ONKOLOŠKI INŠTITUT LJUBLJANA, KATEDRA ZA ONKOLOGIJO, SEKCIJA ZA INTERNISTIČNO ONKOLOGIJO

5.ŠOLA TUMORJEV PREBAVIL

NOVOSTI V ZDRAVLJENJU TUMORJEV PREBAVIL

ONKOLOŠKI INŠTITUT LJUBLJANA

30.NOVEMBER 2016

Strokovni in organizacijski odbor:

Izr.prof.dr.Janja Ocvirk, dr.med.

Mag.Zvezdana Hlebanja, dr.med.

Urednica zbornika:

Asist.dr.Martina Reberšek, dr.med.

Organizator in izdajatelj (založnik):

SEKCIJA ZA INTERNISTIČNO ONKOLOGIJO pri SZD

ONKOLOŠKI INŠTITUT LJUBLJANA

KATEDRA ZA ONKOLOGIJO

Ljubljana, November 2016

5. ŠOLA TUMORJEV PREBAVIL

(NOVOSTI V ZDRAVLJENJU TUMORJEV PREBAVIL)

dne 30. novembra 2016

Organizatorji: Sekcija internistične onkologije pri SZD
Onkološki inštitut Ljubljana
Katedra za onkologijo

LJUBLJANA, Onkološki inštitut, Predavalnica stavba C, Zaloška 2, Ljubljana

Organizacijski in Strokovni odbor: izr. prof. dr. Janja Ocvirk, dr. med.,
mag. Zvezdana Hlebanja, dr. med.

PROGRAM:

7.00 – 8.30 **Registracija udeležencev**

8.30 – 8.50 **Dejavniki, ki vplivajo na odločitev o dopolnilnem zdravljenju kolorektalnega raka**
dr. Neva Volk, dr. med.

8.50 – 9.10 **Vloga biomarkerjev v zdravljenju napredovalih tumorjev prebavil**
asist. dr. Martina Reberšek, dr. med.

9.10 – 9.25 **Razprava**

9.25 – 9.40 **Odmor**

9.40 – 10.00 **Novosti v sistemskem zdravljenju raka trebušne slinavke**
mag. Zvezdana Hlebanja, dr. med.

10.00 – 11.00 **SATELITNI SIMPOZIJ – Novosti v sistemskem zdravljenju karcinoma želodca in predstavitev primerov**
izr. prof. dr. Janja Ocvirk, dr. med.
dr. Neva Volk, dr. med.

11.00 – 11.15 **Razprava**

11.15 – 11.30 **Odmor**

11.30 – 11.50 **Novosti v sistemskem zdravljenju CRC**
dr. Tanja Mesti, dr. med.

11.50 – 12.10 **Novosti v zdravljenju tumorjev danke**
izr. prof. dr. Vaneja Velenik, dr. med.

12.10 – 12.30 **Nove obsevalne tehnike tumorjev prebavil**
Ana Jeromen, dr. med.

12.30 – 13.30 **SATELITNI SIMPOZIJ – Vloga bioloških zdravil v zdravljenju MCRC**
izr. prof. dr. Janja Ocvirk, dr. med.

13.30 – 14.30 **Odmor za kosilo**

14.30 – 14.50 **Toksičnost fluoropirimidinov**
Marko Boc, dr. med., Maja Ravnik, dr. med.

14.50 – 15.10 **Toksičnost tarčnih zdravil v zdravljenju tumorjev prebavil**
Maja Ebert Moltara, dr. med.

15.10 – 15.30 **Pomen zgodnje paliativne oskrbe v zdravljenju napredovalih tumorjev prebavil**
Andrej Žist, dr. med.

15.30 – 15.45 **Odmor**

15.45 – 16.05 **PET-CT in MRI pri načrtovanju obsevanja tumorjev prebavil**
mag. Franc Anderluh, dr. med.

16.05 – 16.45 **Stereotaksija primarnih in sekundarnih tumorjev jeter**
doc. dr. Irena Oblak, dr. med.

16.45 – 17.05 **HIPEC**
Rok Petrič, dr. med.

17.05 – 17.25 **Elektrokemoterapija zasevkov v jetrih**
asist. dr. Ibrahim Edhemović, dr. med.
dr. Erik Brecelj, dr. med.

17.25 – 17.45 **Perkutano lokalno zdravljenje z nanopartikli jetrnih lezij**
doc. dr. Peter Popovič, dr. med.
Nina Boc, dr. med.

17.45- 18.00 **Razprava in zaključek**

Dejavniki, ki vplivajo na odločitev o dopolnilnem zdravljenju raka debelega črevesa in danke

Dr. Neva Volk, dr.med.
Onkološki inštitut
Sektor za internistično onkologijo

Za uvod: preživetje bolnikov z rakom debelega črevesa…..

….pred obdobjem kemoterapije – pred letom 1970…

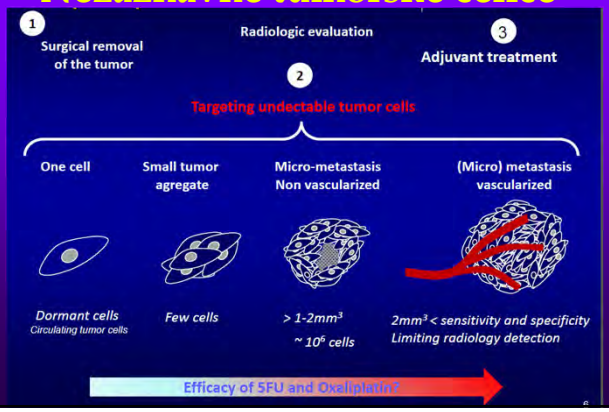
		5-letno preživetje
Dukes*A	Omejen na mukozo	61%-81%
Dukes B	Invazija skozi muskularis mukoze, brez zasevkov v regionalnih bezgavkah	25%-64%
Dukes C	Zasevki v regionalnih bezgavkah	6%-28%

….in leta 2010**

	5-letno preživetje
Stadij II ***	60%-80%
Stadij III	30%-60%

*Klasifikacija po Dukesu (1932)
**De Gramont. Clinical Colorectal Cancer, Vol. 10, No. 4, 218-26 2011
***The TNM staging system, AJCC/UICC 7th edition

Nezaznavne tumorske celice

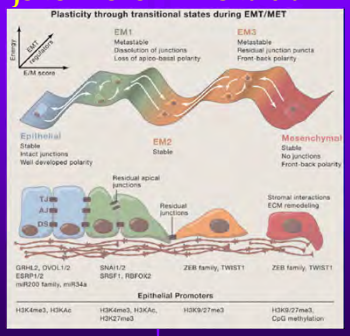


Dejavniki, ki vplivajo na zdravljenje

TUMOR
- Lastnosti tumorja
- TNM
- Perforacija
  - Kirurg/poročilo
  - Čas (od posega)

BOLNIK
- Starost in spol
- Stanje zmogljivosti
- Spremljajoče bolezni
- Poop. morbiditeta
- Odnos do bolezni in zdravljenja

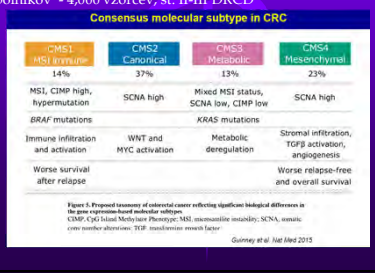
Biologija tumorja
Epitelijsko-mezenhimska tranzicija



Nieto et all. Cell 2016

Molekularni podtipi raka debelega črevesa

- Iskanje podtipov RDČ; predvsem st III, z visokim tveganjem; zaenkrat noben od genskih podpisov ne more napovedati koristi zdravljenja
- **Mezenhimski podtip** – velika ekspresija mezenhimskih genov – slabša prognoza
- Colorectal Cancer Subtyping Consortium – 6 skupin (15+ ustanov) > 30 kohort bolnikov - 4,000 vzorcev, st. II-III DRČD



Guinney et al. Nat Med 2015

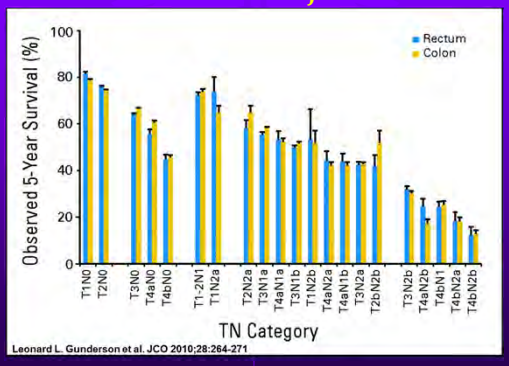
Še niso v klinični praksi !

Rak debelega črevesa in danke - razporeditev po stadijih

Stadiji	I	II	III	IV
	T1, N0, M0	A: T3, N0, M0	A: T1-2, N1/N1c, M0; T1, N2a, M0	A: katerikoli T ali N, M1a
	T2, N0, M0	B: T4a, N0, M0	B: T3-4a, N1/N1c, M0; T2/3, N2a, M0; T1-2, N2b, M0	B: katerikoli T ali N, M1b
		C: T4b, N0, M0	C: T4a, N2a, M0; T3-4a, N2b, M0; T4b, N1-2, M0	
Delež incidence	15 %	25 %	35 %	25 %

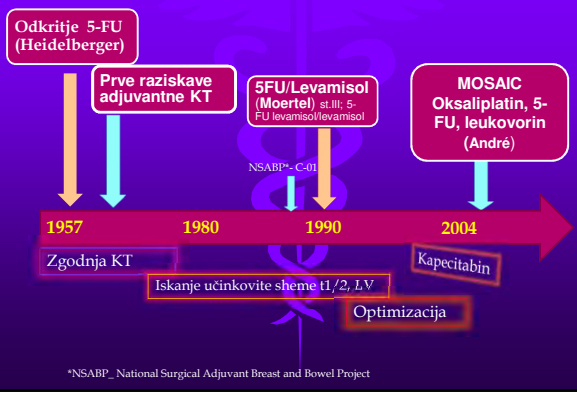
Edge S et al. AJCC Cancer Staging Manual, 7th ed. New York, NY: Springer 2009

Opazovano 5-letno preživetje glede na TN stadij



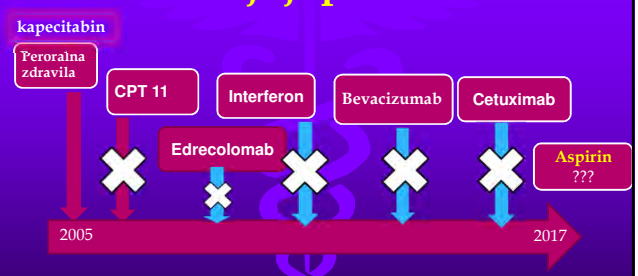
Leonard L. Gunderson et al. JCO 2010;28:264-271

Razvoj adjuvantne kemoterapije RDČ



*NSABP_ National Surgical Adjuvant Breast and Bowel Project

Nadaljnji poskusi?



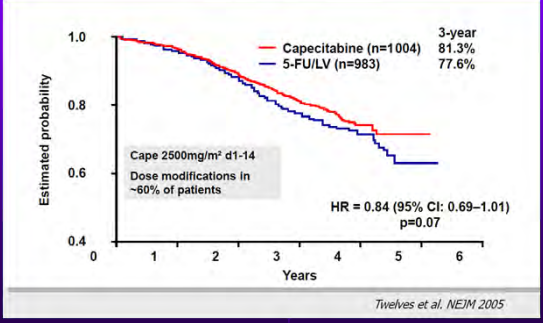
STADIJ III

Izboljšanje celokupnega preživetja: 5FU vs kontrola

Stadij III:

več kliničnih raziskav faze III: **+10-12** %

Stadij III: X-ACT celokupno preživetje



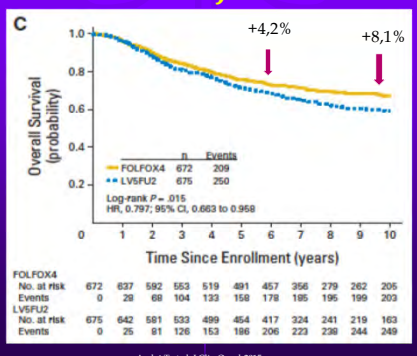
Oksaliplatin

MOSAIC[1] : 2246 bolnikov s st. II (40%) in st. III (60%)

- FOLFOX4
- relaps: 21.1%vs. 26.1%
- 3- letno preživetje brez bolezni (DFS): 78.2% vs 72.9% (5,3 mes.) HR=0.77; p=0.002

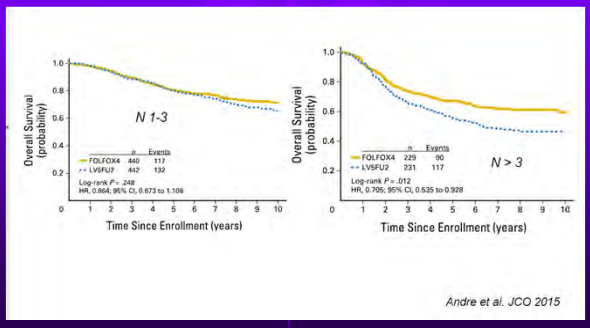
1. André T et. al. N Engl J Med 2004

MOSAIC - 10-letno obdobje stadij III



André T et al. J Clin Oncol 2015

Adjuvantni FOLFOX st. III pT3-4 N+



Andre et al. JCO 2015

Standard za st. III: fluoropirimidini + oksaliplatin

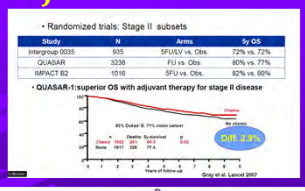
	HR for DFS	P value	DFS Δ (%)	HR for OS	P value	Δ OS (%)
MOSAIC (FOLFOX)[1,2]	0.78 CI, 0.65-0.93 @ 5 year	0.005	Δ 7.5% 58.9% vs 66.4% @ 5 year	0.80 CI, 0.65-0.97 @ 6 year	0.023	Δ 4.2% 68.7% vs 72.9% @ 6 year
NSABP C-07 (FLOX)[3]	0.78 CI, 0.68-0.90 @ 5 year	0.0007	Δ 6.6 % 57.8% vs 64.4% @ 5 year	0.85 CI, 0.72-1.00 @ 5 year	0.052	Δ 2.7% 73.8% vs 76.5% @ 5 year
XELOXA (Xelox)	0.80 CI, 0.69-0.93 @ 3 year	0.0045	Δ 4.4% 66.5% vs 70.9% @ 3 year	0.87 CI, 0.72-1.05 @ 5 year	0.1486	Δ 3.4% ND (57 months FU)

1. Andre T. J Clin Oncol 2009
2. Yothers G. J Clin Oncol 2011
3. Haller D. J Clin Oncol 2011

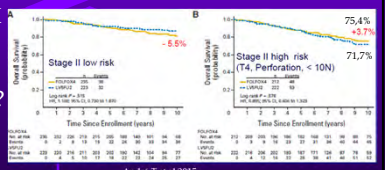
STADIJ II

Stadij II

- Majhna dobrobit s 5FU - le 3%



- Ni izboljšanja s FOLFOX
- Korist FOLFOX V podskupini z visokim tveganjem za ponovitev?



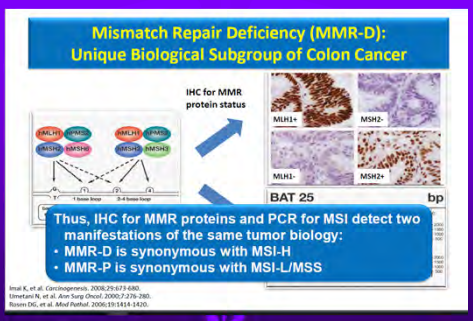
André T et al 2015

Dejavniki visokega tveganja –RDČD stadij II

	ASCO 2004	NCCN 2017	ESMO 2013
T4	+	+	+
Nezadostno število vzorčenih bezgavk	+(<13)	+ (<12)	+ (<12)
Slabo dif. karcinom	+	+ (razen pri MSI-H tumorjih)	+
perforacija	+	+ (lokalizirana)	+
obstrukcija		+	+
LVI	+	+	+
PNI	+	+	+
Robovi R1/ nedoločljivo/blizu		+	

NCCN: trenutna definicija dejavnikov tveganja ni ustrezna!

Mikrosatelitna nestabilnost (MSI)

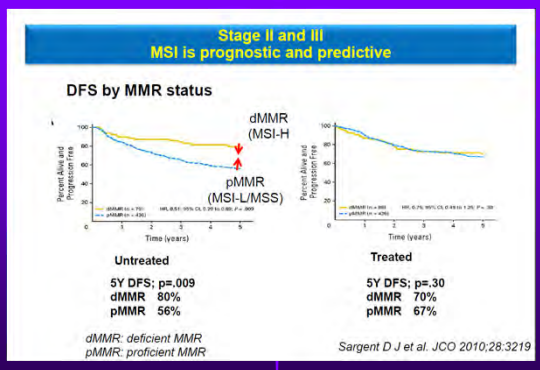


9,4 - 24,4% tumorjev stadija II in III

MSI kot prognostični dejavnik za stadij II in III

			MMR-D vs. MMR-P HR (95% CI); p-Wert
Ribic et al	II/III OP	OS	0.31 (0.14-0.72) P=0.004
Sargent et al	II/III OP	DFS	0.46 (0.22-0.95); p=0.03
Gray et al	II OP	RFS	0.31 (0.15-0.63) p<0.001
Roth et al	II 5FU +/ Irinotecan	RFS	0.30 P=0.004

Ribic, N Engl J Med 2003; Sargent, JCO 2009; Gray, JCO 2011; Roth, JNCI 2009



MSI kot prediktivni dejavnik za učinkovitost floropirimidinopv pri stadiju II?

Nasprotujoči si podatki:

<u>ni škodljivega učinka pri KT v stadiju II:</u>

- Quasar[1]
- CALBG 9581, CALBG 89803[2]

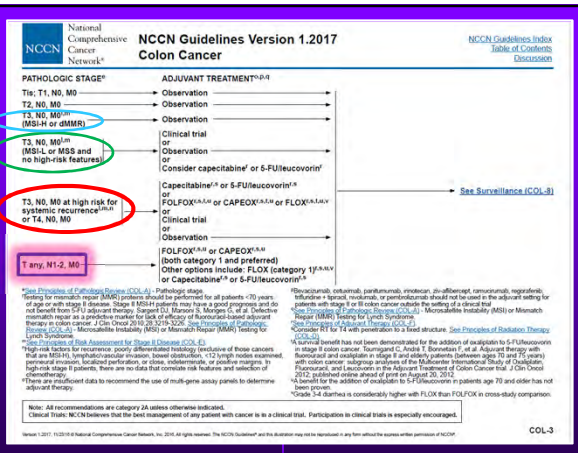
1. Hutchins G et al, 2011
2. Bertagnolli MM et al, 2011

NCCN smernice 2017

testiranje MSI za vse bolnike z RDČD:

- identifikacija bolnikov z Lynchevim sindromom
- odločitve o imunoterapiji pri metastatski bolezni
- odločitev o uvedbi KT pri stadiju II →

NE adj. KT pri stadiju II brez dejavnikov tveganja, če gre za MSI-H tumor (slabo diferenciran tumor ni dejavnik tveganja pri MSI-H!)


