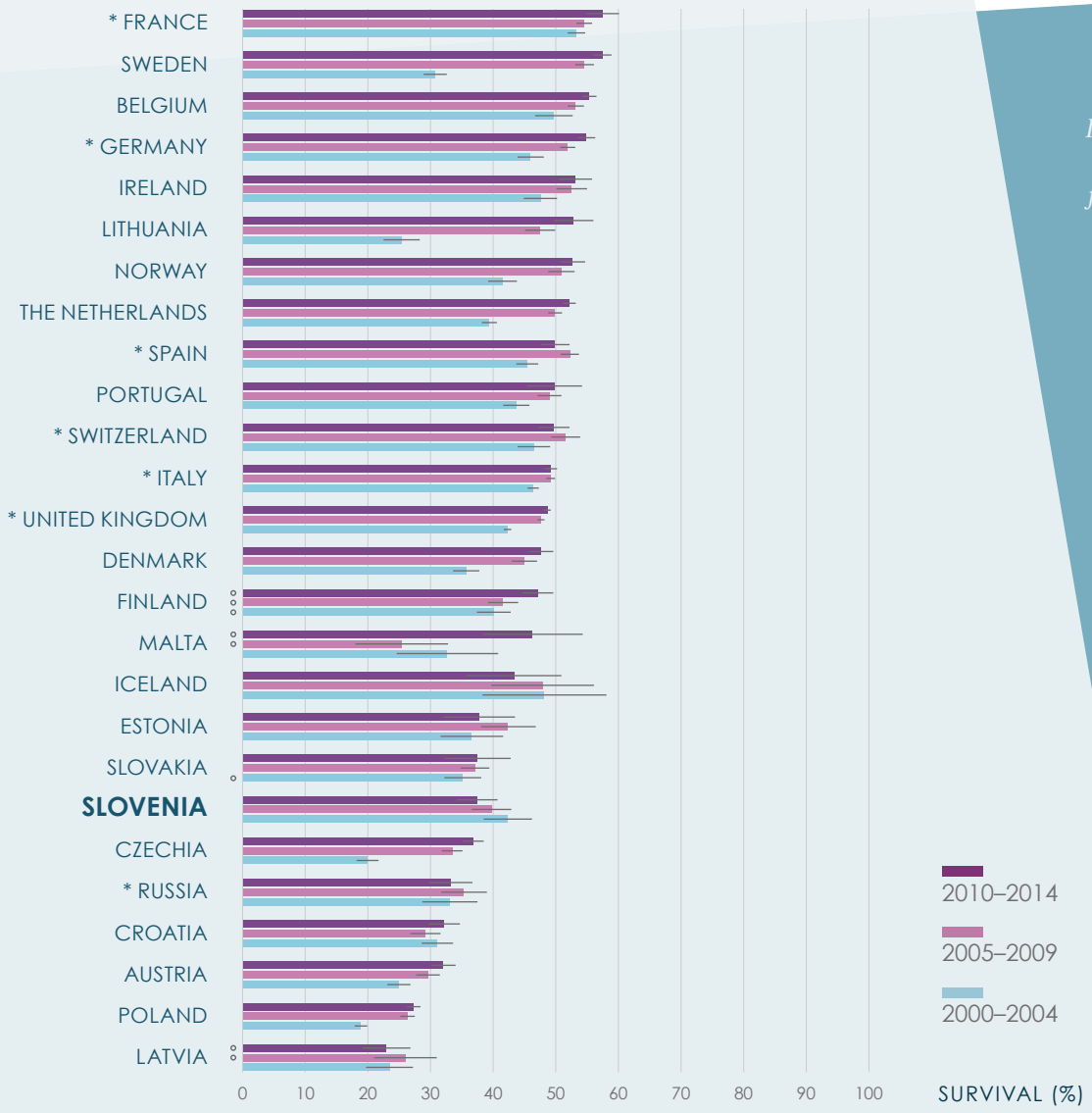


FIGURE 4

International comparison of age-standardised five-year net survival for myeloid malignancies (with 95% confidence intervals) in patients diagnosed in 2000–2004, 2005–2009 and 2010–2014 (CONCORD-3).

** Data doesn't cover a 100% of the country's population.*

° Survival estimate is less reliable.

NOTE FOR FIGURE 4

Myeloid malignancies were defined by HAEMACARE groups 20–25, incorporating morphology codes from the first revision of ICD-O-3: Leukaemia NOS (9800, 9801, 9805-9809), Myeloid leukaemia NOS (9860, 9898), Acute myeloid leukaemia (9840, 9861, 9865-9867, 9869-9874, 9891, 9895-9897, 9910, 9911, 9920, 9930, 9931, 9984, 9987), Myeloproliferative neoplasms (9740-9742, 9863, 9875, 9950, 9960-9964), Myelodysplastic syndrome (9980, 9982, 9983, 9985, 9986, 9989, 9991, 9992), Myelodysplastic/myeloproliferative neoplasms (9876,9945, 9946, 9975).

CLINICAL COMMENTARY

Samo Zver

To comment on leukaemia as a single disease is largely pointless, as different types have completely different incidence (including age) and mortality, and in recent years, some of them can even be treated with new drugs that are extremely effective. We are talking about acute lymphoblastic leukaemia, acute myeloid leukaemia, chronic lymphocytic leukaemia, and chronic myeloid leukaemia. The median age at which the disease is detected was 14 years in the first type, 69 years in the second, 64 in the third, and 67 in the fourth.

The incidence of individual leukaemia types cannot be deduced from the registry data provided for this analysis. In the literature, acute lymphoblastic leukaemia occurs in one person per 100,000 population, acute myeloid leukaemia in three people per 100,000 population, chronic lymphocytic leukaemia in 4.9 people per 100,000 population, and chronic myeloid leukaemia in one person per 100,000 population. In total, the incidence of all leukaemias is more than ten people per 100,000 population, which means about 300 new patients per year in Slovenia. This is consistent with the data provided for this analysis. Incidence has increased in recent periods, and leukaemia is more common in men. The increase in incidence is due to longer life expectancy, therefore an additional increase is expected.

Half of all leukaemia patients are treated at the University Medical Centre Ljubljana, and a disproportionately small number of patients at the University Medical Centre Maribor. A large proportion of patients treated in Ljubljana can be attributed to the policy that all patients under the age of 65–70 who are still candidates for treatment with allogeneic hematopoietic stem cell transplantation are treated in Ljubljana. If it is decided that a patient is going to be treated, the treatment is chemotherapy and/or new biological drugs. Almost 65% of patients do not receive treatment. This can be attributed mainly to chronic lymphocytic leukaemia, in which we treat only half of the patients with this blood disease; the rest do not require treatment, but they are actively monitored. Often, older patients with acute leukaemias are also incapable of any treatment other than palliative.

Leukaemia survival as a whole is difficult to comment on, as each subtype of leukaemia should have separate and specially processed data or curve (such as Figure 2). However, in all time periods under review, the survival curves are without fluctuations. This is due to two facts. First, there is still no effective treatment of acute leukaemias for older patients. Survival in these patients therefore remains the same in all periods: very short. Second, chronic leukaemias have a consistently large proportion of chronic patients, approximately 50% of whom will never need treatment. Patients with chronic lymphocytic leukaemia live the same length of time, regardless of whether or not they are treated. Thus, new drugs are only suitable for a small proportion of patients who need treatment. Because it is a chronic leukaemia, it takes a long time for the difference in survival to be revealed. Since patients with chronic lymphocytic leukaemia predominate, it is they who determine overall survival. The situation is similar with chronic myeloid leukaemia, in which, however, each newly diagnosed patient receives treatment. Since tyrosine kinase inhibitors were introduced into treatment, the survival of patients is long and this type of leukaemia is becoming a chronic disease, similar to what HIV infection is nowadays.

Acute lymphoblastic leukaemia and other rare types have little effect on the overall survival curve.

It is gratifying that between 2012–2016, the survival of younger patients has increased markedly. This trend is not detected in the elderly. The reason is that the modern treatment of acute leukaemias is of higher intensity, which is much more intense and aggressive in younger patients. Modern haematological supportive treatment enables higher intensity. Older patients are less likely to achieve remission, due to less intensive treatment, among other reasons. As a rule, blood disease in older patients has less favourable genetic or specific characteristics and a less favourable course. No matter what, we always make an effort to find the optimal, tailored treatment for each individual patient. It is similar with new biological drugs, the side effects often being pronounced, even life-threatening. With the new drugs, however, we have undoubtedly also helped older patients with chronic lymphocytic and

chronic myeloid leukaemia. Another segment affects the survival of young people with acute leukaemias, especially in those young patients who have unfavourable cytogenetic and clinical laboratory parameters. This is allogeneic haematopoietic stem cell transplantation, with which we treat patients approximately up to the age of 65. With this treatment, we can cure leukaemia in certain patients who otherwise have the least favourable prognoses.

References

Anžej Doma, S, Sever, M, Mlakar, U, et al. Improved survival of patients with AML by addition of cladribine to standard DA3+7 induction chemotherapy (DAC) - single center experience at University Medical Centre Ljubljana, Slovenia. Hematology 2018; 1: 1-2.

Zver S. Mieloične novotvorbe: akutne levkemije (Myeloid malignancies; acute leukemias). In: Košnik M, Štajer D, eds. Interna medicina. 5th ed. Ljubljana: Medical Faculty of University of Ljubljana, Slovene Medical Association, Buča; 2018. p. 1158–66.

