

## Intensity Modulated Radiotherapy – IMRT: now available also at the Institute of Oncology in Ljubljana

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Intensity Modulated Radiotherapy (IMRT) is a modern radiation technique that most cunningly combines the achievements in computer technology and innovations in the industrial production of radiotherapeutic devices. In comparison to conventional radiation techniques, IMRT yields a significant improvement in dose distribution in irradiated tissue. The latter is reflected in higher conformity which is supplemented with steep dose gradient at the edge of target volume. Thereby, these characteristics allow better adjustment of the radiation beam to the target and lower radiation load to the healthy tissue surrounding the target, which in turn reduces the risk of serious radiation side effects. This review presents the basic features of IMRT, the distinc-

tions between IMRT and conventional radiation techniques, the drawbacks or risks of IMRT that require special attention, the procedures during the IMRT preparation and implementation, as well as the indications and the scope of estimated clinical results.

With launching IMRT at the Institute of Oncology Ljubljana, a new era has dawned in the development of radiotherapy in Slovenia. Having considered the reports from the worldwide institutions, where IMRT has longer been a part of clinical routine, we may conclude that medical team gained a new and effective weapon against this malicious and lethal disease and the patients new hope for successful completion of treatment.

## Detection of V600E Mutation in *BRAF* Gene

Petra Cerkovnik, Alenka Ličar and Srdjan Novaković

The most common *BRAF* mutation, which accounts for more than 90% of all *BRAF* mutations described in different malignancies, is a glutamic acid for valin substitution at position 600 (V600E). *BRAF* gene carrying V600E mutation is termed *BrafV600E* oncogene. The product of *BrafV600E* is a protein which induces constitutive signaling in cells through hyperactivation of the RAS-RAF-MAPK pathway leading finally to increased cellular proliferation and malignant transformation. *BrafV600E* oncogene thus plays an important role in cancer induction and progression and is probably mutated early in the process of malignant transformation. According to the literature, *BrafV600E* oncogene is over-expressed in diverse human solid tumors: melanoma, colorectal carcinoma,

papillary thyroid carcinoma, renal cell carcinoma (RCC), hepatocellular carcinoma (HCC), non-small cell lung cancer (NSCLC) and serous ovarian cancer.

At the Department of Molecular Diagnostics, we introduced a method for the detection of V600E mutation in *BRAF* gene based on real-time PCR and on application of specific probes. The method is robust and convenient for routine diagnostics. Its sensitivity and specificity when determined in comparison to the results of direct sequencing are as high as 100%. Due to the high specificity, the method allows the discrimination between normal and mutated *BRAF* genotypes and is therefore suitable for fast and accurate routine diagnostics.

## Results of Population Based Breast Cancer Screening Program – DORA: 86 Newly Detected Breast Cancer Cases

Mateja Krajc, Maksimiljan Kadivec, Kristijana Hertl and Maja Primic Žakelj

National population-based breast cancer screening program – DORA started two years ago. At the end of March 2008, first women from Ljubljana municipality got the invitation letter for screening mammography from DORA invitation office.

First screening mammographies will be taken at the screening unit at the Institute of Oncology (OI). The program will slowly be spreading and, by establishing new screening units, it will cover the target population of the whole Slovenia.

High-quality organized screening program is of essential importance for early detection of breast cancer and reduction of mortality due to this disease. The key elements of a high-quality screening program include appropriate education and professional qualifications of personnel, primarily radiologists and radiological engineers, and also of other personnel participating in further diagnostics and treatment, as well as

ensuring double reading of mammograms, interdisciplinary cooperation, appropriate technical quality of mammography machines, setting up an appropriate information system, monitoring and evaluation of program quality indicators. In addition, the target female population needs to be selected for screening mammography in an organized and systematic way. An appropriate response in this population must be achieved through the use of personal invitations and health education campaigns.

By the end of July, 11,503 invitations to screening mammography were dispatched; 9,686 women responded to the invitation, thereby representing an attendance of 84.2 %. In the observed period, 86 breast cancer cases were detected. Program DORA meets all requirements by the European guidelines in quality control and treatment.