NCCN Guidelines Version 1.2017
Colon Cancer

NCCN Guidelines Index
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Discussion

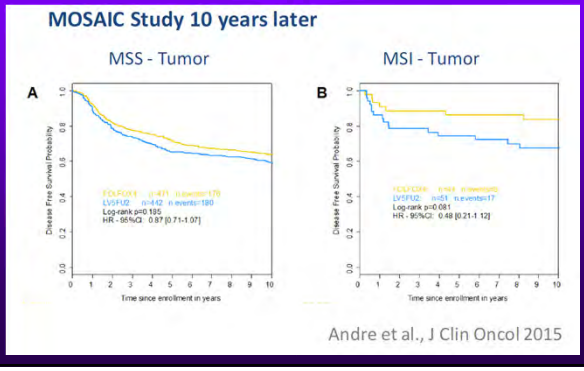
PATHOLOGIC STAGE[a]	ADJUVANT TREATMENT[c,p,q]
Tis; T1, N0, M0	Observation
T2, N0, M0	Observation
T3, N0, M0[l,m] (MSI-H or dMMR)	Observation
T3, N0, M0[l,m] (MSI-L or MSS and no high-risk features)[n]	Clinical trial or Observation or Consider capecitabine[r] or 5-FU/leucovorin[r]
T3, N0, M0 at high risk for systemic recurrence[l,m,n] or T4, N0, M0	Capecitabine[r,s] or 5-FU/leucovorin[r,s] or FOLFOX[r,s,t,u] or CAPEOX[r,s,t,u] or FLOX[r,s,t,u,v] or Clinical trial or Observation
T any, N1-2, M0	FOLFOX[r,s,u] or CAPEOX[r,s,u] (both category 1 and preferred) Other options include: FLOX (category 1)[r,s,u,v] or Capecitabine[r,s] or 5-FU/leucovorin[r,s]

→ See Surveillance (COL-8)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

COL-3

Oksaliplatin in MSI/MSS status



Andre et al., J Clin Oncol 2015

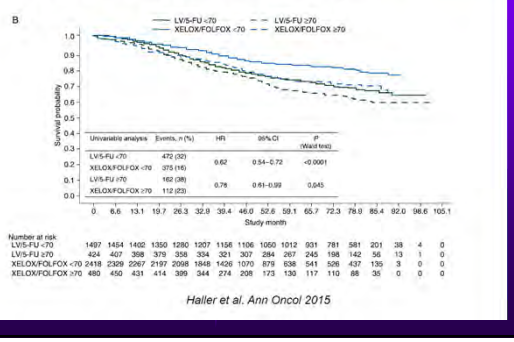
Prognostični in prediktivni dejavniki v raziskavah

- **18q delecija**
- **MSI/dMMR;**
- Timidilat sintetaza (TS) - prekomerna ekspresija in/ali genotip
- K-ras, BRAF mutacije
- p53 mutacije
- Pomanjkanje ekspresije transkripcijskega faktorja CDX2
- Hipermetilacija (epigenetična inaktivacija)- vpliva na gene v poti ekstracelularnega matriksa
- Ekspresija genov
  - 12-gene recurrence score assay (Oncotype DX Colon Cancer Assay)
  - 18-gene classifier (ColoPrint)
  - 13-gene classifier (ColoGuideEx) in drugi seti
- Analiza ekspresije mikroRNA
- Določanje prisotnosti cirkulirajočih tumorskih celic z molekularnimi metodami

STAROSTNIKI IN DOPOLNILNA KEMOTERAPIJA RAKA DEBELEGA ČREVESA

Dopolnilna kemoterapija pri starejših?

XELOXA, X-ACT, and AVANT) survival for age groups

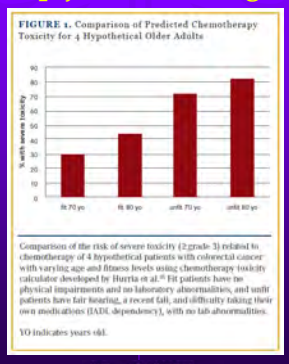


Haller et al. Ann Oncol 2015

Da!

- S fluoropirimidini, pozor pri kapecitabinu
- Priporočeni režim pri st. III: sLV5FU2
- Vloga oksaliplatina kontroverzna; mFOLFOX6 – le za bolnike v odlični kondiciji , posebno pri N2 in/ali ženskem spolu in/ali MSI

Starostniki in tveganje za zaplete pri kemoterapiji raka debelega črvesa



Williams GR. AJHO 2015

Pripomočki za izračunavanje tveganja

- Stadij III: na osnovi ACCENT raziskave: http://www.mayoclinic.org/medical-professionals/cancer-prediction-tools/colon-cancer
- Za stadij II in III: Uptodate – Adjuvant online/Newadjuvant.com; trenutno ne dela!

Renfro LA. J Natl Cancer Inst 2014

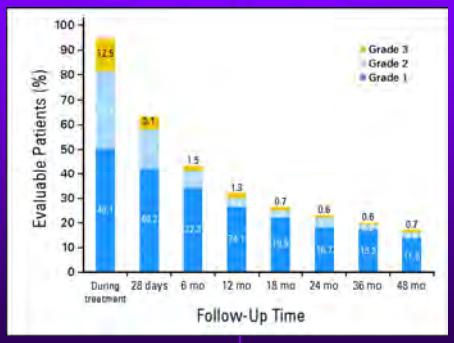
NEŽELENI UČINKI ZDRAVIL

Kardiotoksičnost in fluoropirimidini

- Incidenca (aritmije, nekroza ,miokarda, vazospazem) v raziskavah (N> 400) do 4,3%, posamezna poročila do 12,5%; smrtnost do 0,5% [1]
- Tveganje lahko > koristi adjuvantne KT
- Stadij II – prekiniti
- Stadij III – sodelovanje s kardiologom, monitoring? (težko v praksi)
- Opcije: zamenjava zdravljenja – ralitreksed (Tomudex®). Učinkovitost TOMOX = FOLFOX; ni rand raziskav faze III. Toksičnost ralitrekseda pri ledvični insuficienci! Druga možnost: tegafur- uracil.

1. Polk A. Cancer Treat Rew 2013

Sopojavi: MOSAIC - periferna polinevropatija po zdravljenju s KT po shemi FOLFOX



Andre et al, JCO 2009

Periferna polinevropatija

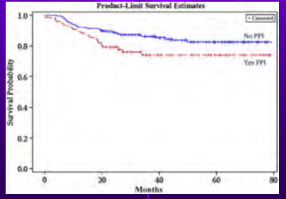
- Simptomi se lahko pokažejo 3 mesece po KT, pri večini izzvenijo 6-12 mesecev po KT
- preeksistentna nevropatija - samo fluoropirimidini

Neplodnost

- Incidenca RDČ med mladimi narašča → pomisliti na načrtovanje družine
- Zelo malo raziskav na živalskih modelih, še manj na ljudeh: 5FU vpliva na spermatogenezo, ni jasno, če si opomore
- Oksaliplatin: 41%izguba menzesa med KT, ne sproži menopavze
- Posvet: napotitev na krioprezervacijo sperme/oocitov, embrijev; GnRH pri ženskah

Kapecitabin in inhibitorji protonske črpalke

- TRIO-013/LOGiC (GE prehod, metastatski): inhibitorji protonske črpalke zmanjšujejo učinkovitost kapecitabina z višanjem pH, kar vodi v spremenjeno disolucijo in absorpcijo.[1]
- Retrospektivna analiza RDČD, st. I-III, 298 bolnikov: krajši RFS v skupini z IPČ (HR, 1.65; 95% CI, 0.93-2.94; P = .09)[2]



1. Chu MP et al. JAMA Oncol. 2016 Oct.
2. Sun J. et al. Clinical Colorectal Cancer, Vol. 15, No. 3, 257-63 ª 2015

Odprta vprašanja - trajanje adjuvantnega zdravljenja in …

- **IDEA** – International Duration Evaluation of Adjuvant Chemotherapy –prospektivna, mednarodna – 6 RCT, > 12.000 bolnikov

3 vs. 6 mesecev XELOX/FOLOX

rezultati 2017???

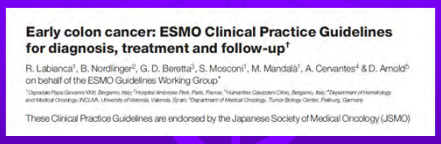
…začetek zdravljenja z adjuvantno KT

- Klinične raziskave: uvedba 4-8 tednov po op
- Metaanaliza[1] : 15510 bolnikov, retrospektivna, razen 1 kohorte: 4 tedne zamika, npr. s 4 na 8 tednov - preživetje (OS) ↓ za 14% [1]
- Začetek KT 8 in 12 tednov po op: 14 in 30 % manjši OS po 5 letih

KONSENZ: uvedba KT takoj ko je bolnik za to sposoben, vsekakor pred 12. tednom po posegu. Korist po 8. tednu pa je večja pri kombinaciji z oksaliplatinom

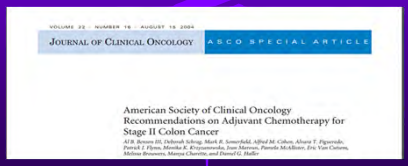
1. Biaggi JJ. JAMA 2011

Smernice


Early colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

R. Labianca[1], B. Nordlinger[2], G. D. Beretta[3], S. Mosconi[1], M. Mandalà[1], A. Cervantes[4] & D. Arnold[5] on behalf of the ESMO Guidelines Working Group*

These Clinical Practice Guidelines are endorsed by the Japanese Society of Medical Oncology (JSMO)


JOURNAL OF CLINICAL ONCOLOGY ASCO SPECIAL ARTICLE

American Society of Clinical Oncology Recommendations on Adjuvant Chemotherapy for Stage II Colon Cancer

NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2017
Colon Cancer

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PRINCIPLES OF RISK ASSESSMENT FOR STAGE II DISEASE[1,2,3]

- Patient/physician discussion regarding the potential risks of therapy compared to potential benefits, including prognosis. This should include discussion of evidence supporting treatment, assumptions of benefit from indirect evidence, morbidity associated with treatment, high-risk characteristics, and patient preferences.
- When determining if adjuvant therapy should be administered, the following should be taken into consideration:
  - Number of lymph nodes analyzed after surgery (<12)
  - Poor prognostic features (eg, poorly differentiated histology [exclusive of those that are MSI-H]; lymphatic/vascular invasion; bowel obstruction; PNI; localized perforation; close, indeterminate, or positive margins)
  - Assessment of other comorbidities and anticipated life expectancy.
- The benefit of adjuvant chemotherapy does not improve survival by more than 5%.
- Microsatellite Instability (MSI) or Mismatch Repair (MMR) Testing
  - Universal MMR* or MSI* testing is recommended in all patients with a personal history of colon or rectal cancer to identify individuals with Lynch syndrome. See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal
  - Stage II MSI-H patients may have a good prognosis and do not benefit from 5-FU adjuvant therapy.[4]

*IHC for MMR and PCR for MSI are different assays measuring the same biological effect.

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NCCN Guidelines Version 1.2017
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PRINCIPLES OF ADJUVANT THERAPY (1 OF 2)

- FOLFOX is superior to 5-FU/leucovorin for patients with stage III colon cancer.[1,2] Capecitabine/oxaliplatin is superior to bolus 5-FU/leucovorin for patients with stage III colon cancer. FLOX is an alternative to FOLFOX or CAPEOX but FOLFOX or CAPEOX are preferred.[3]
- Capecitabine appears to be equivalent to bolus 5-FU/leucovorin in patients with stage III colon cancer.[4]
- A survival benefit has not been demonstrated for the addition of oxaliplatin to 5-FU/leucovorin in stage II colon cancer.[5] FOLFOX is reasonable for stage II patients with multiple high-risk factors and is not indicated for good- or average-risk patients with stage II colon cancer.
- A benefit for the addition of oxaliplatin to 5-FU/leucovorin in patients age 70 and older has not been proven.[5]
- Bevacizumab, cetuximab, panitumumab, irinotecan, ziv-aflibercept, ramucirumab, regorafenib, trifluridine + tipiracil, nivolumab, or pembrolizumab should not be used in the adjuvant setting for patients with stage II or III colon cancer outside the setting of a clinical trial.

5.ŠOLA TUMORJEV PREBAVIL

POMEN BIOMARKERJEV V SISTEMSKEM ZDRAVLJENJU GI tumorjev

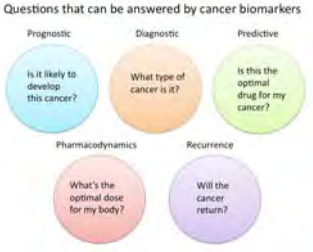
Onkološki inštitut Ljubljana
30.november 2016

Asist.dr.Martina Reberšek,dr.med.

Definicija biomarkerja- NCI Dictionary of Cancer Terms (NATIONALCANCER INSTITUTE)

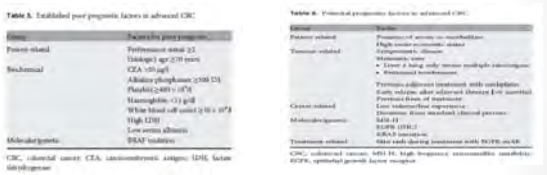
"A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition. Also called molecular marker and signature molecule. "

Vloga biomarkerjev v onkologiji



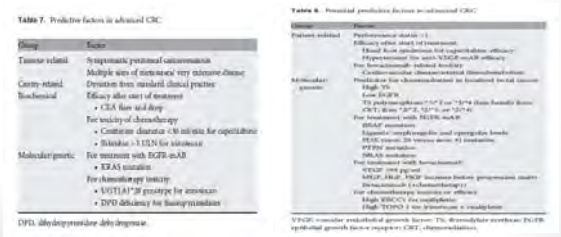
Prognostični dejavniki pri metastatskem karcinomu debelega črevesa in danke

ESMO Consensus Guidelines for management of patients with colon and rectal cancer. A personalized approach to clinical decision making (H.J. Schmoll, et al. Annals of Oncology 23: 2479–2516, 2012)



Prediktivni dejavniki pri metastatskem karcinomu debelega črevesa in danke

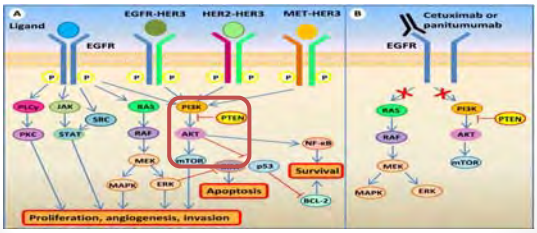
ESMO Consensus Guidelines for management of patients with colon and rectal cancer. A personalized approach to clinical decision making (H.J. Schmoll, et al. Annals of Oncology 23: 2479–2516, 2012)



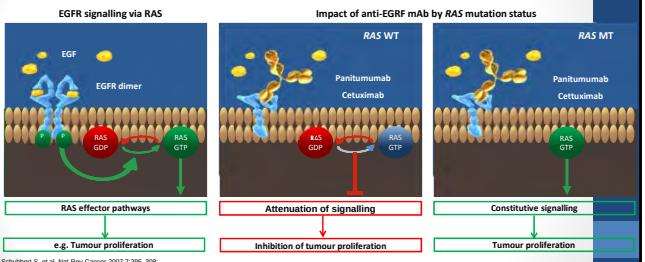
KRAS….RAS

- KRAS status v kodonih 12 in 13 prvi molekularni označevalec za napoved odgovora na zdravljenje z EGFR zaviralci pri bolnikih z mCRC (2008)
- mt*KRAS* v kodonih 12 in 13 ≈ 30-40 %
- Vsi bolniki z wt*KRAS* v kodonih 12 in 13 ne odgovorijo na EGFR zaviralce
- Druge mutacije vzdolž RAS/RAF/MAPK signalne poti, ki napovedujejo odgovor na sistemsko zdravljenje

Mutacije vzdolž EGFR signalne poti pri mCRC



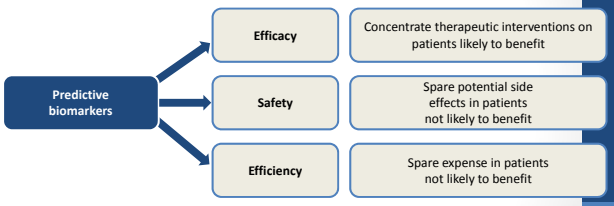
RAS proteins are predictive biomarkers for response to anti-EGFR mAbs



Schubbert S, et al. Nat Rev Cancer 2007;7:295–308;
Foon KA, et al. Int J Radiat Oncol Biol Phys 2004;58:984–90;
Berg M, Soreide K. Discov Med 2012;14:207–14;
Custodio A, Feliu J. Crit Rev Oncol Hematol 2013;85:45–81.

EGF, epidermal growth factor; MT, mutant; WT, wild type.
Example signalling pathways, simplified for illustrative purposes.

Biomarker-guided treatment has the potential to improve clinical outcomes



Conley BA, Taube SE. Dis Markers 2004;20:35–43;
Kelloff GJ, Sigman CC. Eur J Cancer 2005;41:491–501;
President's Council of Advisors on Science and Technology (PCAST): Priorities for Personalized Medicine. 2008 (accessed 13-01-16);
Heinemann V, et al. Cancer Treat Rev 2013; 39:592–601.

NRAS status- nov biomarker v zdravljenju metastatskega raka debelega črevesa in danke

- Status mutacij v KRAS genu je prvi molekularni napovedni dejavnik za odgovor na zdravljenje z EGFR zaviralci pri mCRC: Obvezno testiranje pred zdravljenjem z EGFR zaviralci od leta 2008 (Podatki iz randomiziranih kliničnih raziskav faze II in III)
- **mutacija v *BRAF* genu V600E** – v 5 do 10 odstotkih, prognostični dejavnik (testiranje na OIL od 2010)
- ***KRAS* mutacije v kodonih 61, 146, *NRAS* mutacije v kodonih 12, 13, 61, 146**
- Mutacije v *KRAS, BRAF* in *NRAS* genu se izključujejo
- **Status mutacij v NRAS genu novi molekularni napovedni dejavnik za odgovor na zdravljenje z EGFR zaviralci pri mCRC- obvezno testiranje sept. 2013/jan. 2014**
- **Mutacije v KRAS genu- kodon 61 in 146, in v NRAS genu- v kodoni 12, 13, 61 in 146: prisotne v ≈ 15%**

Retrospektivna analiza prevalence *RAS* mutacije pri bolnikih z mCRC

- malo podatkov iz predhodnih klin.raziskav o prevalenci *RAS* pri bolnikih z mCRC
- Klin.raziskava faze III- PRIME: 52%
- Klin.raziskava faze II- 52%
- mt*BRAF*: 5-15%
- **Rezultati- 5 klin.raziskav faze III in faze Ib/II, II** z wt*KRAS* v eksonu 2: Vključenih 1860 bolnikov: Prevalenca drugih RAS mutacij- mt*KRAS* eksonih 3 in 4, mt*NRAS* v eksonih 2,3,4 **19.1%**

Peeters et al, Prevalence of *RAS* mutations among patients with metastatic colorectal cancer: a pooled analysis of randomized control trials . ASCO GI, 2015

Retrospektivne analize OIL

- Wt *KRAS 54.5 %* (LIČAR et al. *KRAS* mutations in Slovene patients with colorectal cancer : frequency, distribution and correlation with the response to treatment. *Int. j. oncol.*, 2010;36: 1137-1144)
- Wt *KRAS 53.8 %*, m *BRAF 5.1 %* (LIČAR et al. Distribution of some activating *KRAS* and *BRAF* mutations in Slovene patients with colorectal cancer. *Med. oncol. (Northwood)*, 2011:36 (5): 1137-1144)
- Wt *KRAS* 64.5 %, m *BRAF* 7.4 % (Rebersek et al. Efficacy of First- line systemic treatment in correlation with *BRAF* V600E and different *KRAS* mutations colorectal cancer- a single institution retrospective analysis. Radiol Oncol 2011;45(4):285-291.