Zver S. Avtologna in alogenična presaditev krvotvornih matičnih celic (Autologous and allogenic haematopoetic stem cell transplantation). In: Košnik M, Štajer D, eds. Interna medicina. 5th ed. Ljubljana: Medical Faculty of University of Ljubljana, Slovene Medical Association, Buča; 2018. p. 1206–13.

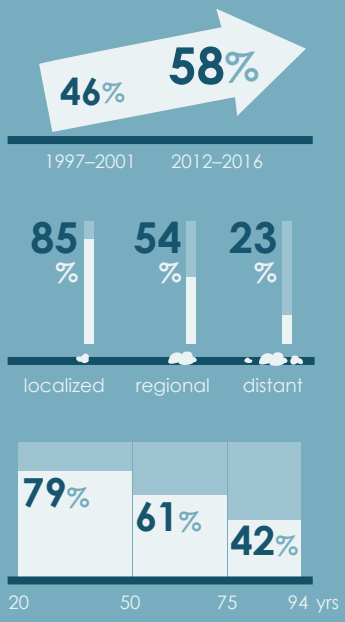
Zver S. Akutne levkemije (Acute leukemias). In: Novaković S, eds., et al. Onkologija: raziskovanje, diagnostika in zdravljenje raka. 1st ed. Ljubljana: Mladinska knjiga; 2009. p. 382–9.

III.

SURVIVAL FOR ALL CANCER SITES

C00–C96 (excl. C44)

ALL CANCERS IN ADULTS (excluding skin)



EPIDEMIOLOGY

Between 1997 and 2016, 234,827 people, 124,721 men and 110,106 women, were diagnosed with any form of cancer. Among them, 37,473 were non-melanoma skin cancer patients. Since this is a very common but almost completely curable disease and almost no one has died of it in recent years, we excluded these patients from the time trend analysis of incidence and mortality, as well as from all further survival analysis.

In the last five-year period (2012–2016), 11,599 people per year on average were diagnosed with cancer in Slovenia, 6,411 men and 5,188 women, and 6,019 people died, 3,379 men and 2,640 women. As shown in Figure 1, the incidence rates of cancer increased throughout the observed period; in the last ten years, the increase was statistically significant at 1.5% per year—1.7% in men and 1.4% in women. Over 70% of the increase in incidence rates in the observed period can be attributed to the ageing of

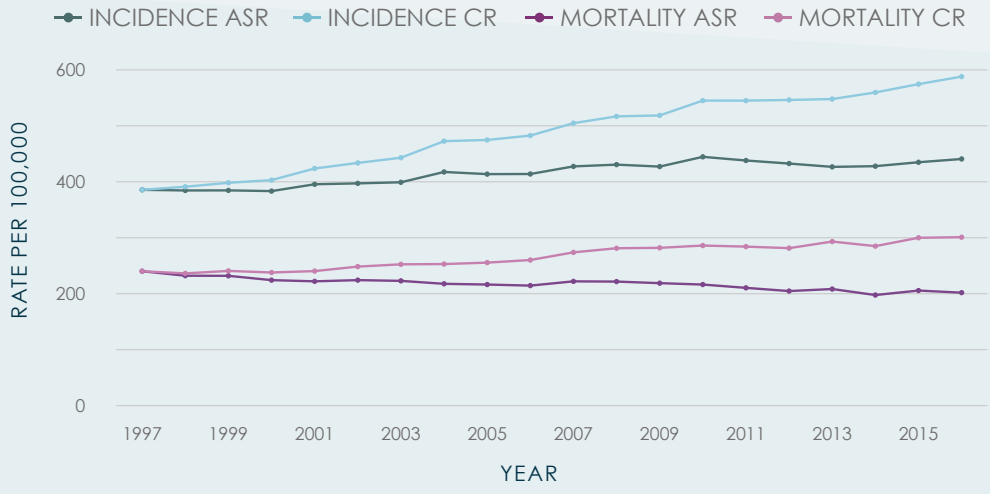


FIGURE 1

The crude (CR) and age-standardized (ASR) incidence and mortality rates of all cancer (excluding skin cancer) in Slovenia in 1997–2016.

the population. Between 2007 and 2016, the crude mortality rate of cancer increased in a statistically significant way by 0.9% per year in both sexes combined, by 0.8 % in men and by 0.9% in women.

At the end of 2016, there were 90,723 people living in Slovenia who had been diagnosed with cancer at some point in their lives. Of those, the diagnosis had been established less than one year ago in 9,811 people, one to four years ago in 26,212 people, and over ten years ago in 32,178 people.

	Sex		Age			Stage (C00–C80, excl. C44)			Total
	Men	Women	20–49 yrs	50–74 yrs	75–94 yrs	Localized	Regional	Distant	
1997–2001	19625	18311	6094	23917	7925	13337	12270	7876	37936
	% 51.7	48.3	16.1	63.1	20.9	35.2	32.3	20.8	
2002–2006	23414	21148	6148	27355	11059	15695	14298	9261	44562
	% 52.5	47.5	13.8	61.4	24.8	35.2	32.1	20.8	
2007–2011	28719	23440	6011	31744	14404	19317	16557	10758	52159
	% 55.1	44.9	11.5	60.9	27.6	37.0	31.7	20.6	
2012–2016	31142	25355	5774	33972	16751	21948	16971	11717	56497
	% 55.1	44.9	10.2	60.1	29.7	38.9	30.0	20.7	

TABLE 1

Number and proportion of patients with cancer (excluding skin cancer) by sex, age, stage and period of diagnosis in Slovenia in 1997–2016.

The survival analysis included 191,154 cases of patients aged 20 to 94 years; 6,200 cases (3%) were excluded because they were diagnosed on the day of death or they did not fulfil the age inclusion criteria.

Depending on the specific observation period, between 6–8% of patients did not have their disease confirmed microscopically. In all the observed periods, adenocarcinoma was the most common histological type among all the microscopically confirmed cases; in the last five-year period, it occurred in 61% of cases. In 2% of cases, the histological type was not defined.

Throughout the observed period, slightly more men than women were diagnosed with cancer; the majority of patients were aged from 50 to 74 years. In the case of solid tumours, the disease was mostly detected at the localized stage (Table 1).

Regarding specific primary cancer treatment between 1997 and 2016, the largest proportion of patients (31%) were treated with surgery alone. About 10% of patients were treated with systemic therapy alone, or surgery in combination with systemic therapy, or surgery in combination with systemic therapy and radiotherapy. A total of 6% of patients were treated with radiotherapy alone and 5% of patients

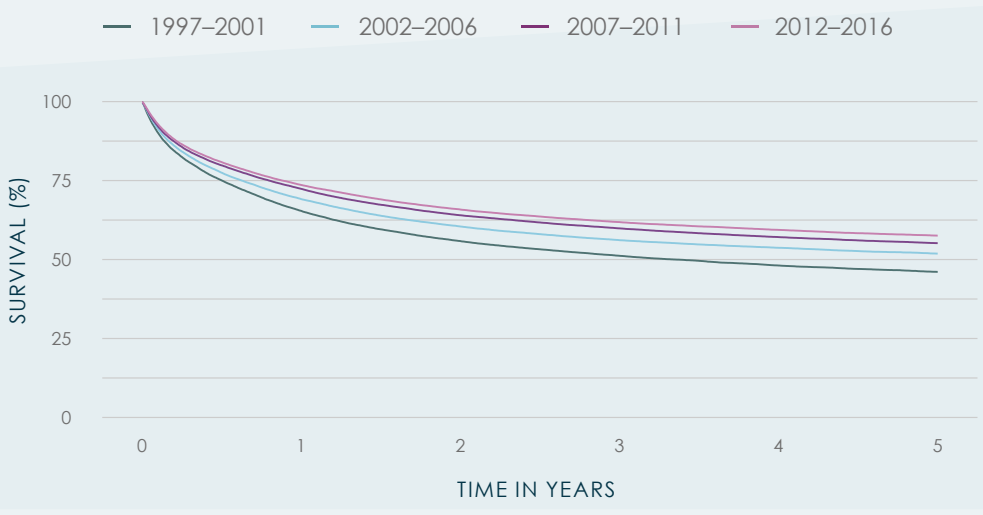


FIGURE 2

Net survival of patients with cancer (excluding skin cancer) by period of diagnosis in Slovenia in 1997–2016.

underwent surgery in combination with radiotherapy or were treated with radiotherapy in combination with systemic therapy. Throughout the observed period, 22% of patients did not receive specific primary treatment, a proportion that did not change significantly over the observed five-year periods.

Throughout the observed period, cancer surgery was performed in most hospitals. In the last five years, most surgeries were performed at the University Medical Centre Ljubljana (31%), the Institute of Oncology Ljubljana (23%), and the University Medical Centre Maribor (17%). Also, systemic cancer treatment was performed in most hospitals throughout the observed period. In the last five-year period, as part of the primary treatment, patients most often received systemic therapy at the Institute of Oncology Ljubljana (65%), followed by the University Medical Centre Maribor (12%), and the University Medical Centre Ljubljana (10%).