## Individualized Systemic Treatment of Lung Cancer - A Real Fact or Utopia?

Tanja Čufer

Lung cancer is the leading cause of cancer-related death in men and women. Over the last decade, lung cancer incidence and mortality in developed countries increased in women, while the corresponding rates in men remained stable. Approximately 1000 new patients are diagnosed with lung cancer in Slovenia each year. During the last 15 years, the 5-year survival rates of patients with lung cancer increased by only 2.2%. Further progress is expected by introducing individualized, patient and tumor characteristics tailored systemic therapy strategies in the treatment of lung cancer. In this article, the current possibilities of individualized systemic therapies tailored to the patient (age, performance status, co-morbidities) as well as primary tumor characteristics are presented. A comprehensive overview of so far explored

targeted therapies, aimed at the two most explored molecular targets in non-small cell lung cancer, i.e. EGFR (epidermal growth factor receptor) and VEGF (vascular epidermal growth factor), is presented. Future individualized treatment strategies and ongoing clinical research in this ever expanding field are outlined.

It is expected that the individualized treatment approach will improve the effectiveness of systemic therapy of lung cancer in near future. However, one must be aware of the fact that there are some prerequisites for effective individualized therapy, i.e. molecular targets have to be defined very precisely, accurately determined in each individual tumor and targeted systemic therapy has to be carefully tailored to each individual patient.

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## Isolated Limb Perfusion

Marko Hočevar

Isolated limb perfusion (ILP) is a form of regional treatment of locally advanced limb cancers. It was first described in 1950s and modified with time. In 1980s, hyperthermia was added and in 1990s TNF (tumor necrosis factor). ILP is indicated in the patients with locoregionally advanced melanoma (in transit metastases) and in the patients with limb sarcomas where amputation would be the only radical treatment. During the procedure, the artery and vein for lower/upper limb is isolated and connected to the heart-lung machine. In the first part of the procedure, the isolated limb is warming to about

40° C and leakage measurements with isotope are performed. If there is no leakage, cytotoxic drug is applied in the dosage 10-20 times higher than the maximal dosages during systemic application. At the end of the procedure, the limb is washed out and the vessels repaired. Postoperative complications are usually regional in the form of erythema and edema. ILP is an effective treatment with complete response rates reaching 70% in patients with melanoma and 80% limb sparing in patients with advanced sarcomas.

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## Intraabdominal Pressure and Intraabdominal Compartment Syndrome

Ksenija Mahkovic Hergouth

Intraabdominal compartment syndrome increases significantly the morbidity and mortality of ICU patients. In the present article, this complication is explained through definitions, pathophysiology, etiology and treatment doctrine. The increased intraabdominal pressure and intraabdominal compartment syndrome can be related to the pathological changes in the abdominal cavity as well as to the extraabdominal causes. The excessive fluid resuscitation, in particular with crystalloids in acute critical illness is an important risk

factor as well. One of the most serious pathophysiological consequences of the increased intraabdominal pressure is the decrease of perfusion pressure and thereby also of blood perfusion of the abdominal organs. The measures to reduce the intraabdominal pressure include: measures to improve the abdominal wall compliance, measures to reduce the content of the abdominal cavity, reduction of the intravascular fluid therapy and the treatment of the primary disease. In worst cases, the surgical abdominal decompression should be performed without delay.

## **The significance of retroperitoneal lymph node dissection in the treatment of non-seminomatous testicular tumors**

Andrej Kmetec

In the last years, effective chemotherapy in non-seminomatous germ cell tumors (NSGCT) diminished the significance of retroperitoneal lymph node dissection (RLND). Nearly 30% of patients have residual tumor after chemotherapy which harbor 60-70% of viable cancer and 30-40% of necrosis or fibrous tissue. The criteria to avoid RPLA, such as reduction of tumor volume by more than 90%, negative tumor markers and residual mass of less than 2 cm in size, are not sufficiently accurate. Postchemotherapy RPLND is recommended in the

patients with normal tumor markers and residual tumor of the size ranging from 1-1.5 cm because of higher probability for active disease. According to tumor mass, considerable modifications in the technique of operation evolved to minimize late consequences of surgery and to improve quality of life. We perform one-side or one-side extended RPLND, while nerve-sparing surgery can be done only in specific patients. Late consequence is the retrograde ejaculation which can be prevented in 80% with unilateral RPLND.

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## **Palliative Surgery Treatment of Cancer Patients**

Erik Brecelj

Palliative surgical treatment has a substantial role in the comprehensive palliative care of patients with incurable cancer. It is primarily aimed at alleviating the symptoms and not at prolonging the survival of patients. The data obtained by

prospective studies on palliative surgical treatment are scarce; therefore, the decision to apply such treatment may not be easy and it definitely requires a multidisciplinary approach to each patient.