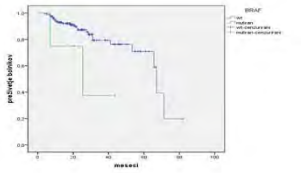
Prevalenca mt*BRAF*- 5 klin.raziskav

- Prevalenca mt*BRAF* 8.1%
- Višja pri ženskah kot pri moških: **10.3% vs 6.9%, p=0.024**
- Višja pri karcinomu kolona kot pri karcinomu rektuma: **10.1% vs 4.5%, p<0.001**
- Mejno statistično značilno višja v histol.vzorcih metastaz kot v primarnem tumorju: **13% vs 7.9%, p=0.059**
- Nižja pri bolnikih z mCRC PS ECOG 0 vs PS ECOG 1-2: **6% vs 10.3%**

Peeters et al, Prevalence of *RAS* mutations among patients with metastatic colorectal cancer: a pooled analysis of randomized control trials . ASCO GI, 2015

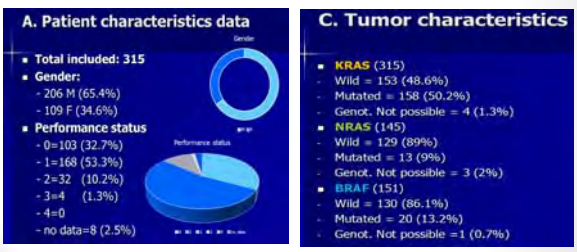
*mt*BRAF kot molekularni biomarker za prognozo bolezni

- Srednje preživetje vseh bolnikov z nemutiranim in mutiranim *BRAF* genom (p= 0.05)

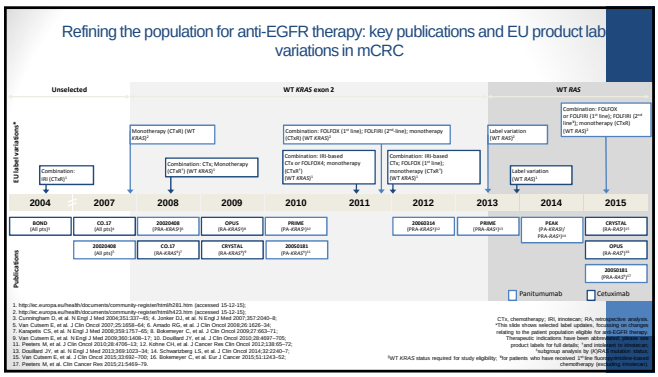


Rebersek M, Doktorska disertacija:VPLIV MUTACIJ V *KRAS* IN *BRAF* GENU TER HISTOLOŠKIH PARAMETROV NA POTEK BOLEZNI PRI BOLNIKIH Z RAZSEJANIM ADENOKARCINOMOM DEBELEGA ČREVESA IN DANKE OB SISTEMSKEM ZDRAVLJENJU, 2013.

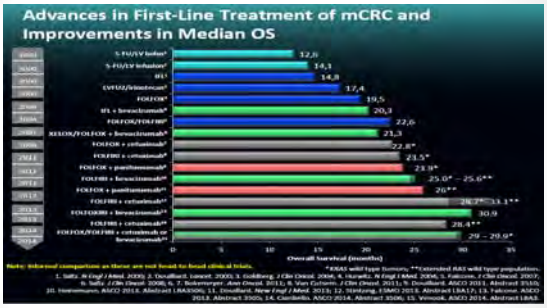
Izkušnje OIL: SLOQUEST



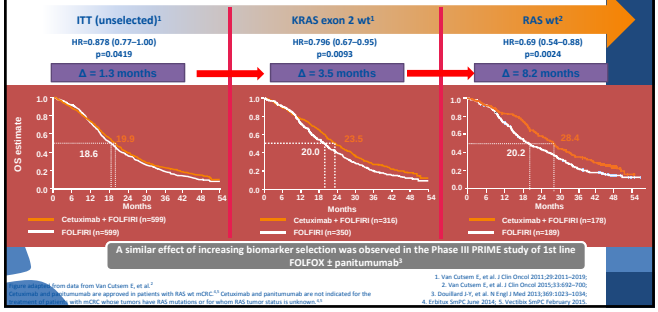
Refining the population for anti-EGFR therapy: key publications and EU product label variations in mCRC



Advances in First-Line Treatment of mCRC and Improvements in Median OS



CRYSTAL: Greater patient selection extended the OS benefit with cetuximab + FOLFIRI



A similar effect of increasing biomarker selection was observed in the Phase III PRIME study of 1st line FOLFOX ± panitumumab[3]

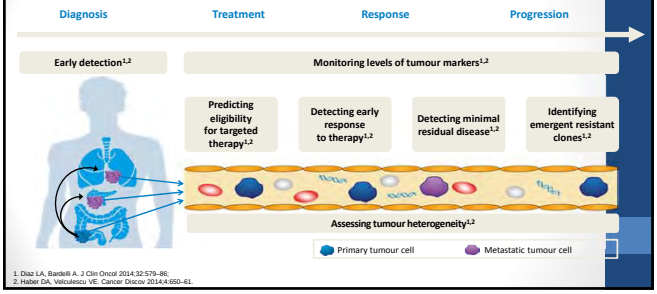
ESMO consensus guidelines for the management of patients with metastatic colorectal cancer (E. Van Cutsem et al. Annals of Oncology 0: 1–38, 2016 doi:10.1093/annonc/mdw235)

Tkivna vs. tekoča biopsija krvi

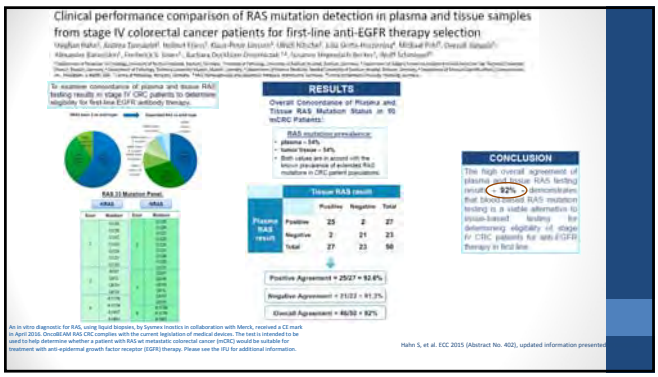
Tissue biopsy	Liquid biopsy
Clinically validated 'gold standard'[1]	Minimally invasive[1]
Source of analysed material known (i.e. primary tumour or metastasis)	Dynamic patient monitoring[1]
Provides tumour histology[2]	Source of fresh DNA[1]
	Suitable for inaccessible tumours[2]
	May reflect tumour heterogeneity[1]

1. Diaz LA, Bardelli A. J Clin Oncol 2014;32:579–86;
2. Crowley E, et al. Nat Rev Clin Oncol 2013;10:472–84.

Potential clinical applications of liquid biopsy



1. Diaz LA, Bardelli A. J Clin Oncol 2014;32:579–86;
2. Haber DA, Velculescu VE. Cancer Discov 2014;4:650–61.



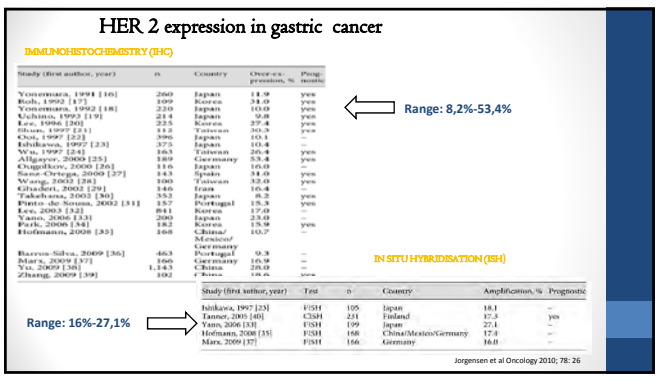
HER 2 testiranje

- Pomen HER 2 pri **mCRC**
- Biomarker pri **metastatskem karcinomu želodca in GE prehoda**
- Ključni faktor v tumorogenezi nastanka karcinoma želodca in GE prehoda
- HER2 je pomnožen ali prekomerno izražen v < 20% karcinoma želodca in GE prehoda

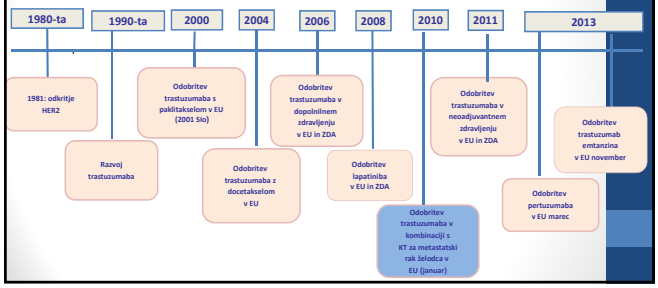
DOLOČANJE:

- Fluorescenčna in situ hibridizacija (FISH)
- Imunohistokemično (IHC)

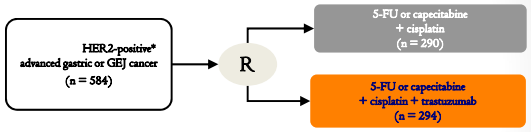
HER2 prekomerna izraženost pogostejša pri intestinalnem tipu (30%) kot pri difuznem tipu (5%) karcinoma želodca



Proti HER 2 usmerjena zdravila



ToGA: Phase III study of trastuzumab in aGC



Primary endpoint: OS

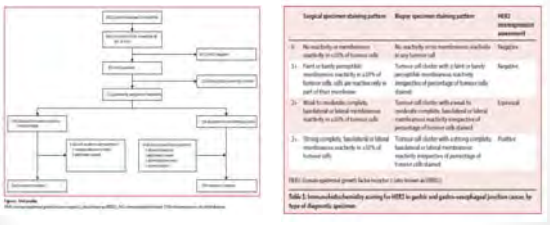
Secondary endpoints: ORR, PFS, TTP, DoR, safety

* IHC 3+ and/or FISH+
DoR, duration of response; PFS, progression-free survival.

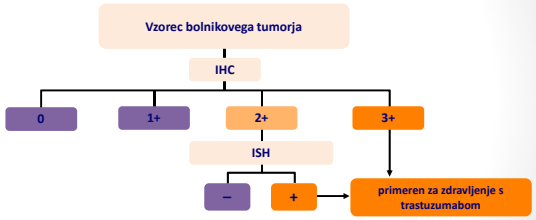
Bang, et al. Lancet 2010.

Klinična raziskava faze III- ToGa

Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial (Bang Y], et al. *Lancet* 2010; 376: 687–97)

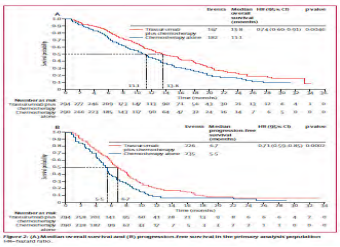


HER2 testiranje pri karcinomu želodca in GE prehoda (algoritem)

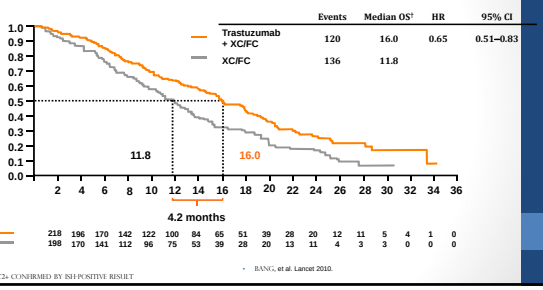


IHC- imunohistokemična metoda
ISH - *in situ* hibridizacijska metoda

Klinična raziskava faze III- ToGa (2)- OS, PFS



ToGA: OS benefit was greatest in patients with high HER2-expressing tumours*



† MONTHS
* IHC3+ OR IHC2+ CONFIRMED BY ISH POSITIVE RESULT

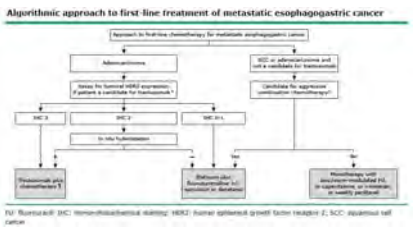
BANG, et al. Lancet 2010.

Testing of HER- 2 positivity in adenokarcinoma of stomach and gastroesophageal junction (THEIA)

Kavalar R, et al. Poster 1079 (XXVIII World Congress of the World Association of Societies of Pathology and Laboratory Medicine)

- V sklopu laboratorijske raziskave je bilo testiranih 802 vzorcev bolnikov z adenokarcinomom želodca in GE prehoda:
  - Bioptični vzorci: 71.3%
  - Resektati primarnih tumorjev: 27.9%
- Pozitivnost 17%, kar je v skladu s ToGA klinično raziskavo (16.6%)

ALGORITEM – 1.red terapije metastatske bolezni

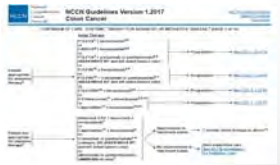


Bendell J, et al. Systemic therapy for locally advanced unresectable and metastatic esophageal and gastric cancer. ©2016 UpToDate

MSI testiranje pri mCRC

- v primeru MSI pozitivnega metastatskega karcinoma debelega črevesa in danke (3.5 - 5%), za odločitev o zdravljenju z imunoterapijo (anti- PD1 monoklonalna protitelesa)

Priporočila **NCCN Guidelines Version 1.2017 Colon cancer**: imunoterapija z nivolumabom ali pembrolizumabom v 2.ali 3.liniji MSI pozitivnega metastatskega mCRC



ZAKLJUČKI

- Biomarkerji:
  - Napovedni dejavnik za odgovor na zdravljenje
  - Prognostični dejavnik za izhod bolezni

- V prihodnosti…….
  - Nove metode določanja biomarkerjev (tekoča biopsija krvi)
  - Novi biomarkerji (MSI pri mCRC za imunoterapijo)

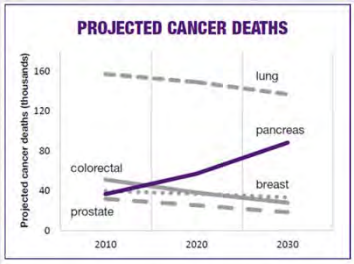
Hvala za pozornost

Novosti v sistemskem zdravljenju raka trebušne slinavke

Zvezdana Hlebanja

Zahrbten, pozno odkrit, hitro potekajoč, smrten

2030:
1 – ca pljuč
2 – ca Pankreasa
3 – ca dojke



Matrisian, Cancer Res 2014

Zahrbten, pozno odkrit, hitro potekajoč, smrten

5 letno preživetje: 5-6%

Radikalna kirurgija: cca 10%

Stage	Description	Possible Treatments	Stage at Diagnosis	5 Year Survival Rate
Stage 0	Local, abnormal cells yet to be formed into a tumor	None needed	7%	20%
Stage I	Tumor about 2 cm found in pancreas only	Surgery, Surgery with chemo and radiation		
Stage II	Spread to nearby tissues and organs and possibly lymph nodes	Surgery, Surgery with chemo and radiation	26%	8.2%
Stage III	Spread to major blood vessels near pancreas and possibly lymph nodes	Surgery with chemo and radiation, chemo with Gemzar, Clinical trial therapies		
Stage IV	Cancer of any size that has spread to distant organs	Chemo with Gemzar, Treatments for pain, Clinical trial therapies	32%	1.8%
Recurrent Cancer	Cancer thought to be removed has return and spread throughout the body	Chemo with Gemzar, Treatments for pain, Clinical trial therapies	N/A	11%

Rak trebušne slinavke

- Pogost: 7. najpogostejši v Evropi
- V Slo zboli skoraj 400 bolnikov letno (več žensk kot moških)
- Zdravljenje zahteva multidisciplinarni pristop
- Edino kurativno zdravljenje je kirurško (15-20%)
- Večinoma le paliativno

Rak trebušne slinavke

- 95% neoplazem trebušne slinavke so exokrini raki
- Simptomi bolezni nastopijo pozno (bolečina, zlatenica, izguba teže)
- Prva diagnostična metoda je običajno UZ (odkrije tu > 3cm)
- ERCP diagnostična in terapevtska metoda za razrešitev zlatenice
- Za določitev stadija bolezni CT prsnega koša in CT trebuha
- Pred zdravljenjem določitev TM CA 19-9
- Histološka potrditev (ni vedno nujna)

Delitev glede na resektabilnost

- V grobem jih delimo na:
  - Jasno resektabilne
  - Neresektabilne
- V primeru dvoma je potrebna laparoskopija ali laparotomija

Sistemsko zdravljenje raka trebušne slinavke

- Adjuvantno
- Napredovale rake trebušne slinavke delimo v:
  - metastatske
  - lokalno napredovale

Adjuvantna kemoterapija

- Po R0 resekciji
- Začetek 4 – 6 tednov po operaciji – skupno 6 mesecev
- Pred uvedbo adjuvantne KT opravimo CT trebuha
- Določimo nivo CA 19-9
- NCCN in ESMO smernice priporočajo adjuvantno KT vsem bolnikom, ki so bili uspešno resecirani, saj je verjetnost sistemskega razsoja visoka (več kot 80%, možnost lokalne ponovitve pa > 20%

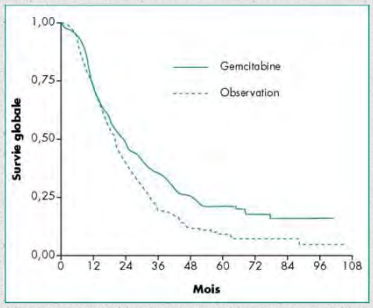
Adjuvantna kemoterapija

- ESMO – adjuvantno priporoča samo zdravljenje s KT
- Radiokemoterapijo pa samo v sklopu randomiziranih raziskav
- NCCN – vključujejo radiokemoterapijo, kot dodatek k adjuvantni kemoterapiji, dopuščajo možnost zdravljenja samo z adjuvantno KT
- Številne randomizirane, kontrolirane študije in meta – analize ugotavljajo, da se celokupno preživetje podaljša, če so bolniki po R0 operaciji adjuvantno zdravljeni s KT

Gemcitabin adjuvantno vs BSC

- CONKO – 001 (faza III)
- Podaljša DFS (13,4 m vs 6,9 m)
- Podaljša OS (22,8 m vs 20,2 m)
- 5 letno preživetje (20,7% vs 10,4%)
- 10 letno preživetje (12,2% vs 7,7%)

CONKO - 001



Citostatiki v adjuvantnem zdravljenju

- Fluoropirimidini (5 – FU, Kapecitabin) – ESPAC-1
- Gemcitabin – CONKO-001
- ESPAC – 3

  - Gemcitabin vs. infuzijski 5 – FU
  - DFS, MS in OS enak (MS 23 mesecev)
  - Gemcitabin manj toksičen

  Potekajo klinične študije s kombinacijami citostatikov GEMCAP, FOLFIRINOX

Sistemsko zdravljenje napredovalega raka trebušne slinavke

- 15 – 20% operabilnih
- Ostali lokalno napredovali ali metastatski
- MS 8 – 12 mesecev za lokalno napredovale
- Samo 3 – 6 mesecev za metastatske
- VRSTO KT DOLOČA ZLASTI PS BOLNIKA !