TABLE 2

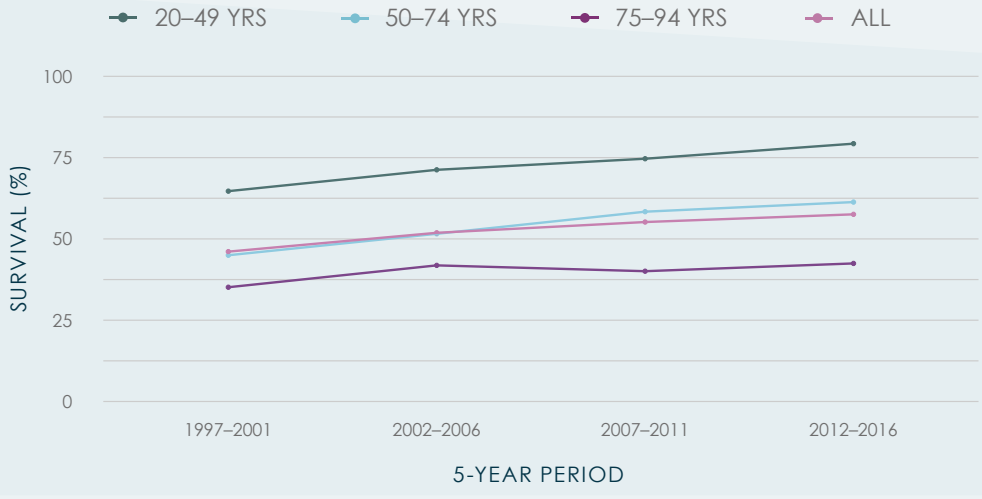
One-, three-, and five-year observed and net survival (with a 95% confidence interval–CI) of patients with cancer (excluding skin cancer) by sex and the period of diagnosis in Slovenia in 1997–2016.

Survival / Period			1997–2001	(95% CI)	2002–2006	(95% CI)	2007–2011	(95% CI)	2012–2016	(95% CI)
Observed	1-year	all	63.5	63.0–64.0	67.1	66.6–67.5	70.4	70.0–70.8	71.7	71.3–72.1
		men	56.8	56.1–57.5	62.1	61.5–62.7	68.4	67.8–68.9	69.7	69.2–70.2
		women	70.7	70.1–71.4	72.6	72.0–73.2	72.8	72.2–73.4	74.1	73.6–74.7
	3-year	all	47.0	46.5–47.5	51.1	50.7–51.6	55.2	54.8–55.6	57.3	56.9–57.7
		men	38.5	37.8–39.2	44.6	44.0–45.3	52.1	51.5–52.6	54.4	53.8–54.9
		women	56.1	55.4–56.8	58.4	57.7–59.0	59.1	58.4–59.7	60.9	60.3–61.5
	5-year	all	39.8	39.3–40.3	44.2	43.7–44.7	48.2	47.8–48.6	50.4	50.0–50.9
		men	31.3	30.7–32.0	37.3	36.7–37.9	44.7	44.1–45.3	47.4	46.8–48.0
		women	49.0	48.3–49.7	51.8	51.1–52.5	52.5	51.9–53.1	54.1	53.5–54.8
Net	1-year	all	65.4	64.9–65.9	69.1	68.7–69.6	72.4	72.0–72.8	73.6	73.2–74.0
		men	59.0	58.3–59.8	64.5	63.9–65.2	70.7	70.2–71.3	71.9	71.4–72.4
		women	72.2	71.5–72.9	74.2	73.6–74.8	74.4	73.8–75.0	75.6	75.1–76.2
	3-year	all	51.2	50.6–51.7	56.1	55.6–56.6	59.9	59.4–60.3	61.9	61.4–62.3
		men	43.3	42.5–44.1	50.3	49.6–51.0	57.5	56.9–58.2	59.7	59.0–60.3
		women	59.6	58.8–60.4	62.5	61.8–63.3	62.7	62.0–63.4	64.5	63.9–65.2
	5-year	all	46.1	45.5–46.7	51.8	51.3–52.4	55.1	54.6–55.7	57.6	57.1–58.1
		men	38.4	37.6–39.2	45.9	45.1–46.7	52.8	52.1–53.5	55.8	55.0–56.5
		women	54.3	53.4–55.1	58.4	57.6–59.3	58.0	57.3–58.8	59.9	59.1–60.6

The net survival of cancer patients has been gradually improving with an increasing year of diagnosis (Figure 2, Table 2). In the 20 years under review, the five-year net survival increased by slightly less than 12 percentage points. In the first two observed periods, between 1997 and 2006, the five-year net survival rate was much better for women than for men, with a difference of 13–16 percentage points.

FIGURE 3

Five-year net survival of patients with cancer (excluding skin cancer) by age group in Slovenia in 1997–2016.



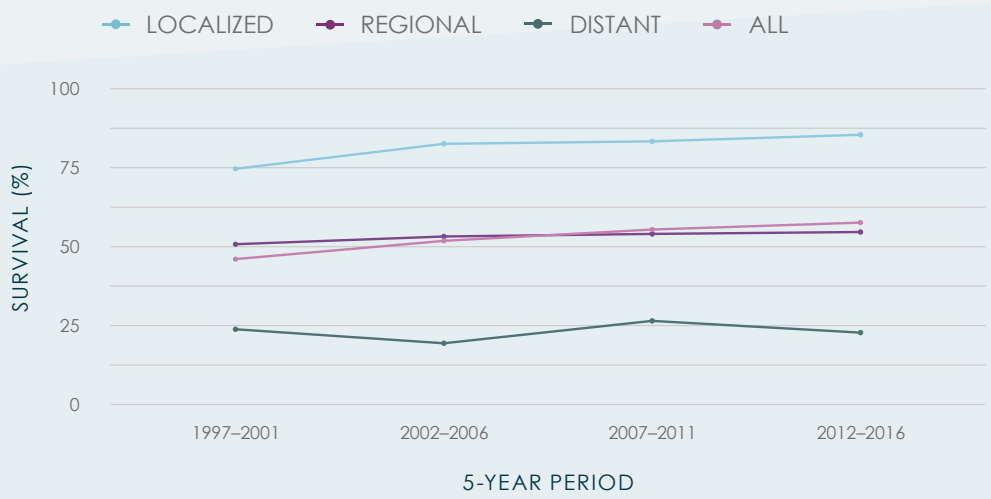


FIGURE 4

Five-year net survival of patients with cancer (excluding skin cancer) by stage in Slovenia in 1997–2016.

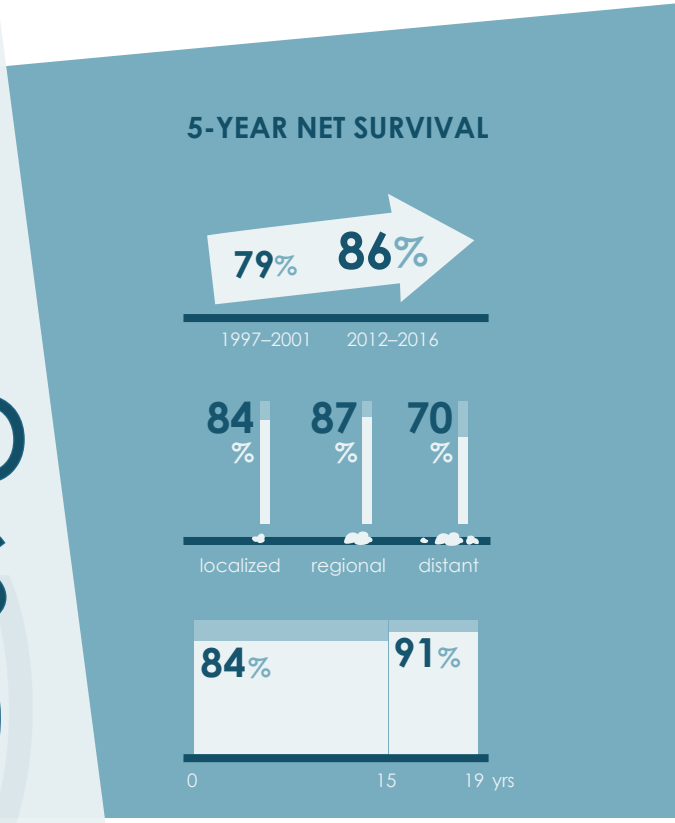
In the last two periods, from 2007 to 2016, the survival of men approached the survival of women and in the last observed period, from 2012 to 2016, it was 47%, and 54% for women (Table 2).

Figure 3 shows the impact of age on the survival of patients with cancer. The five-year net survival is lowest in those aged 75–94 years. In the 20 years under review, it increased by slightly more than 7 percentage points in this age group. The survival of persons aged 20–49 years at diagnosis was the highest compared to other age groups. It improved by 15 percentage points between 2012 and 2016 compared to the period from 1997 to 2001.

The importance of stage at diagnosis is shown in Figure 4. The five-year net survival of patients in the localized stage of the disease increased by almost 11 percentage points over the 20 years under observation and reached 85% in the last five-year period. The five-year net survival of patients in the regional stage at diagnosis approaches 55%, whereas in patients in the distant stage at diagnosis, it is only slightly below 23% and does not improve over time.