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## **Cytopathological Diagnostics of Lymphomas from Lymph Nodes Biopsies**

Veronika Kloboves Prevodnik

Cytology examination is a rapid, low-cost and reliable method in diagnosing lymphatic diseases. In many cases, microscopic examination allows us to distinguish between reactive lymphadenitis, inflammation, metastatic disease and lymphoma. Where this is not feasible, additional techniques, i.e. immunocytochemistry and flow cytometric immu-

nophenotyping, are used. In cytopathological diagnostics of lymphomas, flow cytometric immunophenotyping is the most frequently used because it allows a reliable distinction between reactive lymphadenitis and lymphoma and, in addition, it is also most helpful in classifying lymphomas.

## **Patients with One to Three Positive Axillary Lymph Nodes Following Mastectomy: Dilemma Whether to Use Postoperative Radiation Therapy or Not**

Jasna But Hadžić and Cvetka Bilban Jakopin

Radiation therapy following a modified radical mastectomy (MRM) applied in the patients with one to three positive axillary lymph nodes has long been a primary issue of many debates. Despite most convincing evidence of the benefits of the post-MRM radiation therapy of the patients at moderate risk for local recurrence, a number of issues and questions, such as the effect of improved local control on survival as well as the late cardiotoxic sequelae of radiation therapy ir-

respective of the most up-to-date systemic therapy, accurate radiation field planning and proper selection of subgroups of patients eligible for radiation, have remained unresolved. In general, the majority of international guidelines and agreements recommend, though not without a careful benefit/risk assessment, performing post-MRM radiation therapy in the subgroup of patients with one to three positive axillary lymph nodes.

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## **Treatment with L-Thyroxine during Pregnancy after Thyroid Surgery**

Nikola Bešić

Elevated maternal concentration of TSH during pregnancy is correlated with complications during and after pregnancy and impairment of development of fetus and its brain. Pregnant women in whom the thyroid was surgically removed or who had radioiodine ablation are, with regard to the thyroid hormone concentration, dependant on the input of L-thyroxine with tablets. There are very scarce data in the literature about how the suppression dose of L-thyroxine should be modified in the patients with thyroid carcinoma after total thyroidectomy and radioiodine ablation of the thyroid remnant. In our prospective study we found out that, in 36 pregnant patients with thyroid carcinoma who were on suppressive doses of L-thyroxine, the concentration of TSH could change

vastly. The TSH concentration remained suppressed during pregnancy in only one quarter of the patients. In the patients with suppression during the third trimester, the mean dose of L-thyroxine was 160  $\mu\text{g}$ . In those patients in whom the dose was changed, the mean change of dose was 31.5  $\mu\text{g}$ . In all pregnant women, the concentration of TSH and thyroid hormones should be determined as soon as pregnancy is confirmed. We recommend that, during pregnancy, the concentration of TSH and thyroid hormones is determined every four weeks in all pregnant women who are on L-thyroxine in order to change the dose and prevent the increase of TSH concentration which might be detrimental for the pregnant woman and the fetus.

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## **Approach to A Terminally-Ill Patient and His Family – Coordination of Palliative Care**

Klelija Štrancar, Tanja Žagar and Jernej Benedik

Palliative care is a comprehensive medical care or treatment of a patient facing a progressive and incurable disease. Team approach provides the best possible care of the needs of patients and their relatives. Coordinator of palliative care, who is a member of the palliative team, plays a central role, especially in integrating different levels of palliative care

in each institution and ensures a regular follow-up of the patient after his dismissal to home care. The coordinator is the link between the patient and the palliative care team at the Institute of Oncology. He also offers psychological and spiritual support to patients and their families.

## **The Patient with Neurologic Symptoms Appearing 11 Years after Treatment of Testicular Cancer**

Marija Šoštarič Podlesnik, Tanja Roš and Berta Jereb

Introduction of cisplatin-based chemotherapy (ChT) improved the cure rate of patients with testicular cancer. Polyneuropathy, as the most common side effect of cisplatin, is observed in a high proportion of patients treated with PVB. Peripheral nerve damage of different grade, depending on the cumulative dose of the drug may last for many years after the conclusion of treatment. A large study on neuro-toxic symptoms in subjects treated with 6 cycles PVB is quoted.

In the presented patient, neurologic symptoms appeared 11 years after the treatment with 3 cycles of PVB. The cause of his symptoms is not clear. Years ago, radiation was recognized as the most frequent cause of late effects, with chemotherapy recently increasing its role in this process. Careful life time follow-up by assorted specialists is necessary to gain further experience.