PS bolnika

WHO/ ECOG/ ZUBROD	Karnofsky	Status bolnika
0	100	aktiven, brez znakov bolezni
1	90	aktiven, minimalni znaki bolezni
1	80	zmanjšana aktivnost, zmerni znaki bolezni
2	70	ni normalne aktivnosti, skrbi zase
2	60	potrebuje občasno pomoč
3	50	pogosto potrebuje pomoč in zdravniško oskrbo
3	40	prizadet, potrebuje posebno oskrbo
4	30	močno prizadet, indicirana hospitalizacija
4	20	zelo bolan, nujna hospitalizacija, aktivna terapija
4	10	moribunden
5	0	smrt

Sistemsko zdravljenje napredovalega raka trebušne slinavke

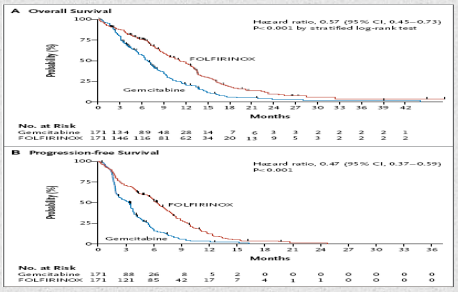
- NOBENA KT NE OZDRAVI METASTATSKEGA RAKA TREBUŠNE SLINAVKE
- OLAJŠA SIMPTOME BOLEZNI
- UPOČASNI NAPREDOVANJE BOLEZNI
- PODALJŠA ŽIVLJENJE

Sistemsko zdravljenje napredovalega raka trebušne slinavke

- Odvisno od PS bolnika, je KT lahko monoterapija, ki ostaja osnovni princip zdravljenja za PS < 1, (Noben od uporabnih citostatikov ne presega ORR > 10% oz MS 6-7 mesecev) **vendar je klinična dobrobit > 27%**
- Razlog relativne kemorezistence raka trebušne slinavke ni povsem znan, verjetno gre za inhibicijo TSG, kar omogoča tumorskim celicam, da se izognejo s KT inducirani apoptozi

- Za bolnike v izrazito dobrem PS priporočamo kombinacije citostatikov, zlasti Folfirinox (ACCORD 11 študija) oz Gemcitabin + Nab Pacli (MPACT študija)

ACCORD 11



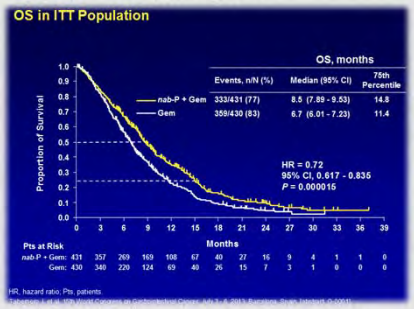
ACCORD 11

- Toksični profil

Table 3. Most Common Grade 3 or 4 Adverse Events Occurring in More Than 5% of Patients in the Safety Population.*

Event	FOLFIRINOX (N=171)	Gemcitabine (N=171)	P Value
	no. of patients/total no. (%)		
Hematologic			
Neutropenia	75/164 (45.7)	35/167 (21.0)	<0.001
Febrile neutropenia	9/166 (5.4)	2/169 (1.2)	0.03
Thrombocytopenia	15/165 (9.1)	6/168 (3.6)	0.04
Anemia	13/166 (7.8)	10/168 (6.0)	NS
Nonhematologic			
Fatigue	39/165 (23.6)	30/169 (17.8)	NS
Vomiting	24/166 (14.5)	14/169 (8.3)	NS
Diarrhea	21/165 (12.7)	3/169 (1.8)	<0.001
Sensory neuropathy	15/166 (9.0)	0/169	<0.001
Elevated level of alanine aminotransferase	12/165 (7.3)	35/168 (20.8)	<0.001
Thromboembolism	11/166 (6.6)	7/169 (4.1)	NS

MPACT

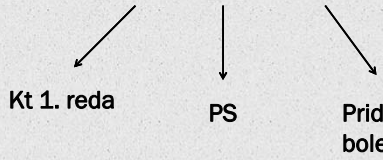


Sistemsko zdravljenje napredovalega raka trebušne slinavke – KT 1. reda

- UP TO DATE 2016
- PS (0-1)
- Ni komorbidnosti
- **Bilirubin < 1,5x zvišan:**
- Folfirinox raje kot Gemcitabin ali GEM + Nab Pacli ali GEM CAP
- Za bolnike z **Bilirubinom >= kot 1,5x zvišan** Folfox (raje kot GEM +/- / metabolizira čez jetra)

- PS = 2
- Zmerna komorbidnost
- Bilirubin < 1,5x zvišan – mono Gemcitabin ali GEM CAP ali Kapecitabin ali S-1 mono
- Zelo selekcionirani bolniki s PS = 2 in izredno visokim tumorskim bremenom GEM + Nab Pacli (boljši RR)
- Bilirubin > 1,5x zvišan – Folfox
- PS >= 3 ➡ izbira KT izrazito individualna priporoča se BSC !

Kemoterapija 2. reda je odvisna od:



Kemoterapija 2. reda

- PS (0-1)
- Za te bolnike ima kt 2. reda prednost pred BSC
- Ni optimalnih kombinacij
- Če je KT 1. reda temeljila na Gemcitabinu, se za te bolnike priporoča da kt 2. reda temelji na derivatih 5 – FU (Folfox, Folfirinox ?, Folfiri)

Kemoterapija 2. reda

- PS (0-1)
- Če je kt 1. reda temeljila na derivatih 5-FU (Folfirinox), se za te bolnike v 2. redu priporočajo kombinacije Gemcitabina (+/- Nab Pacli)
- Če je PS = 2 – monoterapija Gemcitabin
- Če je bila kt 1. reda Folfox (zaradi zvišanega Bilirubina) naj bo kt 2. reda Gemcitabin mono eventuelno GEM +Nab Pacli
- PS >= 3 – BSC !

Povzetek in priporočila

- Vsi bolniki z rakom pankreasa, naj imajo za določitev stadija CT prsnega koša in trebuha
- Določen naj imajo nivo TM CA 19-9 pred začetkom zdravljenja
- Nujna je multidisciplinarna obravnava (+ upoštavanje bolnikovih preferenc, tumorskega bremena in psihičnih vidikov)
- NUJNO JE AGRESIVNO ZDRAVLJENJE BOLEČINE IN DRUGIH, Z RAKOM POVEZANIH SIMPTOMOV
- POTREBNA JE VKLJUČITEV BOLNIKOV V ZGODNO PALIATIVNO OSKRBO

- Vsem bolnikom, kjer je to možno, ponudimo informacije, o potekajočih kliničnih študijah
- Bolnikom z lokalno napredovalo ali metastatsko boleznijo, ponudimo zdravljenje s sistemsko KT, v skladu z ASCO, NCCN, ESMO smernicami
- Zdravljenje s KT zmanjša znake bolezni in podaljša preživetje
- BOLNIKI MORAJO RAZUMETI, DA JE KT PALIATIVNA IN NE KURATIVNA

NOVOSTI V SISTEMSKEM ZDRAVLJENJU METASTATSKEGA KARCINOMA ŽELODCA

Janja Ocvirk

Ljubljana, 30.11.2016

Razkritje

Predavanje sponzorira podjetje Eli Lilly Farmacevtska družba, d.o.o.

Predstavitev odraža mnenja in izkušnje predavatelja, ki niso nujno stališča podjetja Eli Lilly in njihovih zaposlenih.

Ostala sodelovanja s podjetjem Eli Lilly v zadnjih 24 mesecih:

- Članica Svetovalne skupine
- Predavateljica

Napredovala bolezen

- Prognoza napredovale bolezni je slaba z <10% 5-letnim preživetjem
- Vloga kemoterapije je paliativna
- Nove kombinacije KT dajejo višje odgovore, malo CR, čas trajanja odgovorja in OS sta še vedno kratka

NCRI REAL-2 trial

Bolniki z lokalno napredovalim ali metastatskim rakom želodca ali požiralnika, ki niso bili predhodno zdravljeni s kemoterapijo

RANDOMIZACIJA

Epirubicin Cisplatin 5-FU

Epirubicin Cisplatin Kapecitabin (X)

Epirubicin Oksaliplatin 5-FU

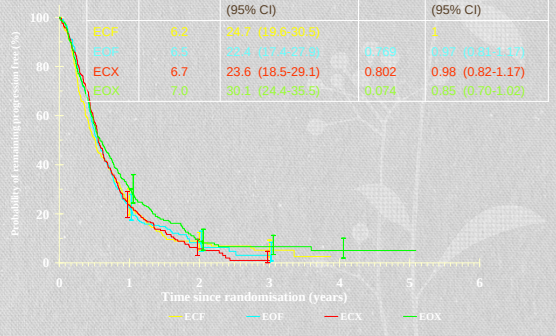
Epirubicin Oksaliplatin Kapecitabin (X)

Načrt 2 X 2
n = 204(interimna analiza)
n celokupno = 1002
Primarni cilj: OS (non-inferiority/superiority)

Sumpter K *et al*. *Br J Can* 2005; 92:1976−1983

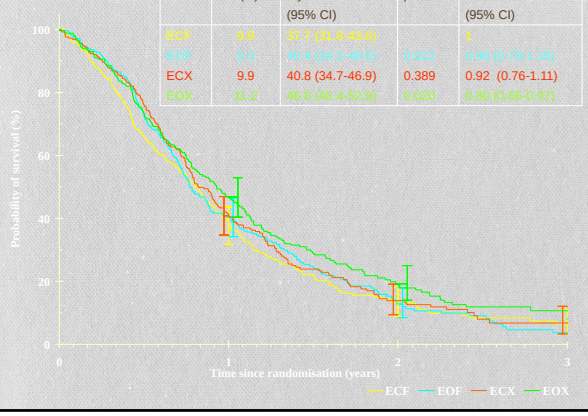
Čas do napredovanja bolezni

Arm	PFS (m)	1 year PFS (95% CI)	p-value	HR (95% CI)
ECF	6.2	24.7 (19.6-30.6)		1
EOF	6.5	22.4 (17.4-27.9)	0.769	0.97 (0.81-1.17)
ECX	6.7	23.6 (18.5-29.1)	0.802	0.98 (0.82-1.17)
EOX	7.0	30.1 (24.4-35.5)	0.074	0.85 (0.70-1.02)



Preživetje m KŽ (ITT)

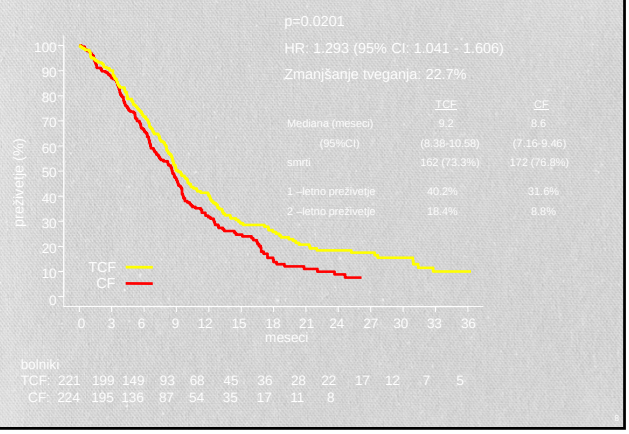
Arm	OS (m)	1 year survival (95% CI)	p-value	HR (95% CI)
ECF	9.9	37.7 (30.5-45.0)		1
EOF	9.3	40.4 (32.7-48.2)	0.872	0.98 (0.79-1.21)
ECX	9.9	40.8 (34.7-46.9)	0.389	0.92 (0.76-1.11)
EOX	11.2	46.8 (40.4-52.9)	0.020	0.80 (0.66-0.97)



Rezultati REAL

- primarni:
  - Kapecitabine ni inferioren 5-FU
  - Oksaliplatin ni inferioren cisplatinu
- Tripleti
  - Kapecitabine lahko nadomesti PVI 5-FU
  - Oksaliplatin lahko nadomesti cisplatin
- EOX izboljša učinkovitost v primerjavi z ECF

Celokupno preživetje Tax 325



ToGA

Zasnova raziskave[1]

[a] po presoji raziskovalca

- **Odprta študija**

3.807 bolnikov testiranih za HER2 status, od tega 810 HER2 pozitivnih (22.1%)

HER2 pozitivni napredovali ali metastatski rak želodca ali GEJ (n=584)

5-FU ali kapecitabin[a] + cisplatin (n=290)

5-FU ali kapecitabin[a] + cisplatin + trastuzumab (n=294)

Stratifikacija

- napredovali vs. metastatski
- rak želodca vs. GEJ
- merljiva vs. nemerljiva bolezen
- ECOG PS 0-1 vs 2
- kapecitabin vs. 5-FU

Odmerki v shemah

- Xeloda 1000 mg/m^2 bid d1-14 q3w x 6
- 5-FU 800 mg/m^2/dan v kontinuirani iv. infuziji d1-5 q3w x 6
- cisplatin 80 mg/m^2 q3w x 6
- Herceptin 8 mg/kg uvajalni, nato 6 mg/kg q3w do progresa

Izbor bolnikov

- **Zožitev tarčne populacije z 22,1% na 16,6%[1]**

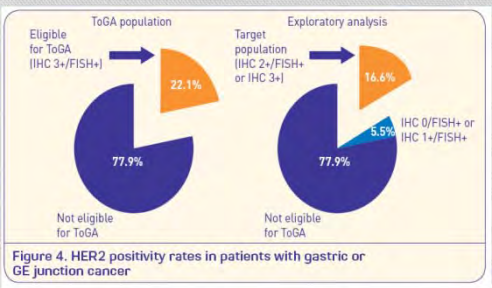


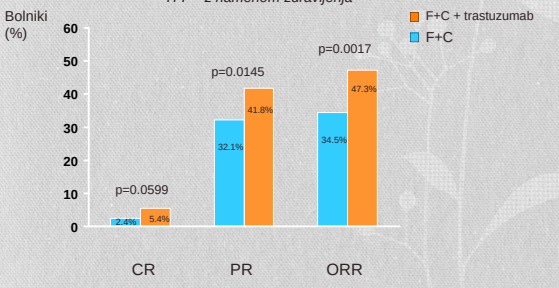
Figure 4. HER2 positivity rates in patients with gastric or GE junction cancer

1. Chung et al. Poster 6511; ECCO-ESMO, 2009

Celokupni odgovor[1]

Sekundarni cilj

ITT – z namenom zdravljenja

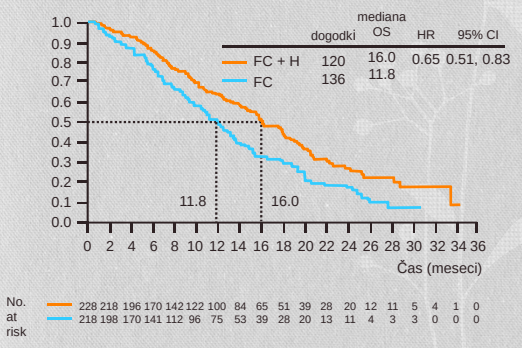


1. Bang et al. Abstract 4556, ASCO 2009,

ORR= CR + PR
CR, popolni odgovor; PR, delni odgovor

Celokupno preživetje pri IHC3+ ali IHC2+/FISH+[1]

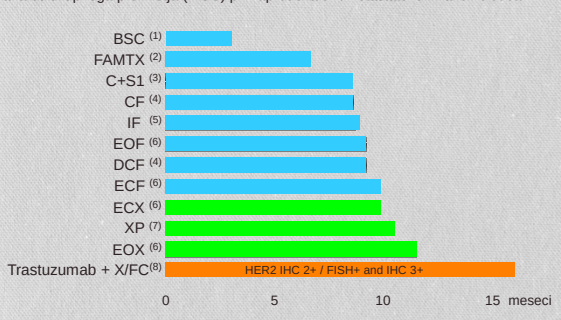
Eksplorativna analiza



1. Bang et al. Abstract 4556, ASCO 2009

Napredek v zdravljenju napredovalega karcinoma želodca 1. linija

mediana celokupnega preživetja (mOS) pri napredovalem/metastatskem raku želodca

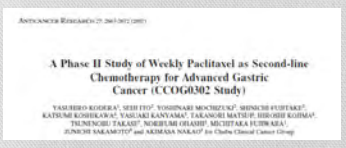


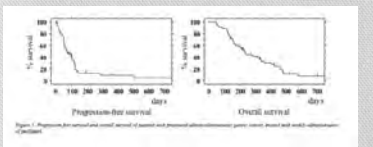
1. Murad, 1993
2. Vanhoefer,2000
3. Ajani, 2009
4. Van Cutsem, 2006
5. Dank, 2008
6. Cunningham, NEIM 2008
7. Kang, 2007
8. Van Cutsem, ASCO 2009

2. Linija zdravljenja

- Irinotekan
- Paklitaksel
- Ramucirumab + paklitaksel
- ramucirumab

1. Wilke H et al. *Lancet Oncol.* 2014;15(11):1224–1235. 2. Fuchs CS et al. *Lancet.* 2014;383(9911):31–39. Ajani JA et al. J Natl Cancer Institut 1994;; 86: 1086-91 4. Sym SJ et al. Cancer Chemother Pharacol 2013; 71: 481-88


A Phase II Study of Weekly Paclitaxel as Second-line Chemotherapy for Advanced Gastric Cancer (CCOG0302 Study)



Mediana preživetja do napredovanje bolezni je bila 2.6 meseca in mediana celokupnaga preživetja 7.8 meseca.

Neželeni učinki so bili blagi, najpogostje neutropenija, ki se je pojavila pri 16% bolnikov v ≥gradus 3.

A randomized phase II study of biweekly irinotecan monotherapy or a combination of irinotecan plus 5-fluorouracil/leucovorin (mFOLFIRI) in patients with metastatic gastric adenocarcinoma refractory to or progressive after first-line chemotherapy

Folfiri in irinotekan v monoterapiji sta enako učinkovita

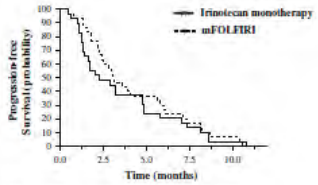


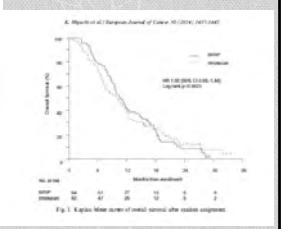
Fig. 1 Kaplan-Meier plot of progression-free survival

ScienceDirect

Biweekly irinotecan plus cisplatin versus irinotecan alone as second-line treatment for advanced gastric cancer: A randomised phase III trial (TCOG GI-0801/BIRIP trial)

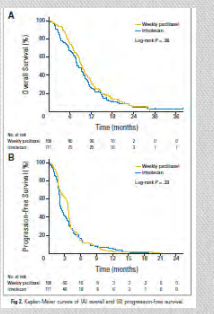
Katsuhiko Higuchi, Satoshi Tatabe, Ken Shimada, Hisashi Hosaka, Eisaku Sasaki, Norisuke Nakayama, Yuiti Takeda, Toshikazu Moriwaki, Kenji Amagai, Takashi Ishikawa, Toshikazu Sakuyama, Taisuo Kanda, Tohru Sasaki, Mitsutomo Azuma, Fumiaki Takahashi, Masahiro Takeuchi, Wasaburo Koizumi, The Tokyo Cooperative Oncology Group, Tokyo, Japan

Med zdarvljenjem z irinotekanom samim ali irinotekanom in cisplatinom ni statistično značilnih razlik



JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Randomized, Open-Label, Phase III Study Comparing Irinotecan With Paclitaxel in Patients With Advanced Gastric Cancer Without Severe Peritoneal Metastasis After Failure of Prior Combination Chemotherapy Using Fluoropyrimidine Plus Platinum: WJOG 4007 Trial



Ni statistično pomembne razlike me zdravlejnje z irinotekanom in paklitakselom v 2 liniji zdarvljenja napredovalega karcinoma želodca

J Clin Oncol 31:4438-4444. 2013

RAMUCIRUMAB (CYRAMZA)

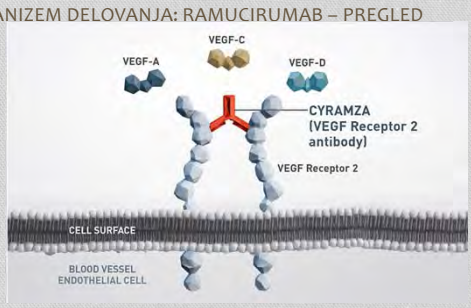
- Humano monoklonsko protitelo, usmerjeno proti receptorjem, je odobreno kot samostojno zdravilo ali v kombinaciji s paklitakselom za zdravljenje bolnikov z napredovalim rakom želodca ali adenokarcinomom OGJ po predhodni kemoterapiji.
- Specifično se veže na receptor VEGF 2 in zavira vezavo VEGF-A, VEGF-C in VEGF-D.[1,2]

OGJ = gastroezofagealni spoj; VEGF = vaskularni endotelijski rastni faktor

References: 1. Clarke JM, Hurwitz HI. *Expert Opin Biol Ther*. 2013;13(8):1187-1196. **2.** Cyramza EU Summary of Product Characteristic, approved 24.9.2015. **3.** Fuchs CS et al. *Lancet*. 2014;383(9911):31-39. **4.** Wilke H et al. *Lancet Oncol*. 2014;15(11):1224-1235.