C00–C96 (excl. C44)

CANCER IN CHILDREN AND ADOLESCENTS (up to 20 years)



EPIDEMIOLOGY

In the last five-year period (2012–2016), on average, 74 children and adolescents were diagnosed with cancer in Slovenia per year, of which 17 had leukaemia (of which 12 cases were acute lymphoblastic leukaemia and 3 cases were acute myeloid leukaemia), 12 had lymphoma (approximately half are Hodgkin's lymphomas and half are non-Hodgkin's lymphomas) and 12 had a malignant brain tumour. On average, nine children and adolescents died per year in the last five-year period, of which two children died of leukaemia, one of lymphoma and three of malignant brain tumours. Figure 1 shows the time trend of the incidence and mortality of childhood cancers. Over the last ten years, the crude incidence rate for all childhood cancers has increased by 1.8% per year; it has decreased by 0.4% per year for leukaemias, increased by 0.9% for lymphomas, and increased by 1.6% for malignant brain tumours. Between 2007 and 2016, the crude mortality rate decreased—by 4.5% per year for all childhood cancers and by 9.2% for leukaemias, while it remained the same for lymphomas and malignant brain tumours. The incidence and mortality trends are not statistically significant, but indicate a stable incidence and a slight decrease in mortality.

At the end of 2016, there were 1,981 people living in Slovenia who had been diagnosed with cancer before the age of 20. Of those, the diagnosis had been established less than one year ago in 71 people, one to four years ago in 245 people, and over ten years ago in 1,396 people.

The survival analysis included 1,379 cases of patients aged 0 to 19 years; five cases (0.4%) were excluded because they were diagnosed on the day of death.

In all the observed periods, slightly more boys than girls were diagnosed with cancer before the age of 20. The finding applies to all cancers combined, as well as separately for leukaemias, lymphomas and malignant brain tumours. Among all the patients, the highest proportion are adolescents aged between 15 and 19 years, followed by children between 0–4 years at diagnosis. Almost half of the children with leukaemia are under the age of five at diagnosis, while more than half of those with lymphoma are aged 15 to 19 years at diagnosis. The proportion of solid tumours (C00-C88, excluding C44) diagnosed in the localized stage is increasing over time. It has reached 64% in the last five-year period, 12% of cancers are detected in the distant stage. Throughout the observed period, only four patients with solid tumours did not have a stage determined at diagnosis. One-third of lymphomas were detected in the third and fourth stage (Table 1); for lymphomas in 14% of patients diagnosed between 2012 and 2016, the stage was not determined.

FIGURE 1

The crude (CR) and age-standardized (ASR) incidence and mortality rates of cancers in children and adolescents (leukaemias, lymphomas, malignant brain tumours and all cancers, excluding skin cancer) in Slovenia in 1997–2016.

TABLE 1

Number and proportion of children and adolescents with cancer (leukaemia, lymphoma, malignant brain tumour and all cancers, excluding skin cancer) by sex, age, stage and period of diagnosis in Slovenia in 1997–2016.

LEUKAEMIAS

		Sex		Age				Total
		Boys	Girls	0–4 yrs	5–9 yrs	10–14 yrs	15–19 yrs	
1997–2001		44	43	30	16	16	25	87
	%	50.6	49.4	34.5	18.4	18.4	28.7	
2002–2006		41	32	33	13	8	19	73
	%	56.2	43.8	45.2	17.8	11.0	26.0	
2007–2011		44	40	37	17	13	17	84
	%	52.4	47.6	44.1	20.2	15.5	20.2	
2012–2016		42	40	37	21	14	10	82
	%	51.2	48.8	45.1	25.6	17.1	12.2	

LYMPHOMAS

		Sex		Age				Stage (Ann Arbor)			Total
		Boys	Girls	0–4 yrs	5–9 yrs	10–14 yrs	15–19 yrs	I	II	III+IV	
1997–2001		35	32	7	6	16	38	13	24	28	67
	%	52.2	47.8	10.5	9.0	23.9	56.7	19.4	35.8	41.8	
2002–2006		41	23	7	11	15	31	12	25	25	64
	%	64.1	35.9	10.9	17.2	23.4	48.4	18.8	39.1	39.1	
2007–2011		36	24	4	10	18	28	4	27	21	60
	%	60.0	40.0	6.7	16.7	30.0	46.7	6.7	45.0	35.0	
2012–2016		37	20	3	17	7	30	8	22	19	57
	%	64.9	35.1	5.3	29.8	12.3	52.6	14.0	38.6	33.3	

MALIGNANT BRAIN TUMOURS

		Sex		Age				Stage			Total
		Boys	Girls	0–4 yrs	5–9 yrs	10–14 yrs	15–19 yrs	Localized	Regional	Distant	
1997–2001		33	12	11	10	11	13	43	2	0	45
	%	73.3	26.7	24.4	22.2	24.4	28.9	95.6	4.4	0.0	
2002–2006		34	16	21	10	7	12	46	2	2	50
	%	68.0	32.0	42.0	20.0	14.0	24.0	92.0	4.0	4.0	
2007–2011		28	24	17	16	9	10	48	1	3	52
	%	53.9	46.2	32.7	30.8	17.3	19.2	92.3	1.9	5.8	
2012–2016		34	26	19	19	11	11	58	1	1	60
	%	56.7	43.3	31.7	31.7	18.3	18.3	96.7	1.7	1.7	

ALL CANCERS (EXCLUDING SKIN CANCER)

		Sex		Age				Stage (C00–C80, excl. C44)			Total
		Boys	Girls	0–4 yrs	5–9 yrs	10–14 yrs	15–19 yrs	Localized	Regional	Distant	
1997–2001		205	146	93	48	78	132	116	59	20	351
	%	58.4	41.6	26.5	13.7	22.2	37.6	59.2	30.1	10.2	
2002–2006		180	149	96	49	51	133	114	52	21	329
	%	54.7	45.3	29.2	14.9	15.5	40.4	60.6	27.7	11.2	
2007–2011		170	161	89	53	69	120	126	33	18	331
	%	51.4	48.6	26.9	16.0	20.9	36.3	70.8	18.5	10.1	
2012–2016		200	168	104	74	56	134	144	53	27	368
	%	54.4	45.7	28.3	20.1	15.2	36.4	64.0	23.6	12.0	

FIGURE 2

Net survival of children and adolescents with cancer (leukaemia, lymphoma, malignant brain tumour and all cancers, excluding skin cancer) by period of diagnosis in Slovenia in 1997-2016.

More than 95% of patients with childhood cancer received specific primary treatment in the observed period, the vast majority at the University Medical Centre Ljubljana. Three-quarters of leukaemia patients received systemic therapy alone and 18% received radiotherapy in addition to systemic treatment. The proportion of patients receiving radiotherapy in addition to systemic treatment almost halved in 20 years. Also in lymphoma patients, the proportion of those receiving radiotherapy alongside systemic treatment has been in decline. In the last five-year period, the proportion of these was 40%, while 51% were treated with systemic therapy alone. The majority of patients (84%) with brain tumours are treated with surgery. In 21%, in addition to surgery, the patient receives systemic treatment as well as radiotherapy; in 14%, surgery is supplemented with systemic treatment alone and in 11% with radiotherapy only.

TABLE 2.A

One-, three-, and five-year observed and net survival (with a 95% confidence interval–CI) of children and adolescents with cancer (leukaemia, lymphoma) by sex and period of diagnosis in Slovenia in 1997–2016.

Survival / Period			1997–2001	(95% CI)	2002–2006	(95% CI)	2007–2011	(95% CI)	2012–2016	(95% CI)
Leukaemias										
Observed	1-year	all	92.0	86.4–97.9	84.9	77.1–93.6	86.9	80.0–94.4	92.7	87.2–98.5
		boys	93.2	86.0–100.0	87.8	78.3–98.4	88.6	79.7–98.5	90.5	82.0–99.9
		girls	90.7	82.4–99.8	81.3	68.8–96.0	85.0	74.6–96.8	95.0	88.5–100.0
	3-year	all	83.9	76.5–92.0	76.7	67.6–87.1	78.6	70.3–87.9	87.8	81.0–95.2
		boys	81.8	71.2–94.1	78.1	66.4–91.8	75.0	63.2–89.0	83.3	72.8–95.4
		girls	86.1	76.3–97.1	75.0	61.4–91.6	82.5	71.5–95.2	92.5	84.7–100.0
	5-year	all	80.5	72.5–89.2	74.0	64.6–84.8	75.0	66.3–84.9	87.8	81.0–95.2
		boys	77.3	65.8–90.7	73.2	60.8–88.1	70.5	58.2–85.3	83.3	72.8–95.4
		girls	83.7	73.4–95.5	75.0	61.4–91.6	80.0	68.5–93.4	92.5	84.7–100.0
Net	1-year	all	92.0	86.5–97.9	85.0	77.2–93.5	86.9	80.1–94.4	92.7	87.3–98.5
		boys	93.2	86.2–100.0	87.8	78.5–98.3	88.7	79.9–98.4	90.5	82.1–99.7
		girls	90.7	82.5–99.7	81.3	69.0–95.7	85.0	74.8–96.7	95.0	88.6–100.0
	3-year	all	84.0	76.6–92.0	76.8	67.7–87.0	78.6	70.4–87.8	87.8	81.1–95.2
		boys	81.9	71.4–94.0	78.1	66.5–91.7	75.1	63.4–88.8	83.4	73.0–95.3
		girls	86.1	76.4–97.0	75.0	61.7–91.3	82.5	71.7–95.0	92.5	84.8–100.0
	5-year	all	80.6	72.7–89.3	74.1	64.7–84.8	75.1	66.4–84.9	87.9	81.1–95.2
		boys	77.4	66.1–90.7	73.3	61.0–88.0	70.5	58.4–85.2	83.4	73.0–95.3
		girls	83.8	73.6–95.4	75.0	61.7–91.3	80.1	68.7–93.3	92.6	84.8–100.0
Lymphomas										
Observed	1-year	all	97.0	93.0–100.0	89.1	81.7–97.1	100.0	100.0–100.0	100.0	100.0–100.0
		boys	94.3	86.9–100.0	82.9	72.2–95.3	100.0	100.0–100.0	100.0	100.0–100.0
		girls	100.0	100.0–100.0	100.0	100.0–100.0	100.0	100.0–100.0	100.0	100.0–100.0
	3-year	all	89.6	82.5–97.2	87.5	79.8–96.0	96.7	92.2–100.0	98.3	94.9–100.0
		boys	82.9	71.3–96.3	80.5	69.2–93.6	97.2	92.0–100.0	97.3	92.2–100.0
		girls	96.9	91.0–100.0	100.0	100.0–100.0	95.8	88.2–100.0	100.0	100.0–100.0
	5-year	all	86.6	78.8–95.1	84.4	75.9–93.8	96.7	92.2–100.0	98.3	94.9–100.0
		boys	82.9	71.3–96.3	78.1	66.4–91.8	97.2	92.0–100.0	97.3	92.2–100.0
		girls	90.6	81.1–100.0	95.7	87.7–100.0	95.8	88.2–100.0	100.0	100.0–100.0
Net	1-year	all	97.1	93.1–100.0	89.1	81.8–97.0	100.0	100.0–100.0	100.0	100.0–100.0
		boys	94.3	87.1–100.0	83.0	72.3–95.1	100.0	100.0–100.0	100.0	100.0–100.0
		girls	100.0	100.0–100.0	100.0	100.0–100.0	100.0	100.0–100.0	100.0	100.0–100.0
	3-year	all	89.6	82.7–97.2	87.5	79.9–96.0	96.7	92.3–100.0	98.3	95.0–100.0
		boys	83.0	71.6–96.1	80.5	69.4–93.4	97.3	92.1–100.0	97.4	92.4–100.0
		girls	96.9	91.2–100.0	100.0	100.0–100.0	95.9	88.4–100.0	100.0	100.0–100.0
	5-year	all	86.7	79.0–95.2	84.5	76.1–93.8	96.7	92.3–100.0	98.4	95.1–100.0
		boys	83.0	71.6–96.1	78.2	66.7–91.8	97.3	92.1–100.0	97.5	92.5–100.0
		girls	90.7	81.3–100.0	95.8	87.9–100.0	95.9	88.4–100.0	100.0	100.0–100.0