ZDRAVILO CYRAMZA JE ANTIANGIOGENO ZDRAVILO, KI SPECIFIČNO ZAVIRA AKTIVACIJO RECEPTORJA ZA VEGF 2[1]

MEHANIZEM DELOVANJA: RAMUCIRUMAB – PREGLED



VEGF = vaskularni endotelijski rastni faktor

Reference: 1. Cyramza EU Summary of Product Characteristic, approved 25.1.2016

CYRAMZA Ramucirumab – 2 raziskavi [1,2]

RAINBOW: KOMBINIRANO ZDRAVLJENJE (N = 665) **REGARD:** MONOTERAPIJA (N = 355)

NEOPERABILEN, LOKALNO NAPREDOVALI ALI METASTATSKI RAK ŽELODCA/GE PREHODA	NEOPERABILEN, LOKALNO NAPREDOVALI ALI METASTATSKI RAK ŽELODCA/GE PREHODA
• Napredovanje med ali v 4 mesecih po 1L kemoterapije • ECOG PS 0–1	• Napredovanje med ali po: - 4 mesecih 1L kemoterapije ALI - 6 mesecih adjuvantne kemoterapije • ECOG PS 0–1
Randomizacija 1 : 1*	**Randomizacija 2: 1** ‡
CYRAMZA + paklitaksel† (n = 330) 8 mg/kg q2w (–60min infuzija) + 80 mg/m² (–60min infuzija)	**Placebo + paklitaksel†** (n = 335) q2w + 80 mg/m2 (–60min infuzija)
CYRAMZA§ (n = 238) 8 mg/kg q2w (–60-min infuzija) + BSC	**Placebo§** (n = 117) q2w + BSC
PRIMARNI OPAZOVANI DOGODEK: CELOKUPNO PREŽIVETJE	**PRIMARNI OPAZOVANI DOGODEK: CELOKUPNO PREŽIVETJE**

GE prehod = gastroezofagealni prehod; ECOG = Eastern Cooperative Oncology Group (Vzhodna skupina za sodelovanje v onkologiji); PS = stopnja zmogljivosti; BSC = najboljše podporno zdravljenje; q2w = na 2 tedna

* Stratifikacijski dejavniki: Geografsko območje, merljiva bolezen proti nemerljivi bolezni in čas do napredovanja bolezni po zdravljenju prve izbire (<6 mesecev proti ≥ 6 mesecem).
†Ciklus je trajal 28 dni.
‡Stratifikacijski dejavniki: Geografsko območje, lokacija primarnega tumorja in izguba telesne mase v zadnjih 3 mesecih (≥ 10 % proti <10 %).
§ Ciklus je trajal 14 dni.

Reference: 1. Wilke H et al. *Lancet Oncol*. 2014;15(11):1224–1235. **2.** Fuchs CS et al. *Lancet*. 2014;383(9911):31–39.

ZDRAVILO CYRAMZA JE PRVO ANTIANGIOGENO ZDRAVILO, S KATERIM SE DOSEŽE ZNAČILNO IZBOLJŠANJE PREŽIVETJA PRI NAPREDOVALEM RAKU ŽELODCA[1,2]

DVE VELIKI MULTICENTRIČNI, DVOJNO SLEPI, RANDOMIZIRANI RAZISKAVI III. FAZE

	C P RAINBOW (kombinirano zdravljenje)	C REGARD (monoterapija)
PRIMARNI OPAZOVANI DOGODEK	**Celokupno preživetje**	**Celokupno preživetje**
SEKUNDARNI OPAZOVANI DOGODEK	**Preživetje brez napredovanja** **Objektivni odziv tumorja** ▪ Objektivni delež odziva ▪ Stopnja nadzora bolezni **Kakovost življenja**	**Preživetje brez napredovanja** **Preživetje brez napredovanja po 12 tednih** ▪ Vnaprej določena časovna točka **Objektivni odziv tumorja** ▪ Objektivni delež odziva ▪ Stopnja nadzora bolezni **Kakovost življenja**

Reference: 1. Wilke H et al. *Lancet Oncol.* 2014;15(11):1224–1235. 2. Fuchs CS et al. *Lancet.* 2014;383(9911):31–39.

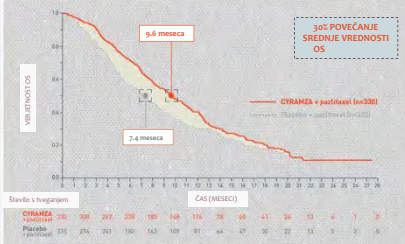
RAINBOW: **OS**[1]

SREDNJA VREDNOST OS: MESECI — **PRIMARNI OPAZOVANI DOGODEK**

CYRAMZA + paclitaxel: **9.6** meseca

Placebo + paclitaxel: **7.4** meseca

HR (95% CI)= 0.807 (0.678, 0.962); *P*=0.0169



OS = celokupno preživetje; HR = razmerje tveganja; CI = interval zaupanja

Referenca: 1. Wilke H et al. *Lancet Oncol.* 2014;15(11):1224–1235.

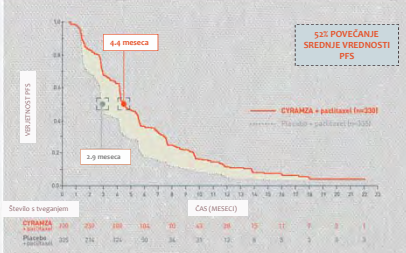
RAINBOW: PFS[1]

SREDNJA VREDNOST PFS: MESECI — **SEKUNDARNI OPAZOVANI DOGODEK**

CYRAMZA + paclitaxel: **4.4** meseca

Placebo + paclitaxel: **2.9** meseca

HR (95% CI)= 0.635 (0.536, 0.752); *P*<0.0001



PFS = preživetje brez poslabšanja bolezni; HR = razmerje tveganja; CI = interval zaupanja

Referenca: 1. Wilke H et al. *Lancet Oncol.* 2014;15(11):1224–1235.

RAINBOW: **ORR**[1,2]

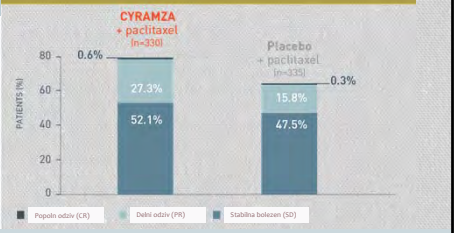
STOPNJA NADZORA BOLEZNI

Objektivna stopnja odziva (ORR) (CR + PR):

CYRAMZA + paclitaxel
27.9%

Placebo + paclitaxel
16.1%

OR (95% CI)= 2.14 (1.45, 3.16); P<0.0001



Stopnja nadzora bolezni (CR + PR + SD) je bila pri zdravljenju s CYRAMZA + paklitaksel 80,0% (n = 330), pri zdravljenju s placebom + paklitaksel (n = 335) pa **63,6 %**
(OR [95 % IZ] = 2,32 [1,63; 3,31]; P < 0,0001).

ORR = objektivna stopnja odziva; OR = razmerje obetov; CI - interval zaupanja

Reference: 1. Wilke H et al. Lancet Oncol. 2014;15(11):1224–1235. 2. Data on file. Eli Lilly and Company. I4T-IE-JVBE (IMCL CP12-0922).

RAINBOW: CYRAMZA JE V KOMBINACIJI S PAKLITAKSELOM V SPLOŠNEM DOSEGLA PROFIL TOKSIČNOSTI, KI SO GA BOLNIKI DOBRO PRENAŠALI[1]

NEŽELENI UČINKI S POGOSTNOSTJO ≥5 % PRI BOLNIKIH, KI SO PREJEMALI CYRAMZA V KOMBINACIJI S PAKLITAKSELOM

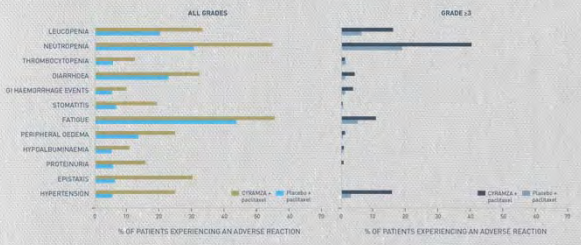
	CYRAMZA + paklitaksel (n = 327)		PLACEBO + paklitaksel (n = 329)	
Neželene reakcije po organskem sistemu (MedDRA)	Vseh stopenj (%)	≥3. stopnje (%)	Vseh stopenj (%)	≥3. stopnje (%)
Levkopenija	33,9	17,4	21,0	6,7
Nevtropenija	54,4	40,7	31,0	18,8
Trombocitopenija	13,1	1,5	6,1	1,8
Driska	32,4	3,7	23,1	1,5
Gastrointestinalne krvavitve[†]	10,1	3,7	6,1	1,5
Stomatitis	19,6	0,6	7,3	0,6
Utrujenost	56,9	11,9	43,8	5,5
Periferni edem	25,1	1,5	13,7	0,6
Hipoalbuminemija	11,0	1,2	4,9	0,9
Proteinurija	16,8	1,2	6,1	0
Epistaksa	30,6	0	7,0	0
Hipertenzija[‡]	25,1	14,7	5,8	2,7

Delež prekinitev zaradi neželenih učinkov je bil podoben v obeh vejah zdravljenja – 12 % bolnikov, zdravljenih z zdravilom CYRAMZA + paklitakselom, proti 11 % bolnikov, zdravljenih s placebom + paklitakselom.

AE = neželeni učinek; MedDRA = Medical Dictionary for Regulatory Activities [Medicinski slovar za regulatorne dejavnosti]; GI = gastrointestinalni
† Vključuje analno krvavitev, krvavitev ob driski, krvavitev v želodcu, gastrointestinalno krvavitev, hematemezo, hematohezijo, krvavitev iz hemoroidov, Mallory-Weissov sindrom, melena, krvavitev požiralnika, krvavitev zadnjika in krvavitev iz zgornjih prebavil.
‡ Vključuje hipertenzivno kardiomiopatijo.

Reference: 1. Cyramza Povzetek glavnih značilnosti zdravila, odobren 25.01.2016

RAINBOW: NAJPOGOSTEJŠI NEŽELENI UČINKI[1]

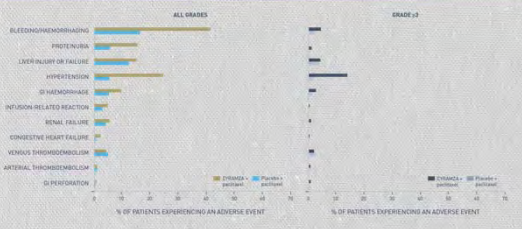


GI = gastrointestinalni

Reference: 1. Cyramza Povzetek glavnih značilnosti zdravila, odobren 25.01.2016

RAINBOW: izbrani neželeni učinki[1]

»IZBRANI NEŽELENI UČINKI« SO UČINKI, POTENCIALNO POVEZANI Z ANTIANGIOGENIM UČINKOM ALI TERAPEVTSKIMI PROTITELESI.*



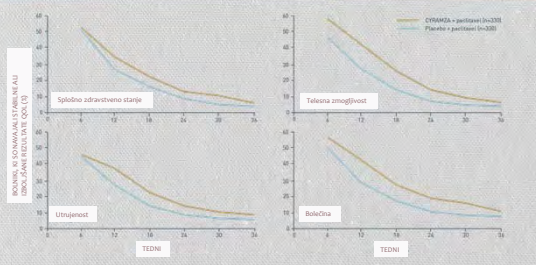
GI=gastrointestinal

- Z zdravljenjem povezani neželeni učinki, ne glede na vzročnost; vključeni so združeni izrazi za neželene učinke

Reference: 1. Wilke H et al. *Lancet Oncol.* 2014;15(11):1224-1235.

RAINBOW: IZBOLJŠANA QOL[1]

PODOBNI VZORCI SO BILI VIDNI TUDI NA VEČINI DRUGIH LESTVIC – EG, ŽIVLJENJSKI SLOG, AKTIVNOSTI IDR.



QOL = kakovost življenja

Reference: 1. Al-Batran S-E et al. *J Clin Oncol.* 2014;32:5s. Abstract 4058.

REGARD[1]

REGARD: MONOTERAPIJA (N = 355)

NEOPERABILEN, LOKALNO NAPREDOVALI ALI METASTATSKI RAK ŽELODCA/GE PREHODA

- **Napredovanje med ali po:**
  - **4 mesecih 1L kemoterapije**
  - **ALI**
  - **6 mesecih adjuvantne kemoterapije**
- **ECOG PS 0–1**

Randomizacija 2: 1 ‡

CYRAMZA§ (n = 238)	**Placebo**§ (n = 117)
8 mg/kg q2w (–60-min infuzija) + BSC	q2w + BSC

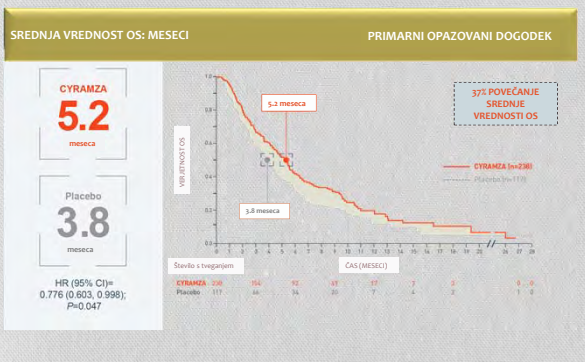
PRIMARNI OPAZOVANI DOGODEK: CELOKUPNO PREŽIVETJE

GE prehod= gastroezofagealni prehod; ECOG = Eastern Cooperative Oncology Group [Vzhodna skupina za sodelovanje v onkologiji]; PS = stopnja zmogljivosti; BSC = najboljše podporno zdravljenje; q2w = na 2 tedna

‡ Stratifikacijski dejavniki: Geografsko območje, lokacija primarnega tumorja in izguba telesne mase v zadnjih 3 mesecih (≥ 10 % proti < 10 %).
§ Ciklus je trajal 14 dni.

1. Fuchs CS et al. *Lancet.* 2014;383(9911):31-39.

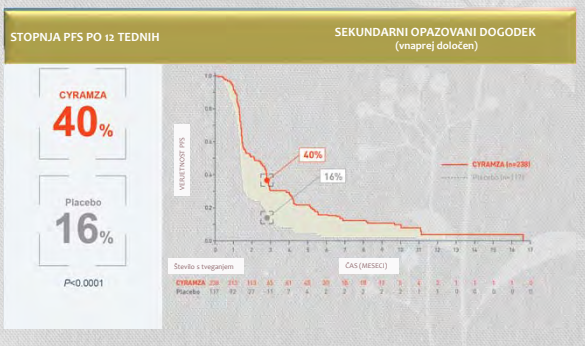
REGARD: CELOKUPNO PREŽIVETJE[1]



HR = razmerje tveganja; CI= interval zaupanja; OS = celokupno preživetje

Reference: 1. Fuchs CS et al. *Lancet*. 2014;383(9911):31-39.

REGARD: PFS[1]

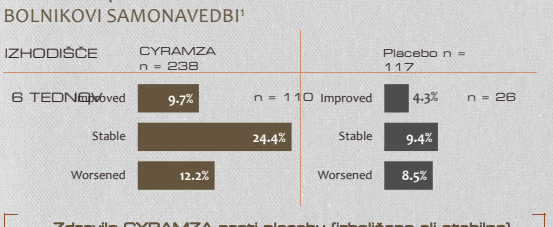


PFS = preživetje brez napredovanja

Referenca: 1. Fuchs CS et al. *Lancet*. 2014;383(9911):31-39.

REGARD: SEKUNDARNI OPAZOVANI DOGODEK QOL

GLOBALNI QOL 6 TEDNOV PO ZAČETKU ZDRAVLJENJA PO BOLNIKOVI SAMONAVEDBI[1]



Zdravilo CYRAMZA proti placebu (izboljšano ali stabilno) 34,0 % proti 13,7 % (*P* = 0,23 zaradi manjkajočih podatkov)

Manjkajoči podatki so večinoma posledica prekinitve zdravljenja pred načrtovanim ocenjevanjem QOL.

- Napredovanje bolezni je prispevalo k > 70 % prekinitev zdravljenja.[2]

QOL = kakovost življenja

References: 1. Fuchs CS et al. *Lancet*. 2014;383(9911):31-39. **2.** Chau I et al. Poster presented at: European Cancer Congress 2013; 27 September–1 October 2013; Amsterdam, Netherlands. Abstract 8018.

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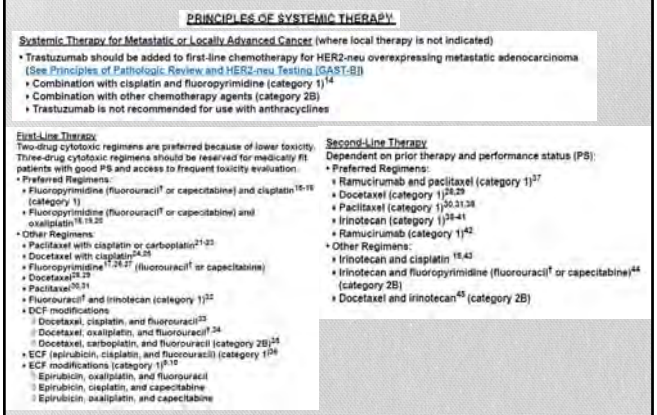

PRINCIPLES OF SYSTEMIC THERAPY

Systemic Therapy for Metastatic or Locally Advanced Cancer (where local therapy is not indicated)

- Trastuzumab should be added to first-line chemotherapy for HER2-neu overexpressing metastatic adenocarcinoma (See Principles of Pathologic Review and HER2-neu Testing [GAST-B])
  - Combination with cisplatin and fluoropyrimidine (category 1)[14]
  - Combination with other chemotherapy agents (category 2B)
  - Trastuzumab is not recommended for use with anthracyclines

First-Line Therapy

Two-drug cytotoxic regimens are preferred because of lower toxicity. Three-drug cytotoxic regimens should be reserved for medically fit patients with good PS and access to frequent toxicity evaluation.

- Preferred Regimens:
  - Fluoropyrimidine (fluorouracil† or capecitabine) and cisplatin[15-19] (category 1)
  - Fluoropyrimidine (fluorouracil† or capecitabine) and oxaliplatin[18,19,20]
- Other Regimens:
  - Paclitaxel with cisplatin or carboplatin[21-23]
  - Docetaxel with cisplatin[24,25]
  - Fluoropyrimidine[17,26,27] (fluorouracil† or capecitabine)
  - Docetaxel[28,29]
  - Paclitaxel[30,31]
  - Fluorouracil† and irinotecan (category 1)[32]
  - DCF modifications
    - Docetaxel, cisplatin, and fluorouracil[33]
    - Docetaxel, oxaliplatin, and fluorouracil†,34
    - Docetaxel, carboplatin, and fluorouracil (category 2B)[35]
  - ECF (epirubicin, cisplatin, and fluorouracil) (category 1)[36]
  - ECF modifications (category 1)[9,10]
    - Epirubicin, oxaliplatin, and fluorouracil
    - Epirubicin, cisplatin, and capecitabine
    - Epirubicin, oxaliplatin, and capecitabine

Second-Line Therapy

Dependent on prior therapy and performance status (PS):

- Preferred Regimens:
  - Ramucirumab and paclitaxel (category 1)[37]
  - Docetaxel (category 1)[28,29]
  - Paclitaxel (category 1)[30,31,38]
  - Irinotecan (category 1)[39-41]
  - Ramucirumab (category 1)[42]
- Other Regimens:
  - Irinotecan and cisplatin [18,43]
  - Irinotecan and fluoropyrimidine (fluorouracil† or capecitabine)[44] (category 2B)
  - Docetaxel and irinotecan[45] (category 2B)

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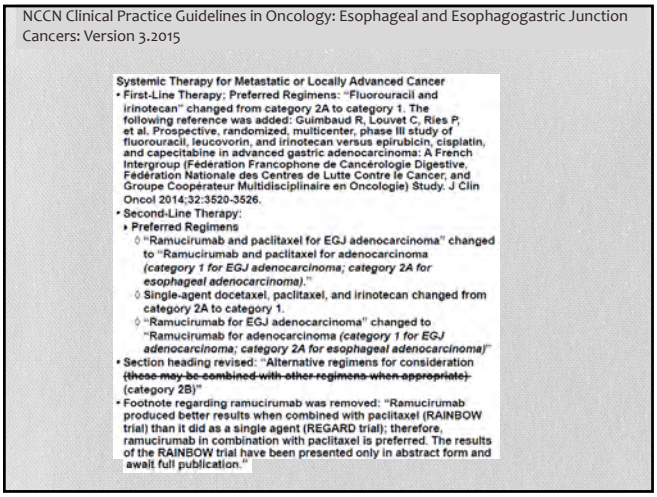

Systemic Therapy for Metastatic or Locally Advanced Cancer

- First-Line Therapy; Preferred Regimens: "Fluorouracil and irinotecan" changed from category 2A to category 1. The following reference was added: Guimbaud R, Louvet C, Ries P, et al. Prospective, randomized, multicenter, phase III study of fluorouracil, leucovorin, and irinotecan versus epirubicin, cisplatin, and capecitabine in advanced gastric adenocarcinoma: A French Intergroup (Fédération Francophone de Cancérologie Digestive, Fédération Nationale des Centres de Lutte Contre le Cancer, and Groupe Coopérateur Multidisciplinaire en Oncologie) Study. J Clin Oncol 2014;32:3520-3526.
- Second-Line Therapy:
  - Preferred Regimens
    - "Ramucirumab and paclitaxel for EGJ adenocarcinoma" changed to "Ramucirumab and paclitaxel for adenocarcinoma *(category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma)*."
    - Single-agent docetaxel, paclitaxel, and irinotecan changed from category 2A to category 1.
    - "Ramucirumab for EGJ adenocarcinoma" changed to "Ramucirumab for adenocarcinoma *(category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma)*"
- Section heading revised: "Alternative regimens for consideration ~~(these may be combined with other regimens when appropriate)~~ (category 2B)"
- Footnote regarding ramucirumab was removed: "Ramucirumab produced better results when combined with paclitaxel (RAINBOW trial) than it did as a single agent (REGARD trial); therefore, ramucirumab in combination with paclitaxel is preferred. The results of the RAINBOW trial have been presented only in abstract form and await full publication."

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PRINCIPLES OF SYSTEMIC THERAPY

Systemic Therapy for Metastatic or Locally Advanced Cancer [where local therapy is not indicated]

- Trastuzumab can be added to first-line chemotherapy for HER2-neu overexpressing adenocarcinoma [See Principles of Pathologic Review and HER2-neu Testing (ESOPH-B)]
  - Combination with cisplatin and fluoropyrimidine (category 1)[16]
  - Combination with other chemotherapy agents (category 2B)
  - Trastuzumab is not recommended for use with anthracyclines

First-Line Therapy

Two-drug cytotoxic regimens are preferred because of lower toxicity. Three-drug cytoxic regimens should be reserved for medically fit patients with good PS and access to frequent toxicity evaluation.

- Preferred Regimens:
  - DCF (docetaxel, cisplatin, and fluorouracil†) (category 1)[17]
  - DCF modifications
    - Docetaxel, cisplatin, and fluorouracil[18]
    - Docetaxel, oxaliplatin, and fluorouracil[19]
    - Docetaxel, carboplatin, and fluorouracil (category 2B)[20]
  - ECF (epirubicin, cisplatin, and fluorouracil) (category 1)[21]
  - ECF modifications (category 1)[22]
    - Epirubicin, oxaliplatin, and fluorouracil
    - Epirubicin, cisplatin, and capecitabine
    - Epirubicin, oxaliplatin, and capecitabine
  - Fluorouracil† and irinotecan (category 1)[23]
  - Fluoropyrimidine (fluorouracil† or capecitabine) and cisplatin[24-27] (category 1)
  - Fluoropyrimidine (fluorouracil† or capecitabine) and oxaliplatin[28,29,29]
- Other Regimens:
  - Paclitaxel with cisplatin or carboplatin[30-32]
  - Docetaxel with cisplatin[33,34]
  - Docetaxel and irinotecan[35] (category 2B)
  - Fluoropyrimidine[26,36,37] (fluorouracil† or capecitabine)
  - Docetaxel[38,39]
  - Paclitaxel[40,41]

Second-Line Therapy

Dependent on prior therapy and PS:

- Preferred Regimens:
  - Ramucirumab and paclitaxel for adenocarcinoma (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma)[42]
  - Docetaxel (category 1)[38,39]
  - Paclitaxel (category 1)[40,41,42]
  - Irinotecan (category 1)[43-46]
  - Ramucirumab for adenocarcinoma (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma)[47]
- Other Regimens:
  - Irinotecan and cisplatin[28,48]
  - Irinotecan and fluoropyrimidine (fluorouracil† or capecitabine)[27,49] (category 2B)
  - Docetaxel and irinotecan[35] (category 2B)

Alternative Regimens for Consideration (category 2B)

- Mitomycin and irinotecan[50-52]
- Mitomycin and fluorouracil†[53]

NCCN Clinical Practice Guidelines in Oncology: Esophageal and Esophagogastric Junction Cancers: Version 3.2015

PRINCIPLES OF SYSTEMIC THERAPY

Systemic Therapy for Metastatic or Locally Advanced Cancer [where local therapy is not indicated]

- Trastuzumab can be added to first-line chemotherapy for HER2-neu overexpressing adenocarcinoma [See Principles of Pathologic Review and HER2-neu Testing (ESOPH-B)]
  - Combination with cisplatin and fluoropyrimidine (category 1)[16]
  - Combination with other chemotherapy agents (category 2B)
  - Trastuzumab is not recommended for use with anthracyclines

First-Line Therapy

Two-drug cytotoxic regimens are preferred because of lower toxicity. Three-drug cytoxic regimens should be reserved for medically fit patients with good PS and access to frequent toxicity evaluation.

- Preferred Regimens:
  - DCF (docetaxel, cisplatin, and fluorouracil†) (category 1)[17]
  - DCF modifications
    - Docetaxel, cisplatin, and fluorouracil[18]
    - Docetaxel, oxaliplatin, and fluorouracil[19]
    - Docetaxel, carboplatin, and fluorouracil (category 2B)[20]
  - ECF (epirubicin, cisplatin, and fluorouracil) (category 1)[21]
  - ECF modifications (category 1)[22]
    - Epirubicin, oxaliplatin, and fluorouracil
    - Epirubicin, cisplatin, and capecitabine
    - Epirubicin, oxaliplatin, and capecitabine
  - Fluorouracil† and irinotecan (category 1)[23]
  - Fluoropyrimidine (fluorouracil† or capecitabine) and cisplatin[24-27] (category 1)
  - Fluoropyrimidine (fluorouracil† or capecitabine) and oxaliplatin[28,29,29]
- Other Regimens:
  - Paclitaxel with cisplatin or carboplatin[30-32]
  - Docetaxel with cisplatin[33,34]
  - Docetaxel and irinotecan[35] (category 2B)
  - Fluoropyrimidine[26,36,37] (fluorouracil† or capecitabine)
  - Docetaxel[38,39]
  - Paclitaxel[40,41]

Second-Line Therapy

Dependent on prior therapy and PS:

- Preferred Regimens:
  - Ramucirumab and paclitaxel for adenocarcinoma (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma)[42]
  - Docetaxel (category 1)[38,39]
  - Paclitaxel (category 1)[40,41,42]
  - Irinotecan (category 1)[43-46]
  - Ramucirumab for adenocarcinoma (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma)[47]
- Other Regimens:
  - Irinotecan and cisplatin[28,48]
  - Irinotecan and fluoropyrimidine (fluorouracil† or capecitabine)[27,49] (category 2B)
  - Docetaxel and irinotecan[35] (category 2B)

Alternative Regimens for Consideration (category 2B)

- Mitomycin and irinotecan[50-52]
- Mitomycin and fluorouracil†[53]

ESMO priporočila 2016

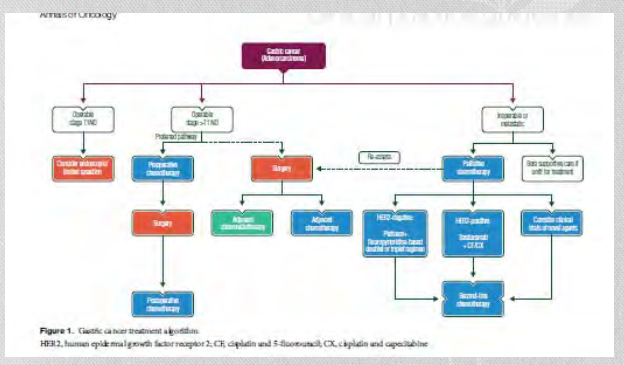


Figure 1. Gastric cancer treatment algorithm.
HER2, human epidermal growth factor receptor 2; CF, cisplatin and 5-fluorouracil; CX, cisplatin and capecitabine.

Zaključki

- kemoterapija na osnovi 5FU in platine
- kapecitabin in oksaliplatin sta uporabni alternativi 5FU in cisplatina
- docetaksel +5FU – večja učinkovitost v primerjavi 5FU/cisplatin
- vloga antraciklinov pri adenokarcinomu
- Trastuzumab je prvo tarčno zdravilo, ki ima dobrobit na preživetje bolnikov z napredovalim adenokarcinomom HER2+ .

Zdravljenje metastatske bolezni - 2 linija

- Kemoterapija s paklitakselom samim ali v kombinaciji ali kemoterapija z irinotekanom lahko podaljšata preživetje.
- Ramucirumab podaljša preživetje in preživetje do napredovanja bolezni bolnikom z napredovalim adeno-karcinomom želodca in gastroezofagealnega prehoda v 2. liniji v monoterapiji ali v kombinicaiji s paklitakselom.

Hvala za pozornost

Zdravljenje metastatskega adenokarcinoma kardije z ramucirumabom in paklitakselom – primer bolnika

Dr. Neva Volk, dr.med.
Sektor za internistično onkologijo
Onkološki inštitut

Razkritje

- Predavanje sponzorira podjetje Eli Lilly Farmacevtska družba, d.o.o.
- Predstavitev odraža mnenja in izkušnje predavatelja, ki niso nujno stališča podjetja Eli Lilly in njihovih zaposlenih.

J.A., ♂ (67 let)

- 21.9.2015 prvi pregled na OI, v radioterapevtski ambulanti
- FA: mati imela kožni limfom, brat raka na želodcu – je zdrav
- Anamneza: že eno leto hujša (10 kg), 2 meseca bolečine v trebuhu
- PS po WHO 0, klinični status bp

Diagnostika

- UZ trebuha, Rtg pc – bp
- Gastroskopija 3.9.2015: 1 cm nad zobato linijo eksulceriran tumor, distalno nekaj cm prerašča kardijo
- Hi: dobro dif. tubulni adenokarcinom kardije
- Endo UZ: preraščanje tumorja kardije skozi vse sloje stene želodca do m. proprije (T2) na 45cm, širi se do globine 38 cm, na tej globini v zadnjem mediastinumu 11 mm patološka bezgavka

Dodatna diagnostika

- CT prsnega koša in trebuha 22.9.2015: 4 mm suspektna velika zgostitev v pljučih D, v jetrih v 2 seg. 17 mm, v 7 seg. 15 mm- metastazi, tik pod kardijo s tumorjem 4 suspektne bezgavke do 9mm
- Tumorski markerji 28.9.2015:

  CEA 35.8, CA 19-9 687, CA 72-4 58

Konzilij

- MDT 30.9.2015: sistemsko specifično zdravljenje

I. red zdravljenja

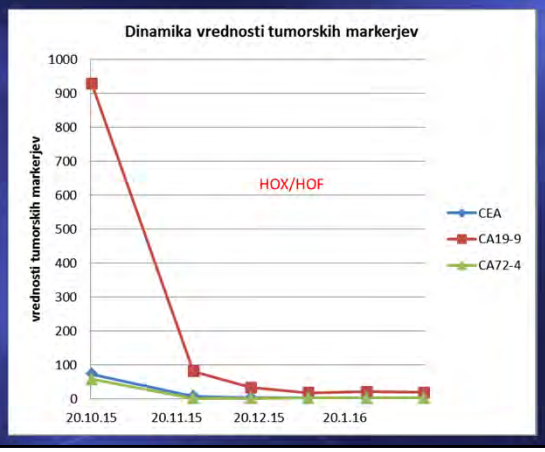
- FISH:– gen za Her-2 pomnožen
- 20.10.2015 – HOX; po 10 dneh kapecitabina enterokolitis III. stopnje
- 2.-6. ciklus KT po shemi HOF – zaradi driske I. st. 5-FU v 75% odmerku do 18.2.2016, po 6. ciklu periferna polinevropatija I. st.

Evaluacija

- CT prsnega koša in trebuha 5.1.2016:

ni več jasnega tumorja v želodcu, ni več povečanih regionalnih bezgavk; v jetrih 2 leziji v 5 seg. 10 mm, v 3 seg. 20 mm. V D zg. pljučih še vedno ovalna sprememba, nesumljiva za metastazo

- Normalizacija tumorskih markerjev po 3. ciklu KT



....vzdrževalno zdravljenje?

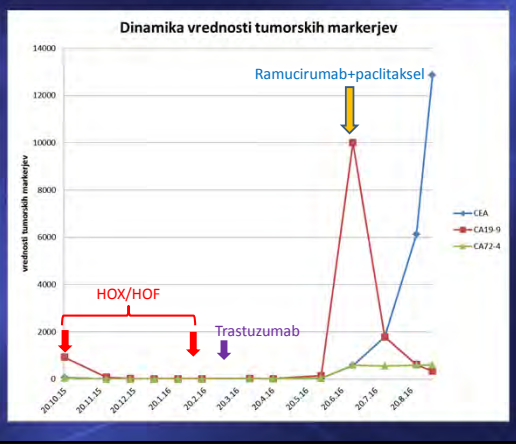
- Trastuzumab vzdrževalno 10.3.2016 -2.6.2016
- Že 31.3.2016 povišan tumorski marker CEA, v naslednjih tednih naraščanje še drugih markerjev (CA 19-9 in CA 72-4)
- CT prsnega koša in trebuha 15.4.2016: nadaljnji regres dveh zasevkov v jetrih (4 in 6 mm), v pljučih drobna interlobarna bezgavka
- CT prsnega koša in trebuha 29.6.2016: v jetrih številne novo nastale metastaze do 25 mm, ponovno viden tumor kardije 40x45 mm, zelo zožen lumen požiralnika

II. red sistemskega zdravljenja

- **30.6.2016** uvedena Cyramza (**ramucirumab)** v kombinaciji s **paklitakselom** (100 %)
- Ob uvedbi disfagija, pasaste bolečine v zg. delu trebuha, PS po WHO 0
- Laboratorijski izvidi ob uvedbi:
  - transaminaze: AST 1,44 ALT 1,63
  - encimi holestaze: AF 3,28, GGT 4,26
  - LDH: 14,49
  - markerji: CEA 579,8, CA 19-9 >10000, CA 72-4 >600

II. red - nadaljevanje

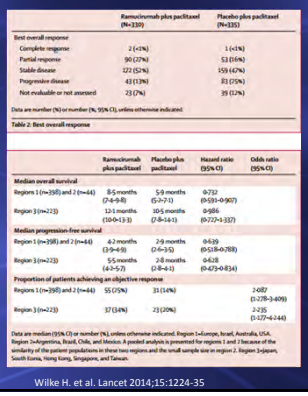
- Po 1A ciklu disfagija prehodno izzveni, hrani se normalno, izboljšanje hepatograma, prehoden padec LDH
- Prejel 3 popolne cikle do **8.9.2016 –** disfagija manjša, poslabšanje polinevropatije po prstih rok in podplatih (2. st.), brez drugih neželenih učinkov
- CT prsnega koša in trebuha 12.9.2016: povečane bezgavke med jetri in trunkus celiakus so večje in številčnejše, merijo do 19x28 mm, patološke bezgavke segajo do odcepišča renalnega žilja, največja meri prečno 17 mm, številne lezije v jetrih so večje, največja do 45 mm (prej 20 mm) metastaz, povečanje primarnega tumorja kardije, stena zadebeljena na 35 mm (prejšnjič 23 mm) dolžina 7 mm (prej 65 mm). Mnenje: progres.



Paliativna oskrba

21.9.2016 – doma melena; v oskrbi mobilnega paliativnega tima, † 3.10.2016

Rainbow



	Ramucirumab plus paclitaxel (N=330)	Placebo plus paclitaxel (N=335)
Best overall response		
Complete response	2 (<1%)	1 (<1%)
Partial response	90 (27%)	52 (16%)
Stable disease	172 (52%)	159 (47%)
Progressive disease	43 (13%)	83 (25%)
Not evaluable or not assessed	23 (7%)	39 (12%)

Data are number (%) or number (%, 95% CI), unless otherwise indicated.

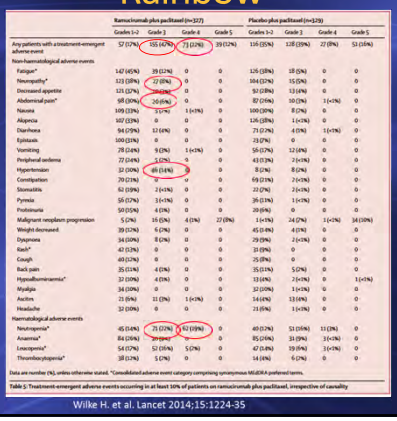
Table 2: Best overall response

	Ramucirumab plus paclitaxel	Placebo plus paclitaxel	Hazard ratio (95% CI)	Odds ratio (95% CI)
Median overall survival				
Regions 1 (n=358) and 2 (n=44)	8·5 months (7·4–9·8)	5·9 months (5·3–7·1)	0·732 (0·591–0·907)	
Region 3 (n=223)	12·1 months (10·0–13·3)	10·5 months (7·8–14·1)	0·984 (0·727–1·337)	
Median progression-free survival				
Region 1 (n=358) and 2 (n=44)	6·2 months (3·9–6·9)	2·9 months (2·6–3·5)	0·439 (0·318–0·768)	
Region 3 (n=223)	5·5 months (4·2–5·7)	2·8 months (2·8–4·1)	0·628 (0·479–0·834)	
Proportion of patients achieving an objective response				
Regions 1 (n=358) and 2 (n=44)	55 (35%)	31 (14%)		2·687 (1·278–5·609)
Region 3 (n=223)	37 (34%)	23 (20%)		2·231 (1·127–4·244)

Data are median (95% CI) or number (%), unless otherwise indicated. Region 1=Europe, Israel, Australia, USA. Region 2=Argentina, Brazil, Chile, and Mexico. A pooled analysis is presented for regions 1 and 2 because of the similarity of the patient populations in these two regions and the small sample size in region 2. Region 3=Japan, South Korea, Hong Kong, Singapore, and Taiwan.