The net survival of patients with childhood cancer has been gradually increasing with respect to the year of diagnosis (Figure 2, Table 2). In the observed 20 years, the five-year net survival for all childhood cancers combined increased by more than 7 percentage points, and in lymphomas by as much as 12 percentage points. Survival is improving in both sexes. Boys have a slightly lower survival than girls, but the gap between the sexes has been narrowing over time (Table 2).

Figure 3 shows the impact of age on the survival of patients with childhood cancer. The five-year net survival was similar in both age groups (0–14 years, 15–19 years) in all the observed periods. In the first two observed periods, between 1997 and 2006, it was slightly better in the 0 to 14 years age group, and in the last two periods, between 2007 and 2016, in the 15 to 19 years age group. In the last observed period, from 2012 to 2016, it reached 84–91% (Figure 3).

TABLE 2.B

One-, three-, and five-year observed and net survival (with a 95% confidence interval–CI) of children and adolescents with cancer (malignant brain tumour and all cancers, excluding skin cancer) by sex and period of diagnosis in Slovenia in 1997–2016.

Survival / Period			1997 - 2001	(95% CI)	2002 - 2006	(95% CI)	2007 - 2011	(95% CI)	2012 - 2016	(95% CI)
Brain										
Observed	1-year	all	82.2	71.8–94.2	84.0	74.4–94.8	80.8	70.7–92.2	83.3	74.4–93.3
		boys	81.8	69.7–96.1	79.4	66.9–94.2	82.1	69.1–97.6	88.2	78.0–99.8
		girls	83.3	64.7–100.0	93.8	82.6–100.0	79.2	64.5–97.2	76.9	62.3–95.0
	3-year	all	66.7	54.2–82.0	72.0	60.6–85.6	71.2	59.9–84.6	73.3	62.9–85.4
		boys	63.6	49.2–82.4	64.7	50.5–82.9	71.4	56.5–90.3	73.4	59.9–89.9
		girls	75.0	54.1–100.0	87.5	72.7–100.0	70.8	54.8–91.6	73.1	57.9–92.3
	5-year	all	62.2	49.6–78.1	64.0	52.0–78.8	69.2	57.8–83.0	69.2	58.2–82.3
		boys	60.6	46.0–79.8	61.8	47.4–80.5	67.9	52.6–87.6	70.4	56.5–87.6
		girls	66.7	44.7–99.5	68.8	49.4–95.7	70.8	54.8–91.6	67.0	50.2–89.4
Net	1-year	all	82.3	71.9–94.1	84.0	74.6–94.7	80.8	70.9–92.1	83.4	74.5–93.2
		boys	81.9	69.9–95.9	79.4	67.1–94.0	82.2	69.4–97.3	88.3	78.2–99.6
		girls	83.4	65.5–100.0	93.8	82.9–100.0	79.2	64.8–96.8	76.9	62.6–94.5
	3-year	all	66.7	54.4–81.8	72.1	60.7–85.5	71.2	60.0–84.5	73.3	63.0–85.3
		boys	63.7	49.5–82.1	64.8	50.8–82.6	71.5	56.8–89.9	73.5	60.2–89.7
		girls	75.0	55.0–100.0	87.6	73.2–100.0	70.9	55.2–91.0	73.1	58.2–91.8
	5-year	all	62.4	49.8–78.0	64.1	52.2–78.7	69.3	57.9–82.9	69.3	58.4–82.2
		boys	60.8	46.4–79.6	61.9	47.7–80.2	67.9	52.9–87.2	70.4	56.8–87.4
		girls	66.7	45.6–97.6	68.8	50.1–94.6	70.9	55.2–91.0	67.0	50.6–88.7
All cancers, excluding skin cancer										
Observed	1-year	all	91.7	88.9–94.7	89.4	86.1–92.8	92.8	90.0–95.6	92.9	90.4–95.6
		boys	90.7	86.9–94.8	86.1	81.2–91.3	93.5	89.9–97.3	93.5	90.2–97.0
		girls	93.2	89.1–97.3	93.3	89.4–97.4	91.9	87.8–96.2	92.3	88.3–96.4
	3-year	all	82.1	78.1–86.2	83.0	79.0–87.1	87.6	84.1–91.2	87.4	84.1–90.9
		boys	78.5	73.1–84.4	78.9	73.2–85.1	86.5	81.5–91.8	85.4	80.7–90.5
		girls	87.0	81.7–92.6	87.9	82.8–93.3	88.8	84.1–93.8	89.9	85.4–94.5
	5-year	all	78.6	74.5–83.0	79.0	74.8–83.6	85.8	82.1–89.6	86.4	82.9–90.0
		boys	75.1	69.4–81.3	75.6	69.5–82.1	84.1	78.8–89.8	84.3	79.4–89.6
		girls	83.6	77.8–89.8	83.2	77.4–89.4	87.6	82.6–92.8	88.8	83.9–93.9
Net	1-year	all	91.8	89.0–94.7	89.4	86.1–92.8	92.8	90.0–95.6	93.0	90.4–95.6
		boys	90.8	86.9–94.8	86.2	81.3–91.3	93.6	89.9–97.3	93.5	90.2–97.0
		girls	93.2	89.2–97.4	93.3	89.4–97.4	92.0	87.9–96.2	92.3	88.3–96.4
	3-year	all	82.2	78.2–86.3	83.1	79.1–87.2	87.7	84.2–91.3	87.5	84.2–91.0
		boys	78.7	73.3–84.5	79.0	73.2–85.1	86.6	81.6–91.8	85.5	80.7–90.6
		girls	87.0	81.8–92.6	88.0	82.9–93.4	88.9	84.1–93.9	89.9	85.5–94.6
	5-year	all	78.8	74.6–83.2	79.2	74.9–83.7	85.9	82.2–89.7	86.5	83.0–90.1
		boys	75.3	69.7–81.5	75.7	69.7–82.3	84.2	78.9–89.9	84.5	79.6–89.7
		girls	83.7	77.9–89.9	83.3	77.5–89.5	87.7	82.7–92.9	88.8	84.0–94.0

FIGURE 3

Five-year net survival of children and adolescents with cancer (all cancers, excluding skin cancer) by age group in Slovenia in 1997–2016.

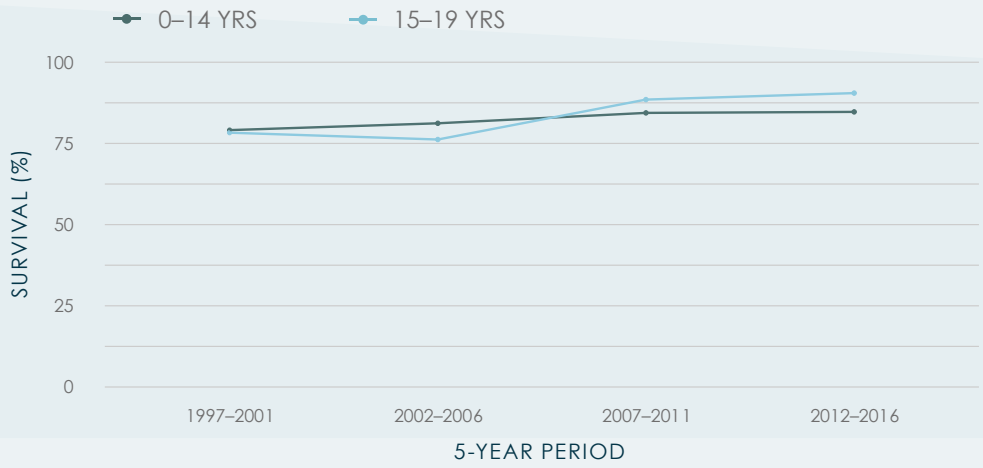
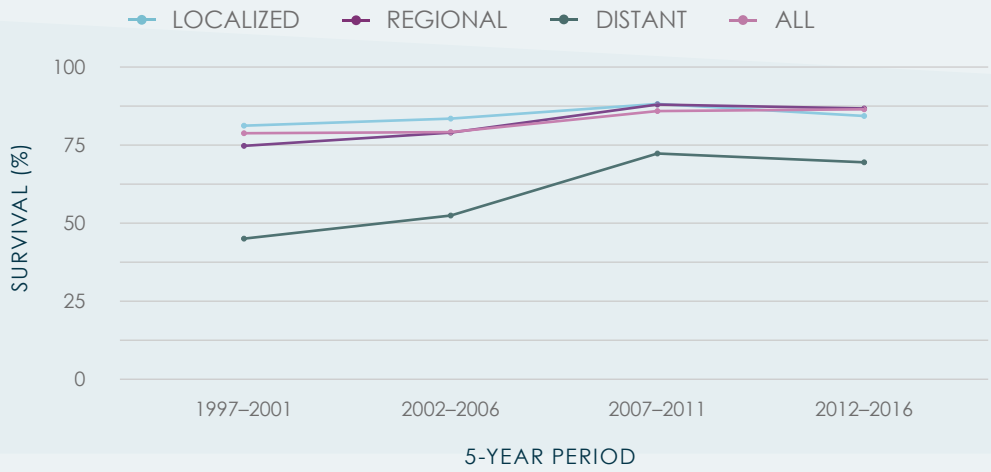


FIGURE 4

Five-year net survival of children and adolescents with solid tumours (C00–C80, excluding C44) by stage in Slovenia in 1997–2016.



The importance of the stage at diagnosis is shown in Figure 4. The five-year net survival rates of children and adolescents with solid tumours with localized and regional stage diseases at diagnosis exceeds 85% in the last ten years. In children and adolescents with the distant stage of the disease, the five-year net survival is 70%. All patients with lymphomas diagnosed in the first and second stages survived for five years. The five-year net survival of children and adolescents with cancer for all stages combined is improving.

CLINICAL COMMENTARY

Janez Jazbec

Cancer is a rare disease in childhood, accounting for less than 1% of all newly diagnosed cancer cases in the population. Despite its rarity, it is one of the most common disease-related causes of child and adolescent mortality in the developed world. It is a very heterogeneous group of diseases whose treatment requires specific team-based multidisciplinary treatment early in the diagnostic phase, so it is somewhat surprising that about 10% of patients in this age group start specific treatment at institutions where staff have not been trained in such treatment.

Acute leukaemias are the most common malignancy of children and adolescents. The number of cases in the observed period was more or less constant, without any pronounced trend. In most cases, patients have acute lymphoblastic leukaemia, while a smaller proportion have acute myeloblastic leukaemia. Chronic leukaemia in childhood is not a common disease. Treatment of leukaemias in children during the observed period was based on multi-line chemotherapy in combination with prophylactic

radiotherapy of the neurocranium. The number of children in need of radiotherapy has been gradually declining, mainly due to additional intrathecal applications of cytostatics.

In interpreting the results of the analysis of childhood leukaemia survival, it is important to keep in mind that there is a significant difference in the survival of patients with acute lymphoblastic leukaemia and patients with acute myeloblastic leukaemia. In acute lymphoblastic leukaemia especially, where current treatment regimens have reached and exceeded 90%, the impression is that a plateau has been reached, while further gains could potentially be achieved through the introduction of new treatments, particularly those using monoclonal antibodies and CAR T-cell technology.

A specificity of non-Hodgkin's lymphomas in childhood is that in most cases, they are highly malignant lymphomas that clinically respond to treatment in a similar manner as acute lymphoblastic leukaemias. The treatment of mature B-cell lymphomas (Burkitt's lymphoma) is based on high-intensity chemotherapeutic blocks without maintenance treatment, while T-cell and precursor B-cell non-Hodgkin's lymphomas in children have almost identical treatment regimens to those used for acute lymphoblastic leukaemia.

We have recently switched how we treat Hodgkin's disease in children and adolescents to the EuroNet scheme, in which the role of radiotherapy is significantly reduced by undertaking an assessment of the early response to induction chemotherapy with PET/CT. This is intended to reduce the incidence of the late effects of treatment while maintaining a high long-term survival rate.

Tumours of the central nervous system are the most common solid tumours of childhood, accounting for about 20% of malignant diseases in children and adolescents. Most are malignant gliomas. Histologically indeterminate cases are mostly pons gliomas, in which the diagnosis is based on radiological criteria. The treatment of children with central nervous system tumours involves surgical treatment in combination with radiotherapy and chemotherapy. Despite improvements in radiotherapy techniques and intensification of chemotherapy regimens, we have not seen any discernible trend towards improved survival. Although in the table of the five-year net survival by age groups for the individual observed periods, we can see that in the age group from 0 to 4 years, survival increased from 46% to 79% between the 1997-2001 and 2012-2016 periods, while we observed the opposite trend in the 10 to 14 years age group. It should be borne in mind that the number of cases included in the analysis is very small.

IV.

THE MOST IMPORTANT FINDINGS AND CHALLENGES FOR THE FUTURE

REVIEW OF THE MOST IMPORTANT FINDINGS

1. The survival of Slovenian cancer patients is increasing over time. During the 20 years observed (1997–2001 and 2012–2016), the five-year net survival increased by 11 percentage points. The increase was significantly higher in men, for whom the five-year net survival increased by 17 percentage points (from 38% to 55%). In women, the five-year net survival increased by 6 percentage points (from 54% to 60%).

2. Age and stage at diagnosis are still key when it comes to the survival of cancer patients. The five-year net survival is lowest in those aged 75-94, though even in this age group, the five-year net survival has also improved by 7 percentage points over the past 20 years. The five-year net survival of patients with localized stage disease increased by 10 percentage points over the observed 20 years and reached 85% in the last period; the survival of patients with a distant disease has not improved.

3. In both sexes, survival has improved significantly over the last 20 years for three common cancers: colorectal cancer (by 14 percentage points, from 48% to 62%), melanoma of the skin (by nearly 12 percentage points, from 79% to 90%), and lung cancer (by 8 percentage points, from 10% to 18%). These results reflect earlier diagnostics and advances in systemic treatment.

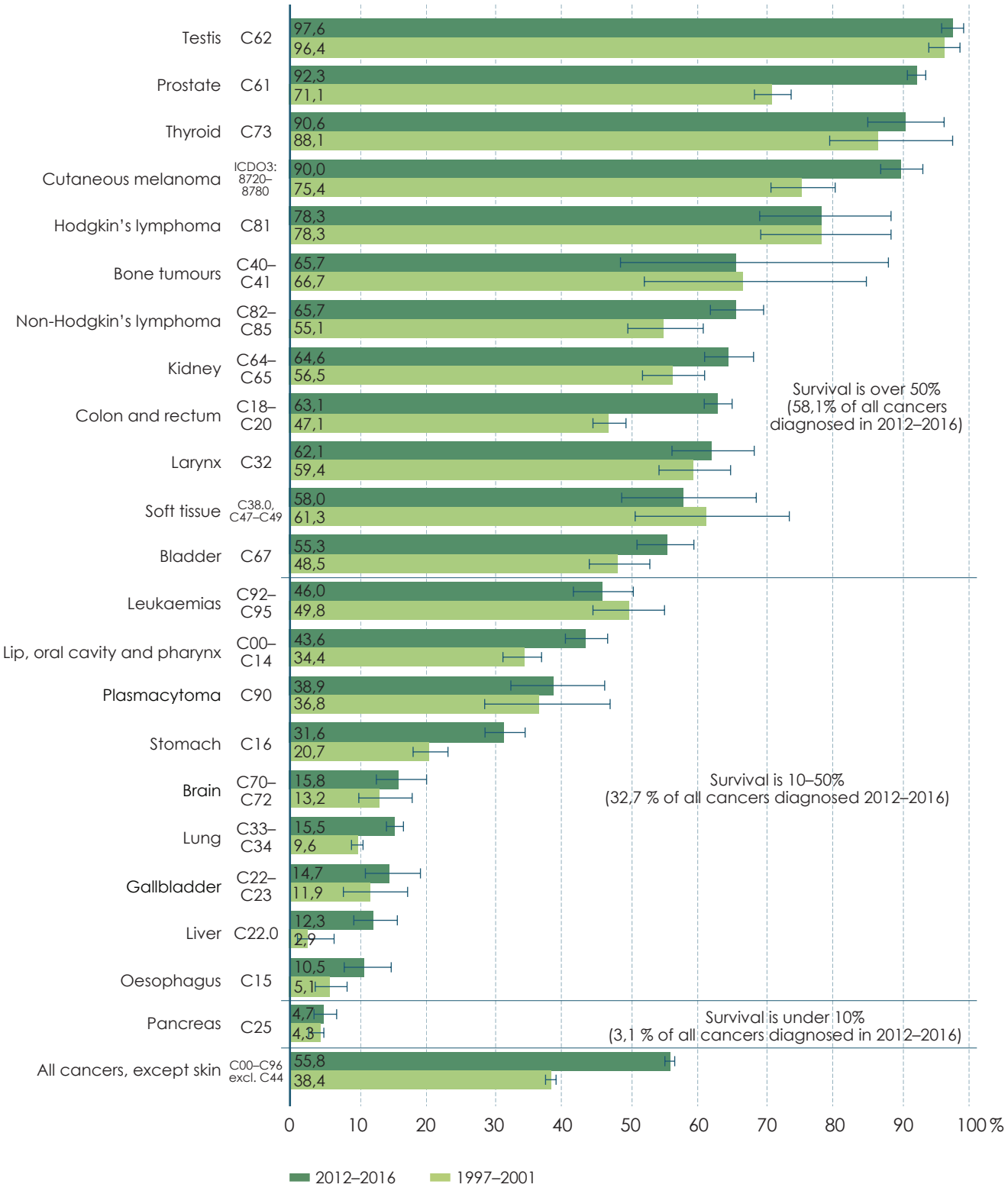
4. Progress has also been made in the two most common cancers by sex: breast cancer in women and prostate cancer in men. The five-year net survival of breast cancer patients has increased by 10 percentage points in the last 20 years, while the five-year net survival of prostate cancer patients has increased by more than 20 percentage points. The significant improvement in prostate cancer survival is probably merely on paper since in the period under review, PSA testing in Slovenia was performed rather uncritically and resulted in the detection of prostate cancers that would have otherwise remained clinically silent for a long time in the natural course of disease, thus artificially prolonging survival due to early diagnosis.