Wilke H. et al. Lancet 2014;15:1224-35

Rainbow



	Ramucirumab plus paclitaxel (n=327)				Placebo plus paclitaxel (n=329)			
	Grades 1–2	Grade 3	Grade 4	Grade 5	Grades 1–2	Grade 3	Grade 4	Grade 5
Any patients with a treatment-emergent adverse event	57 (17%)	155 (47%)	73 (22%)	39 (12%)	116 (35%)	128 (39%)	27 (8%)	51 (16%)
Non-haematological adverse events								
Fatigue*	147 (45%)	39 (12%)	0	0	126 (38%)	18 (5%)	0	0
Neuropathy*	123 (38%)	22 (6%)	0	0	104 (32%)	15 (5%)	0	0
Decreased appetite	121 (37%)	20 (6%)	0	0	92 (28%)	13 (4%)	0	0
Abdominal pain*	98 (30%)	20 (6%)	0	0	87 (26%)	10 (3%)	1 (<1%)	0
Nausea	169 (33%)	3 (<1%)	1 (<1%)	0	100 (30%)	8 (2%)	0	0
Alopecia	107 (33%)	0	0	0	126 (38%)	1 (<1%)	0	0
Diarrhoea	94 (29%)	12 (4%)	0	0	71 (22%)	4 (1%)	1 (<1%)	0
Epistaxis	100 (31%)	0	0	0	23 (7%)	0	0	0
Vomiting	78 (24%)	9 (3%)	1 (<1%)	0	55 (17%)	12 (4%)	0	0
Peripheral oedema	72 (22%)	5 (2%)	0	0	43 (13%)	2 (<1%)	0	0
Hypertension	32 (10%)	48 (14%)	0	0	8 (2%)	8 (2%)	0	0
Constipation	70 (21%)	2	0	0	69 (21%)	2 (<1%)	0	0
Stomatitis	62 (19%)	2 (<1%)	0	0	22 (7%)	2 (<1%)	0	0
Pyrexia	56 (17%)	3 (<1%)	0	0	36 (11%)	1 (<1%)	0	0
Proteinuria	50 (15%)	4 (1%)	0	0	20 (6%)	0	0	0
Malignant neoplasm progression	5 (2%)	16 (5%)	4 (1%)	27 (8%)	1 (<1%)	24 (7%)	1 (<1%)	34 (10%)
Weight decreased	39 (12%)	6 (2%)	0	0	45 (14%)	4 (1%)	0	0
Dysp noea	34 (10%)	8 (2%)	0	0	29 (9%)	2 (<1%)	0	0
Rash*	47 (12%)	0	0	0	31 (9%)	0	0	0
Cough	40 (12%)	0	0	0	25 (8%)	0	0	0
Back pain	35 (11%)	4 (1%)	0	0	35 (11%)	5 (2%)	0	0
Hypoalbuminaemia*	32 (10%)	4 (1%)	0	0	13 (4%)	2 (<1%)	0	1 (<1%)
Myalgia	34 (10%)	0	0	0	32 (10%)	1 (<1%)	0	0
Ascites	21 (6%)	11 (3%)	1 (<1%)	0	14 (4%)	13 (4%)	0	0
Headache	32 (10%)	0	0	0	21 (6%)	1 (<1%)	0	0
Haematological adverse events								
Neutropenia*	45 (14%)	75 (23%)	62 (19%)	0	40 (12%)	51 (16%)	11 (3%)	0
Anaemia*	84 (26%)	39 (12%)	0	0	85 (26%)	31 (9%)	3 (<1%)	0
Leucopenia*	54 (17%)	51 (16%)	5 (2%)	0	47 (14%)	19 (6%)	3 (<1%)	0
Thrombocytopenia*	38 (12%)	5 (2%)	0	0	14 (4%)	6 (2%)	0	0

Data are number (%), unless otherwise stated. *Consolidated adverse event category comprising synonymous MEDDRA preferred terms.

Table 3: Treatment-emergent adverse events occurring in at least 10% of patients on ramucirumab plus paclitaxel, irrespective of causality

Wilke H. et al. Lancet 2014;15:1224-35

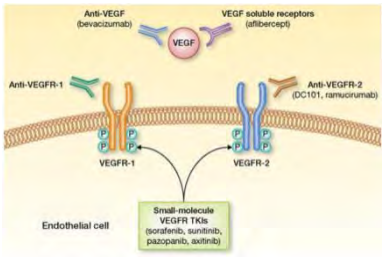
HVALA ZA POZORNOST!

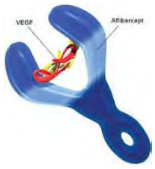
Novosti v sistemskem zdravljenju CRC

Dr.Tanja Mesti, dr.med

AFLIBERCEPT – VEGF zaviralec

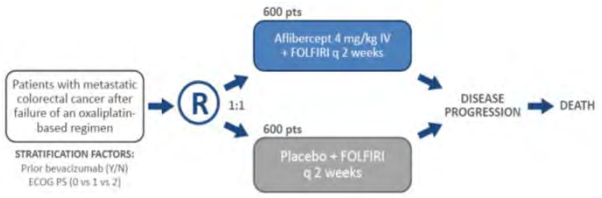
Bevacizumab (humanizirano protitelo)





Aflibercept (himerno protitelo)

VELOUR: Aflibercept pri predhodno zdravljenih bolnikih z mRDČD

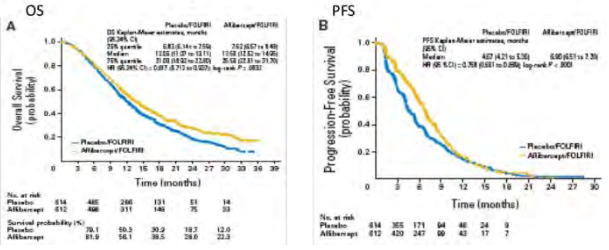


FIRST PATIENT IN: November 2007
ENROLLMENT COMPLETED:
1226 randomized, 1216 treated
Final analysis at 863 OS events

PRIMARY ENDPOINT: OS
SECONDARY ENDPOINTS:
ORR, PFS, safety, PK

Van Cutsem E et al. JCO 2012

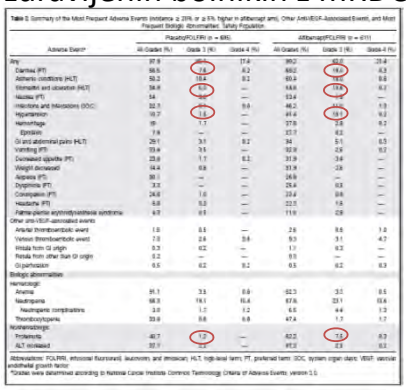
VELOUR: Aflibercept pri predhodno zdravljenih bolnikih z mRDČD



Trial	Treatment	Control	RR%	Median OS, mo (HR)	Median PFS, mo (HR)
Velour	Aflibercept + FOLFIRI (n=612)	FOLFIRI (n=614)	19.8 vs 11.1 p<0.001 (n=531/530)	13.5 vs 12.1 (0.82; p=0.0032)	6.9 vs 4.7 (0.76; p<0.0001)

Van Cutsem E et al. JCO 2012

VELOUR: Aflibercept pri predhodno zdravljenih bolnikih z mRDČD

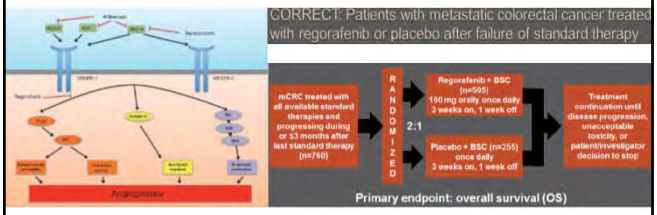


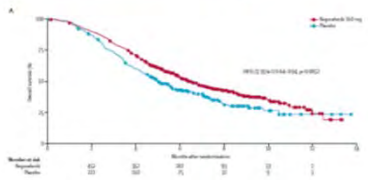
Van Cutsem E et al. JCO 2012

Aflibercept

- Zdravljenje RAS WT in MT bolnikov
- 2L zdravljenja
- Neželeni učinki:
- krvavitve
- perforacije prebavil/nastanek fistule
- arterijska hipertenzija
- tromboembolični dogodki
- proteinurija
- neutropenija
- driska

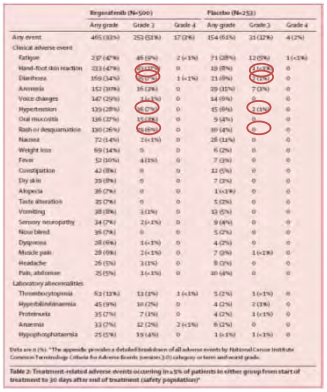
REGORAFENIB – Multikinazni zaviralec





Grothey A et al. Lancet 2013; 381:303–312

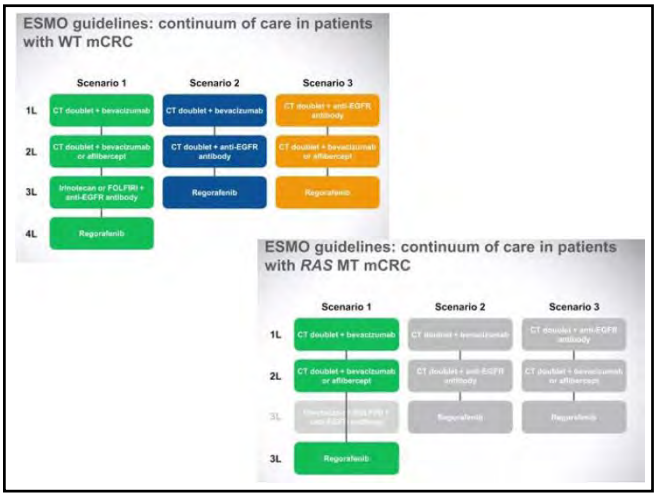
Regorafenib



Grothey A et al. Lancet 2013; 381:303–312

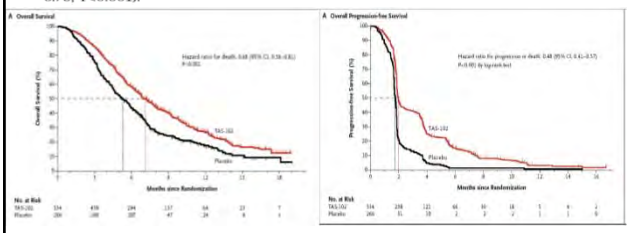
Regorafenib

- Zdravljenje RAS WT in RAS MT bolnikov
- 3L ali 4L zdravljenja
- Neželeni učinki:
- krvavitve
- miokardna ishemija in infarkt
- sindrom posteriorne reverzibilne encefalopatije
- gastrointestinalna perforacija in fistula
- arterijska hipertenzija
- zapleti pri celjenju ran
- neželeni učinki na kožo (hand and foot sindrom)



TAS-102 (trifluridine + tipiracil hydrochloride)

The median overall survival improved from 5.3 months with placebo to 7.1 months with TAS-102, and the hazard ratio for death in the TAS-102 group versus the placebo group was 0.68 (95% confidence interval [CI], 0.58 to 0.81; P<0.001). The most frequently observed clinically significant adverse events associated with TAS-102 were neutropenia, which occurred in 38% of those treated, and leukopenia, which occurred in 21%; 4% of the patients who received TAS-102 had febrile neutropenia, and one death related to TAS-102 was reported. The median time to worsening performance status (a change in Eastern Cooperative Oncology Group performance status [on a scale of 0 to 5, with 0 indicating no symptoms and higher numbers indicating increasing degrees of disability] from 0 or 1 to 2 or more) was 5.7 months with TAS-102 versus 4.0 months with placebo (hazard ratio, 0.66; 95% CI, 0.56 to 0.78; P<0.001).



N Engl J Med 2015;372:1909-19.
RJ Mayer, E Van Cutsem and al.

TAS-102

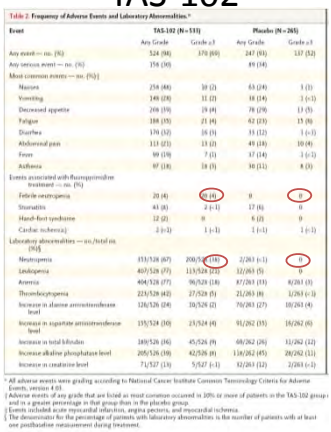


Table 2. Frequency of Adverse Events and Laboratory Abnormalities.*

Event	TAS-102 (N=533)		Placebo (N=265)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any event — no. (%)	524 (98)	370 (69)	247 (93)	137 (52)
Any serious event — no. (%)	156 (30)		69 (26)	
Most common events — no. (%)†				
Nausea	258 (48)	10 (2)	63 (24)	3 (1)
Vomiting	148 (28)	11 (2)	38 (14)	3 (<1)
Decreased appetite	108 (19)	19 (4)	78 (29)	13 (5)
Fatigue	188 (35)	21 (4)	62 (23)	15 (6)
Diarrhea	170 (32)	16 (3)	33 (12)	3 (<1)
Abdominal pain	113 (21)	13 (2)	49 (18)	10 (4)
Fever	99 (19)	7 (1)	37 (14)	3 (<1)
Asthenia	97 (18)	18 (3)	30 (11)	8 (3)
Events associated with fluoropyrimidine treatment — no. (%)				
Febrile neutropenia	20 (4)	20 (4)	0	0
Stomatitis	41 (8)	2 (<1)	17 (6)	0
Hand–foot syndrome	12 (2)	0	6 (2)	0
Cardiac ischemia‡	3 (<1)	1 (<1)	1 (<1)	1 (<1)
Laboratory abnormalities — no./total no. (%)§				
Neutropenia	353/526 (67)	200/526 (38)	2/263 (<1)	0
Leukopenia	407/526 (77)	113/526 (21)	12/263 (5)	0
Anemia	404/526 (77)	96/526 (18)	87/263 (33)	8/263 (3)
Thrombocytopenia	223/526 (42)	27/526 (5)	21/263 (8)	1/263 (<1)
Increase in alanine aminotransferase level	126/526 (24)	10/526 (2)	70/263 (27)	10/263 (4)
Increase in aspartate aminotransferase level	155/524 (30)	23/524 (4)	91/262 (35)	16/262 (6)
Increase in total bilirubin	169/526 (16)	45/526 (9)	69/262 (26)	11/262 (12)
Increase alkaline phosphatase level	265/526 (50)	42/526 (8)	118/262 (45)	28/262 (11)
Increase in creatinine level	71/527 (13)	5/527 (<1)	32/263 (12)	2/263 (<1)

* All adverse events were grading according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.
† Adverse events of any grade that are listed as most common occurred in 30% or more of patients in the TAS-102 group and in a greater percentage in that group than in the placebo group.
‡ Events included acute myocardial infarction, angina pectoris, and myocardial ischemia.
§ The denominator for the percentage of patients with laboratory abnormalities is the number of patients with at least one postbaseline measurement during treatment.

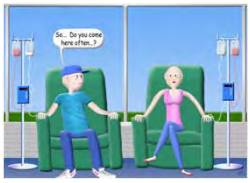
N Engl J Med 2015;372:1909-19.
RJ Mayer, E Van Cutsem and al.

Povzetek

- Aflibercept – 2L
- Regorafenib – monoterapija, po izžčpani sist.ter.
- Neželjeni učinki obeh: žilni zapleti (tromboze, embolije), perforacija notranjih votlih organov, arterijska hipertenzija, proteinurija
- TAS-102 – ko fluoropiridini odpovejo
- Neželjeni učinek: neutropenija

Novosti v zdravljenju raka danke

Vaneja Velenik

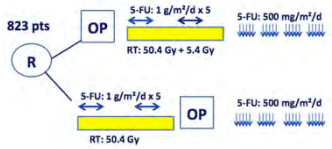


Multimodalno zdravljenje

Kaj je standard?

Predop CRT je učinkovitejša kot poop CRT

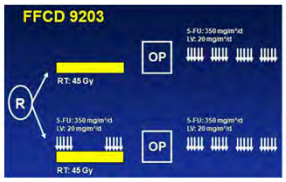
CAO/ARO/AIO-04

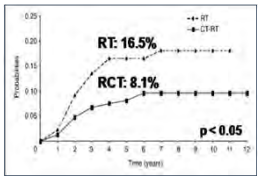


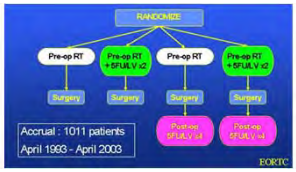
5 let (11 let)	Poop CRT	Preop CRT	p
Lok.ponovitev	13%	6%	0.006
Ohranitev sf	19%	39%	0.004
Akut.toks. G 3-4	40%	27%	0.001
Pozna toks. G 3-4	24%	14%	0.01
Odd.zasevki	38%	36%	0.84
OS	76%	74%	0.80

Sauer et al. N Eng J Med 2008

Predop CRT je učinkovitejša kot predop RT



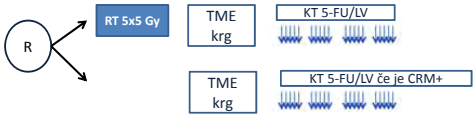




Gerard JP et al. J Clin Oncol 2006
Bosset JF et al. N Eng J Med 2006

Kratek režim RT

- **3 ključne raziskave**



	CONTROL		PREOPERATIVE RADIATION			
	No.	Local Relapse Rate at 5 y	No.	Local Relapse Rate at 5 y	Hazard Ratio	CI at 95%
SWEDISH (1997)	585	26%	583	9% p<0.001	NR	NR
DUTCH (2001)	924	11.4%	937	5.8% p<0.001	3.42	2.05-5.71
MRC CR07 (2006)	676	17%	674	5% P<0.0001	2.47	1.61-3.79
TOTAL	2185	17.3%	2194	6.9%		

Kapiteijn E et al. N Eng J Med 2001
Sebaq-Montefiori D et al. Lancet 2009

RT ne izboljša LK ob “slabi krg“

- **MRC CR 07 raziskava**

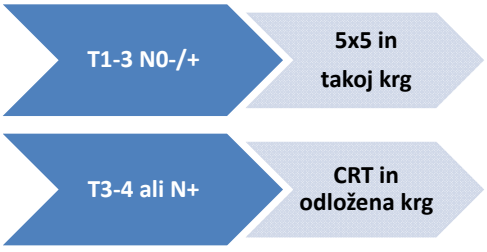
TME kakovost	Stopnja lokalnih ponovitev (3 leta)			
	N	RT+TME	TME	HR
„Poor“ Defekti v muskularis proprii	154 (13%)	10%	16%	2.0
„Moderat“ Intra-mezorektalna ekscizija	398 (34%)	4%	10%	2.8
„Optimal“ Mezorektalna ekscizija	604 (52%)	1%	7%	4.5

Sebaq-Montefiori D et al. Lancet 2009

Kaj vemo?