5. The group of cancers where no progress has been observed over time or where survival still remains low includes pancreatic cancer, oesophageal cancer, liver, gallbladder and bile duct cancers, as well as brain tumours.

6. In the CONCORD-3 study, the five-year net survival of adult patients with 15 different cancer locations diagnosed between 2010 and 2014 was compared among 26 European countries. In most cases, the survival rates of Slovenian cancer patients are below the European average, which highlights the need and creates an incentive for future improvements.

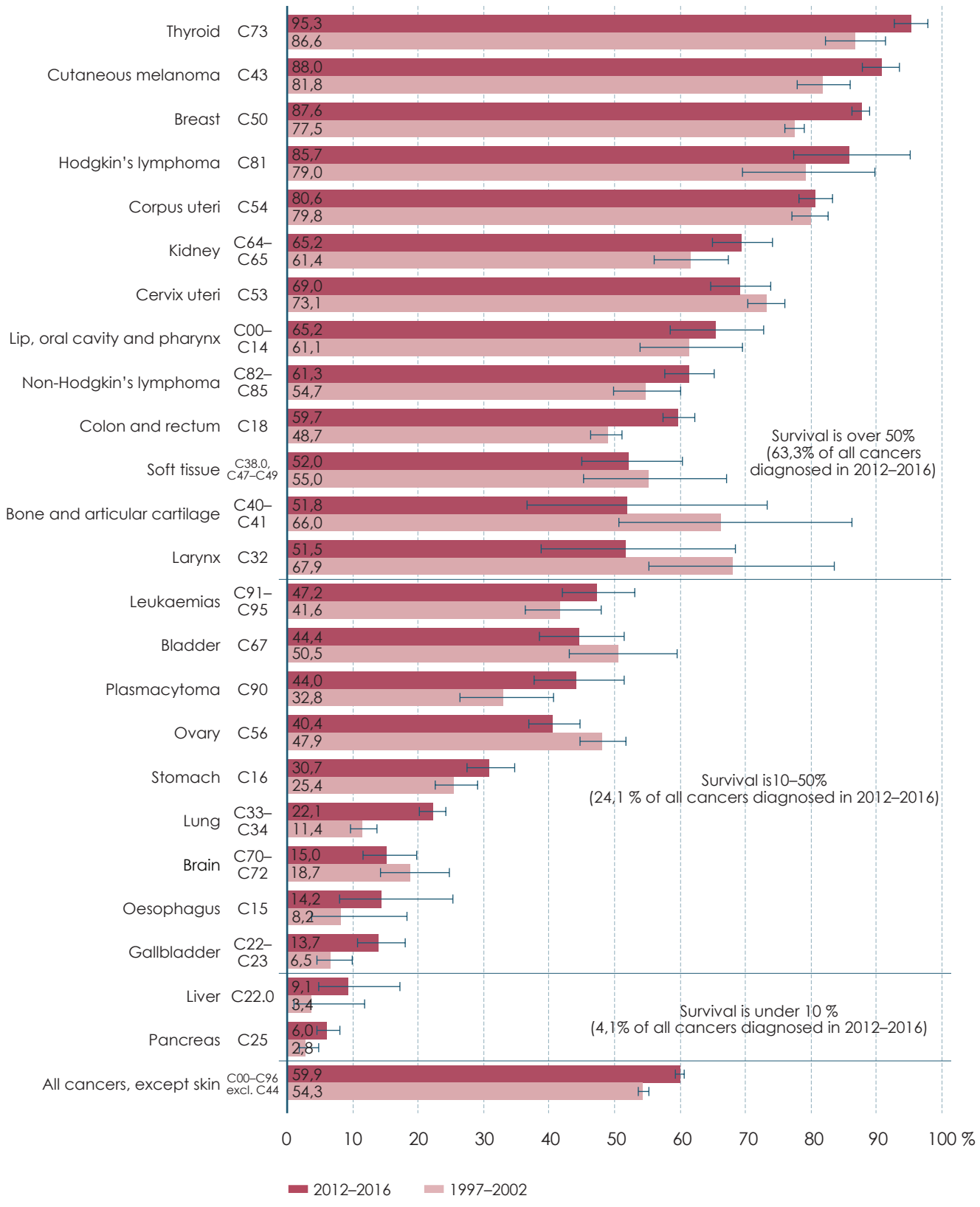
7. Less than 1% of cancer patients are children and adolescents; they are mainly diagnosed with leukaemia, central nervous system tumours and lymphomas, and have a better five-year survival compared to adults. In the last 20 years (1997–2001 and 2012–2016), the five-year survival of children and adolescents with cancer has increased by 7 percentage points (from 79% to 86%).

Men



Five-year net survival (with a 95% confidence interval) of patients with selected cancers in 1997–2001 in 2012–2016 by sex (men - p. 211, women - p. 212).

Women


Thyroid C73
95,3
86,6
Cutaneous melanoma C43
88,0
81,8
Breast C50
87,6
77,5
Hodgkin's lymphoma C81
85,7
79,0
Corpus uteri C54
80,6
79,8
Kidney C64–C65
65,2
61,4
Cervix uteri C53
69,0
73,1
Lip, oral cavity and pharynx C00–C14
65,2
61,1
Non-Hodgkin's lymphoma C82–C85
61,3
54,7
Colon and rectum C18
59,7
48,7
Soft tissue C38.0, C47–C49
52,0
55,0
Bone and articular cartilage C40–C41
51,8
66,0
Larynx C32
51,5
67,9
Survival is over 50%
(63,3% of all cancers
diagnosed in 2012–2016)
Leukaemias C91–C95
47,2
41,6
Bladder C67
44,4
50,5
Plasmacytoma C90
44,0
32,8
Ovary C56
40,4
47,9
Stomach C16
30,7
25,4
Lung C33–C34
22,1
11,4
Brain C70–C72
15,0
18,7
Oesophagus C15
14,2
8,2
Gallbladder C22–C23
13,7
6,5
Survival is10–50%
(24,1 % of all cancers diagnosed in 2012–2016)
Liver C22.0
9,1
8,4
Pancreas C25
6,0
2,8
Survival is under 10 %
(4,1% of all cancers diagnosed in 2012–2016)
All cancers, except skin C00–C96 excl. C44
59,9
54,3
0
10
20
30
40
50
60
70
80
90
100 %
2012–2016
1997–2002

HOW DO WE MANAGE THE EPIDEMIC OF THE MODERN WORLD IN OUR COUNTRY?

Branko Zakotnik,
coordinator of the National Cancer Control Programme

The data presented in this publication tells us what has changed in the field of cancer control in Slovenia in 20 years. What should be done to deal with today's cancer epidemic, and where could we do more?

Advances in medical science, oncology and molecular biology in the last 20 years have brought many revolutionary insights into the field of oncology, which undoubtedly have an impact and will have an even more significant impact on the survival of cancer patients in the future. However, survival is not the only measure of how we control cancer. A very important criterion is the incidence and, of course, the quality of life for survivors, which unfortunately the survival data does not show. All national cancer control programmes, including the Slovenian, have the primary strategic goal of reducing incidence, so in addition to survival, based on the data presented in this publication, I will also comment briefly on incidence. The result of incidence and survival, however, is mortality, an indicator that, in addition to incidence, often appears when comparing countries as a measure of cancer burden control.

Incidence. Incidence is influenced by the age structure of the population, genetic factors, lifestyle factors and the environment in which we live, as well as how accurately incidence is recorded. All the predictions of an extraordinary increase in incidence by 2030 really frighten us—much of the projected increase in the number of new patients can be attributed to the ageing population. Even today, a lack of staff makes it difficult to manage large numbers of oncology patients, so it is a serious question how we will cope with the projected patient numbers in the future. Life expectancy has increased in the last 25 years for men by as much as nine years and for women by six years; the gap in life expectancy between men and women is narrowing. If we exclude the ageing of the population and thus evaluate the effects of other factors on the incidence of cancer, we can clearly see in the time trend of the age-standardised incidence of all cancers that it has not increased since 2010. In men, it has even declined. Undoubtedly, this reflects the impact of primary prevention measures on chronic non-communicable diseases, which, in addition to a significant impact on incidence and mortality due to cardiovascular diseases in Slovenia, also show an impact on cancer incidence. One of the more important influences is certainly the reduced rates of smoking among men, as tobacco is, without a doubt, the most important unhealthy lifestyle factor that causes cancer. Unfortunately, we see a reverse trend in women, as shown in the chapter on lung cancer.

The Svit and ZORA screening programmes have also contributed to the reduction in incidence (see Figure 1 for the incidences of colorectal cancer and cervical cancer). We can only hope that this downward trend in incidence will continue. Undoubtedly, the impact on incidence is one of the greatest achievements in cancer control in our country in the last decade, in terms of the quality of life of the population of Slovenia, the impact on cancer mortality and cost-effectiveness. Of course, these are only brief observations, as a detailed analysis of the factors influencing the trends of cancer incidence in our country is not the subject of this publication.

Survival. The data presented shows that the five-year survival, both net (as a measure of cancer survival) and observed in the studied periods, has improved significantly. The five-year net survival in the last five-year period, between 2012 and 2016, is almost 60% (and the observed survival is just over 50%), which is 11 percentage points higher than at the turn of the millennium, in the period from 1997 to 2001. The factors that influenced these changes in individual cancers were commented on by fellow clinicians for each type of cancer, as they are very different diseases with different approaches and options for diagnosis and treatment. At this point, however, I want to comment on some general facts that affect the survival of cancer patients as a whole.

A very interesting observation is the convergence in the five-year net survival of men and women. For men, it increased by almost 17 percentage points over the observed period—for women, only by six percentage points. At a first glance, it seems that men have also started to take better care of their health and the 'macho' male population is disappearing. The increased survival in men can to a significant degree be attributed to the survival of patients with prostate cancer, in whom it has risen by over 20 percentage points. Further comments are provided in the chapter on prostate cancer. The greatest progress has probably been made through widespread opportunistic screening and the associated better survival due to the so-called lead-time bias. The number of distant-stage cancers at diagnosis has also decreased significantly for prostate cancer. However, the most common cancer in women, breast cancer, has not seen such a large improvement in survival. The breast cancer screening programme (DORA programme) was only introduced nationwide in 2018, so it could not have made a significant contribution to the results of our current analysis. Undoubtedly, breast and prostate cancer, which affect as many as a fifth of all cancer patients in men and women, contribute the most to reducing the gap between the sexes.

The survival of cancer patients is influenced by several factors. Among the most important are: (i) the stage of the disease at diagnosis, (ii) comorbidities that may affect the implementation of oncological treatment, and (iii) the specific primary treatment carried out in accordance with the guidelines and within professionally acceptable timeframes; and (iv) access to treatment for recurrences. Which of these factors can be identified with the available data, and how can we explain the reasons why survival improves over the years or why it has not improved even more?

Stage of the disease. Despite a number of new insights into prognostic and predictive factors with the advent of molecular biology, traditional TNM staging remains the basic predictor of disease outcome. Reports of cancer registries simplify TNM staging into three groups: localized, regional and distant. From the analysis by five-year periods, we see that the disease is frequently diagnosed in the localized stage and less often in the regional stage. The percentage of patients with a distant stage disease remains the same, most likely due to more accurate and accessible diagnostic methods.

From the data, we can conclude that the partial improvement in survival can be explained by the disease being diagnosed at an earlier stage. This is certainly the case for the last period for colorectal cancers and breast cancer. For all patients who respond to the screening invitation, the five-year risk of death is four to five times lower than for those who do not respond to the invitation, due to diseases being diagnosed during a lower stage. Of course, survival is not a measure of the effectiveness of a screening programme (lead-time bias), but the treatment of the disease at an earlier stage undoubtedly affects recovery and consequently the mortality associated with the disease for which the screening programme is performed. The successful implementation of organized screening programmes and sufficient population participation rates will, therefore, further improve survival.

What can we say about comorbidities? The table on the number of patients by periods of diagnosis and age groups clearly shows how fast the number of older oncology patients is increasing. In the age group of 75-94 years at the time of diagnosis, the number of patients has more than doubled, and it is precisely these patients who have the most comorbidities, which can severely limit the feasibility of oncological treatment. Despite the increasing complexity of oncological treatments, the percentage of patients without specific primary oncological treatment remains the same over time—around 22%. We can conclude that doctors increasingly decide to treat older patients with comorbidities, although more complex treatment is often accompanied by many more side effects. However, in the last three five-year time periods, the five-year net survival of the oldest group of patients has remained almost the same, while in the younger groups, it has been increasing steadily and significantly. Apparently, age and comorbidities are a brick wall that we cannot yet overcome with today's treatments. The fact that cancer is becoming the leading cause of death is thus not surprising; in Slovenia, it has held this position among men for several years.

However, we cannot deduce from the data what the quality of the primary treatment was, whether it was carried out in accordance with the guidelines, or within professionally acceptable time limits. If these indicators are to be monitored, a different and more accurate way of recording data in so-called clinical registries should be introduced, where a much larger data set is monitored than currently recorded by population-based cancer registries. This would be much easier to achieve if the Slovenian

healthcare system utilised a unified information system. Collecting data in the Slovenian Cancer Registry following the brilliant approach introduced by Prof Božena Ravnihar in 1950 will probably not be able to solve this problem. As part of the National cancer control programme of 2017-2021, we have already proposed the establishment of so-called clinical registries for common cancers sites. In doing so, we hope we do not encounter obstacles that cannot be overcome.

Mortality. The mortality curves show that the age-standardised mortality rate is declining significantly, while the crude mortality rate is rising, though less steeply in recent years. We can say that increasingly more patients are cured, but also that more people are being diagnosed with and dying from cancer. Interestingly, age-standardised mortality rates have declined much more in men than in women. This also coincides with the survival data that I have discussed above. All the data shows positive trends in male cancers. It is difficult to predict what impact the incidence and survival trends described above will have; I do not know the formula that links these three parameters, and the relationship is quite complex. Nevertheless, in addition to incidence, mortality is one of the main public health indicators, especially in comparisons between countries. Among the most cited is the report on health indicators Health at a Glance, published by the Organisation for Economic Co-operation and Development (OECD), in which Slovenia ranks fourth in Europe in terms of mortality from cancer, mainly due to the high mortality in men. From what has been said, it is clear that the interpretation of cancer control is very complex and multifaceted.

I hope that a healthy lifestyle will become a habit for most Slovenes, that new screening options will eventually emerge and that, combined with genetic testing, there will be increasingly effective screening programmes for a greater range of cancers and that participation in these programmes will be high. In this way, we will reduce the cancer burden to such an extent that it will be possible to provide equal care to all patients taking into account the available human and financial resources. For cancer patients, highly professional, evidence-based and above all timely, specific primary treatment is extremely important. Without the ability to monitor the quality of cancer care, we risk wasting a considerable amount of energy and money. We need to be aware that most cancer patients die and will die due to the progress of the disease, where systemic treatment plays a major role. Systemic treatment has achieved unprecedented developments and new findings in recent decades, and this treatment method is credited with extending patient survival. A feature of systemic treatments is that they are applied life-long, with patients either taking tablets on a daily basis or receiving injections at intervals of a few weeks. Relying on such treatments as the only way to control cancer will probably never be economically viable, even for the richest countries. Therefore, in order to balance quality of life and economic sustainability considerations, evidence-based primary and secondary prevention programmes must be established and utilised, and evidence-based treatments provided within professionally acceptable timeframes. How we manage the cancer epidemic of today and how effective we are in doing so cannot be assessed without up-to-date and ongoing monitoring of incidence, survival, mortality and the factors that influence them. A very important criterion should also be the quality of life for survivors, which is even more difficult to measure and compare.

References

International Agency for Research on Cancer and Cancer Research UK. World cancer factsheet. London: Cancer Research UK; 2012. Available from: https://gicr.iarc.fr/public/docs/20120906-WorldCancerFactSheet.pdf

OECD. Cancer mortality in year 2015. In: Health at a glance: Europe 2018. Paris: OECD Publishing; 2015. Available from: https://doi.org/10.1787/health_glance_eur-2018-graph33-en

Statistical Office of Republic of Slovenia. SiStat: Annual life expectancy by sex in Slovenia, years 1960 - 1961 and 1986 - 1987. Ljubljana: Statistical Office of Republic of Slovenia; 2021. Available from: https://pxweb.stat.si/SiStat/sl

National Institute of Public Health. Srčno-žilne bolezni. (Cardiovascular diseases). Ljubljana: National Institute of Public Health of Republic of Slovenia; 2021. Available from: https://www.nijz.si/sl/srcno-zilne-bolezni

Zakotnik B, Zadnik V, Žagar T, et al. 1637PD - Reaching sustainable oncology care via the National Cancer Control Program (NCCP). Annals of Oncology 2019; 30(Suppl 5): v673.

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