- Zaporedje RT, KT, krg je pomembno
  (CAO/ARO/AIO-94)
- Sinergističen učinek RT- KT s 5-FU
  (FFCD 9303, EORTC 22921)
- RT lahko dopolni le optimizirano operacijo
  (Dutch TME, MRC CR 07)

5x5 ali CRT?



5x5 ali CRT?

T1-3 N0-/+ → **5x5 + krg vs krg**

Švedi	Dutch TME	MRC CR 07
N= 1168	N=1861	N=1350
LR po 13 L **9% vs 26%** p<0.001	LR po 10 L **5% vs 11%** p<0.001	LR po 5 L **5% vs 12%** p<0.001
OS po 13 L **38% vs 30%** p<0.008	OS po 10 L **48% vs 49%** n.s.	OS po 5 L **70% vs 68%** n.s.
Fokesson et al. JCO 2005	Van Gijn et al. Lancet Oncol2011	Sebag-Montefiore et al. Lancet 2009

5x5 ali CRT?

T3-4 ali N+ → **CRT s 5-FU+ krg vs...**

CAO/ARO/AIO	FFCD 9203	EORTC 22921
N= 823	N=762	N=1011
LR po 10 L preCRT vs post CRT **7% vs 10%** P=0.04	LR po 10 L preCRT vs preRT **8% vs 16%** p<0.05	LR po 10 L preCRT vs preRT **12% vs 22%** p<0.001
OS po 10 L **60% vs 60%** n.s.	OS po 10 L **68% vs 67%** n.s.	OS po 5 L **51% vs 49%** n.s.
Sauer et al. JCO 2012	Gerard et al. JCO 2006	Bosset et al. Lancet Oncol 2014

5x5 ali CRT?

5x5 Gy → ← CRT s 5-FU

Poljska	Trans-Tasman
N=312	N=326
Vstopni kriteriji (DRE) Nizki T3-4 Nvsi	Vstopni kriteriji (EUZ;MRI) T3 Nvsi
Primarni cilj Ohranitev sfinkra (15% razlika)	Primarni cilj Lokalna ponovitev (10% razlika po 3 L)

Bujko K et al. Radiother Oncol 2004
Bujko K et al. Br J Surg 2006
Pietrzak L et al. Radiother Oncol 2007

5x5 ali CRT?

Poljska študija	5x5 Gy	CRT	p
Akut. toksičnost (G3-4, %)	3	18	<0.001
pCR (%)	1	16	<0.001
CRM+ (%)	13	4	0.02
Ohranitev sfinktra (%)	**61**	**58**	**n.s.**
LR (4L, %)	11	16	n.s.
OS (4L, %)	67	66	n.s.
Pozna toksičnost (G3-4, %)	10	7	n.s.

Bujko K et al. Radither Oncol 2004
Bujko K et al. Br J Surg 2006
Pietrzak L et al. Radiother Oncol 2007

5x5 ali CRT?

Trans-Tasman študija	5x5 Gy	CRT	p
Akut. toksičnost (G3-4, %)	2	28	<0.001
pCR (%)	1	15	<0.001
Ohranitev sfinktra (%)	63	69	0.22
LR (3L, %)	**7.5**	**4.4**	**0.24**
OS (5L, %)	74	70	0.62
Pozna toksičnost (G3-4, %)	5.8	8.2	0.53

*< 5cm od AKČ 12.5% vs 0%

Ngan SY al. JCO 2012

5x5 ali CRT?

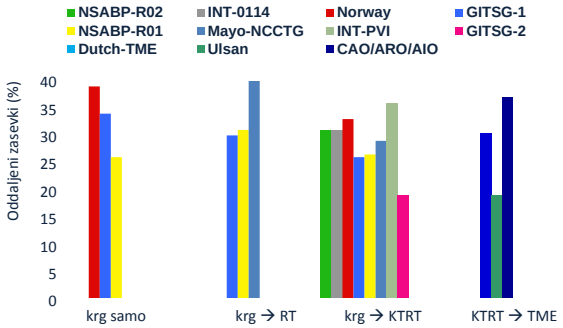
- Nižja akutna toksičnost
- Bolniku prijazna th
- Nižja cena

- Večje zmanjšanje tumorja
- Manjša kirurška morbiditeta
- Lahko varno kombiniramo s KT

Kaj vemo?

- Standardna CRT zagotavlja:
  - boljšo LK
  - Večji delež pts z ohranjenim sfinktrom
- Kratek režim je bolj toksičen
- Večji delež LR pri kratkem režimu (7.5% vs 4.4% CRT), posebno pri nizko ležečih (12.5% vs 0% CRT)

Delež oddaljenih zasevkov



Adjuvantna KT izboljša preživetje


International Journal of Colorectal Disease
April 2015, Volume 30, Issue 4, pp 447-457

A systematic review and meta-analysis of adjuvant chemotherapy after neoadjuvant treatment and surgery for rectal cancer

Authors — Authors and affiliations

Fausto Petrelli, Andrea Coinu, Veronica Lonati, Sandro Barni

5457 pts

- Adj KT izboljša 5y OS (RO 0.64) in 5y DFS (RO 0.71), zmanjša delež DM (RO 0.88) in LR (RO 0.72)
- 5y OS je boljše pri bolniki z downstagingom in v retrospektivnih serijah
- 5y DFS je boljše v vseh raziskavah zaradi boljše LK

Adj. KT z oksaliplatinom je učinkovitejša

Systematic review

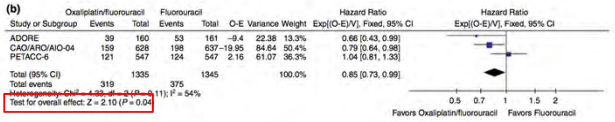
doi:10.1111/codi.13381

Oxaliplatin/fluorouracil-based adjuvant chemotherapy for locally advanced rectal cancer after neoadjuvant chemoradiotherapy and surgery: a systematic review and meta-analysis of randomized controlled trials

L. Zhao*, R. Liu*†, Z. Zhang*†, T. Li*, F. Li*, H. Liu* and G. Li*

*Department of General Surgery, Nanfang Hospital, Southern Medical University, Guangzhou, China and †Tianjin Medical University Cancer Institute and Hospital, Tianjin, China

Received 19 September 2015; accepted 25 February 2016; Accepted Article online 12 May 2016



Zhao L et al. Colorectal Dis 2016

Bolniki s pCR imajo boljšo prognozo

Meta-analysis

Br J Surg 2012

Systematic review and meta-analysis of outcomes following pathological complete response to neoadjuvant chemoradiotherapy for rectal cancer

S. T. Martin, H. M. Heneghan and D. C. Winter

Institute for Clinical Outcomes, Research and Education (ICORE) and Department of Colorectal Surgery, St Vincent's University Hospital, Dublin, Ireland
Correspondence to: Mr S. T. Martin, Department of Colorectal Surgery, St Vincent's University Hospital, Elm Park, Dublin 4, Ireland
(email: drstmartin@gmail.com)

4x manjša verjetnost za lokalno ponovitev
4x manjša verjetnost pojava oddaljenih zasevkov
3.3x večja verjetnost boljšega celokupnega preživetja
4.3 x večja verjetnost biti brez bolezni čez 5 let

Bolniki s pCR imajo boljšo prognozo

Meta-analysis

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Systematic review and meta-analysis of outc
pathological complete response to ne
chemoradiotherapy for rectal c

S. T. Martin, H. M. Heneghan a

Institute for Clinical Outcomes, R
Dublin, Ireland
Correspondence to: M
(email:

Bolniki s pCR ne dobijo adjuvantne KT

verjetnost za lokalno ponovitev
anjša verjetnost pojava oddaljenih zasevkov
3.3x večja verjetnost boljšega celokupnega preživetja
4.3 x večja verjetnost biti brez bolezni čez 5 let

Večina ne zaključi zdravljenja

- četrtina bolnikov kljub priporočilom ne prejme adj KT
- Manj kot polovica jo dokonča po protokolu

Association Between Time to Initiation of Adjuvant Chemotherapy and Survival in Colorectal Cancer
A Systematic Review and Meta-analysis

James J. Biagi, MD; Michael J. Raphael; William J. Mackillop, MB, ChB; Weidong Kong, MD, MSC; Will D. King, PhD; Christopher M. Booth, MD

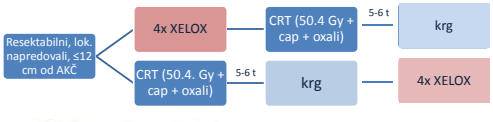
JAMA. 2011;305(22):2335-2342. doi:10.1001/jama.2011.749.

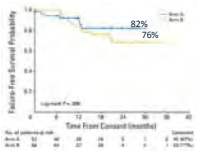
Zamuda s pričetkom adj KT za 4 tedne zmanjša OS in DFS za 14%

Kaj vemo?

- Bolniki s pCR imajo boljšo prognozo
- Bolniki ne dokončajo zdravljenja po operaciji

Celotno zdravljenje je neoadjuvantno

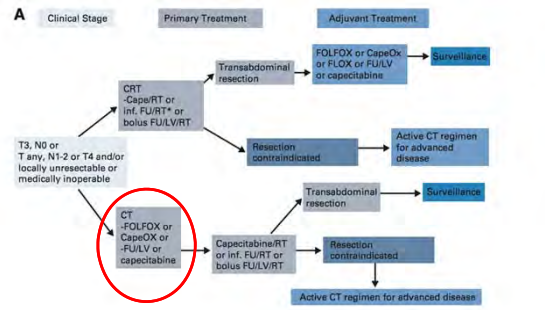




	Indukcijska KT	Adjuvantna KT
G3-4 toks. med KT	19%	54%
Pričeli z ind/adj KT	100%	92%
Prejeli ind/adj KT	75%	51%

Fernandez-Martos C et al. JCO 2010

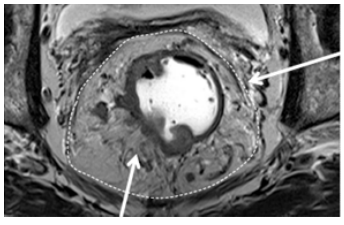
NCCN v 1.2015 shema zdravljenja



http://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf

Kaj je tudi pomembno danes?

Skupine tveganja na osnovi MRI



Oddaljenost tumorja/lgl od MRF (v mm)

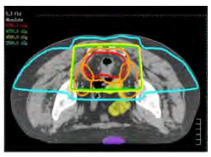
Prodor tumorja v mezorektalno maščevje v mm

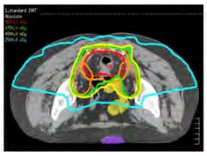
Evropska/Skandinavska shema zdravljenja

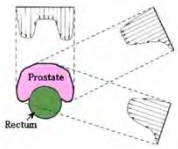
LOW RISK	INTERMEDIATE RISK	HIGH RISK
T1-2 N0 T3 < 5mm (sr. in zg tretjina) MRF+, EMVI-	T3> 5mm N1-2 MRF – (>1 mm) EMVI+	T4 MRF+
↓	↓	↓
TME	Predoperativna 5x5 Gy ali CRT TME Adjuvantna KT	Predoperativna 5x5 Gy ali CRT TME Adjuvantna KT

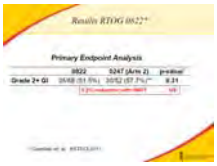
Glimelius B et al. Ann Oncol 2013 (ESMO guidelines)

Intenzitetno Modulirano RT izpodriva 3D RT





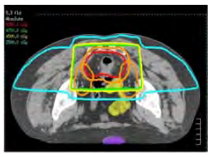


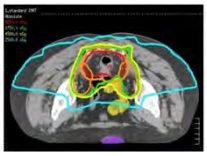


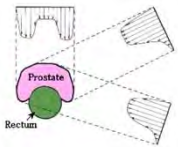
- Konkaven volumen
- Hitrejši padec doze
- ↓doza na kritične organe
- SIB
- ↓toksičnost
- *boljši odziv tarče

Rodel C et al. Curr Opin Oncol 2012

Intenzitetno Modulirano RT izpodriva 3D RT

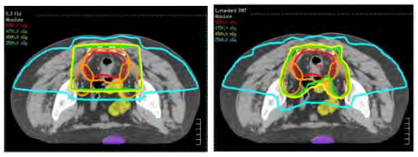


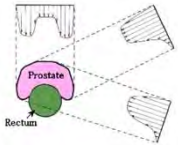




Raziskava faze II	Št. pts	pCR	R1	LK	OS
Belgijska Engels 2014	108	8 %	8 %	97 % (5 l)	68 % (5 l)
Kitajska Jin-luan 2012	63	31 %	0 %	94 % (2 l)	96 % (2 l)
Španska Hernando 2014	72	30,6 %	3 %	95 % (3 l *)	86 % (3 l *)
Slovenska But 2016	51	25.5%	0%		

Intenzitetno Modulirano RT izpodriva 3D RT





Raziskava faze II	Št. pts	pCR	Znižanje T	Znižanje N
But 2015	51	25.5 %	68 %	83 %
Velenik 2006	55	9 %	40 %	53 %

Velenik V et al. Cro Med j 2006
But J et al. IJROBP 2016

Kako od tu dalje?

Raziskave s 5x5 Gy

- cT3N1 → 5x5 Gy in takojšnja vs odložena op
- cT2-3 nizki → 5x5 Gy in lokalna ekscizija pri odgovoru
- „high risk“ ali M1 → 5x5 Gy, sledi KT + odložena op

Raziskave s 5x5 Gy

cT3N1 — 5x5 Gy in takojšnja vs odložena op

Stockholm III
(klinično resektabilni RD <15 cm od AKČ)

Primarni cilj: čas do LR
Sekundarni cilji: akutna i pozna toksičnost, OS, QOL

Raziskave s 5x5 Gy

cT3N1 — 5x5 Gy in takojšnja vs odložena op

Stockholm III
(klinično resektabilni RD <15 cm od AKČ)

First interim analysis after 300 pts (1998-2005)	5x5 Gy immediate TME	5x5 Gy delayed TME	25x2 Gy delayed TME
Number of pts	118	120	65
Severe RT-induced Tox (hospital admission, %)	0	4.2	5
Postop. Complications (%)	47	40	32
Reoperations (%)	10	11	5
Anastomotic leak (%)	13	11	4

Pettersons et al. Br J Surg 2010

Raziskave s 5x5 Gy

cT3N1 — 5x5 Gy in takojšnja vs odložena op

Stockholm III
(klinično resektabilni RD <15 cm od AKČ)

Second interim analysis after 500 pts in 5x5 Gy arms (1998-2010)	5x5 Gy immediate TME	5x5 Gy delayed TME
Number of pts	234	228
ypT0 (%)	2.1	11.8
ypN0 (%)	63.7	71.5
CRM + (%)	11	9
Abdominoperineal Resection (%)	33	38

Pettersons et al. Br J Surg 2015

Raziskave s 5x5 Gy

cT1-3 nizki → 5x5 Gy → 4-8 ted → Lokalna ekscizija

Poljska prospektivna multicentrična (64 pts): ypT0-1 67%
LR (2L) 12%

Bujko C et al. Radiother Oncol 2013

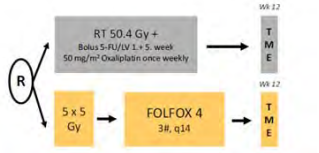
cTx M1 → 5x5 Gy → 6x CAPOX+bev → op

Nizozemska „M1“(50 pts): pCR 26%, Ro resekcija vseh lokalizacij v 72%

Van Dijk et al. Ann Oncol 2013

Raziskave s 5x5 Gy vs CRT

- Poljska II: randomizirana faza III
  - kriteriji „High risk“ fiksirani T3 ali T4, neresektabilni



Primarni cilj: delež R0 resekcij (potrebnih 540 pts)

Raziskave s 5x5 Gy vs CRT

- Poljska II: randomizirana faza III
  - kriteriji „High risk“ fiksirani T3 ali T4, neresektabilni

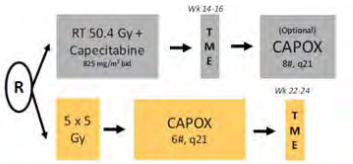
Srednji čas sledenja 35 mes

	50.4 Gy 5-FU/Ox	5x5 Gy FOLFOX	P-value
Number of pts	254	261	
R0 resection (%)	**71**	**77**	**.07**
pCR (%)	12	16	.21
Acute tox grade 1+2/ 3+4 / 5	50 / 21 / 3	60/ 23 / 1	.006
Postop complication	25	29	.18
Local Failure @3y (%)	21	22	.82
Disease-free Survival @ 3y (%)	52	53	.85
Overall Survival @ 3y (%)	65	73	.046

Bujko C et al. ASCO GI 2016

Raziskave s 5x5 Gy vs CRT

- RAPIDO: randomizirana faza III
  - kriteriji „High risk“ definiran z MRI: cT4 ali MRF+ ali N2 ali lat N+ ali EMVI+



Primarni cilj: 3L DFS (potrebnih 850 pts)

Potekajoče raziskave s CRT

cT3-4 M0	CRT s 5-FU/oxali ali tarčnimi zdravili
cT3-4 M0	CRT + „wait and see“pri cCR
cT3-4 M0	indukcijska KT (+ CRT) odložena op

↑pCR =daljši čas od CRT do op

Increasing the Interval Between Neoadjuvant Chemoradiotherapy and Surgery in Rectal Cancer: A Meta-analysis of Published Studies

Petrelli, Fausto; Sgroi, Giovanni; Sarti, Enrico; More

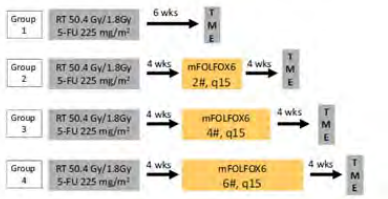
Annals of Surgery. 263(3):458-464, March 2016.

RESULTS: Thirteen trials, including 3584 patients, were identified, and overall, an interval longer than 6 to 8 weeks from the end of neoadjuvant CRT and surgery significantly improved the pCR (RR = 1.42, 95% confidence interval: 1.19-1.68; P < 0.0001). Pathological complete responses increased from 13.7% to 19.5% in the longer interval group, and the OS, DFS, R0 resection rates, sphincter preservation, and complication rates were similar in the 2 groups.

↑ pCR za 6%

Potekajoče raziskave s CRT

- TIMING raziskava



Garcia-Aquilar J et al. Lancet Oncol 2015

Potekajoče raziskave s CRT

- TIMING raziskava

cT3/4 or N+	G 1	G 2	G 3	G 4	p
Number of pts	60	67	67	65	
ypT0N0 (%)	18	25	30	38	.004
Pelvic Fibrosis (mean) (scale 1-10)	2.4	3.9	4.4	3.9	.0001
Surgical technical difficulty (scale 1-10)	4.5	4.9	5.1	4.8	.80

Garcia-Aquilar J et al. Lancet Oncol 2015

Potekajoče raziskave s CRT

- US- Rectal Cancer Consortium (randomizirana faza II)
  - Z MRI definirani T2-3N0 ali Tvsi N1-2

Primarni cilj: 3L DFS

Zaključki (I): kaj smo se

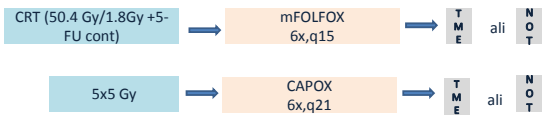
- Zaporedje RT, KT, krg je pomembno (CAO/ARO/AIO-94)
- Sinergističen učinek RT- KT s 5-FU (FFCD 9303, EORTC 22921)
- RT lahko dopolni le optimalno operacijo (Dutch TME, MRC CR 07)
- Pomemben je interval od RT do op (Timing, Stockholm III)
- Več bolnikov dokonča predoperativno kot pooperativno zdravljenje (CAO/ARO/AIO-94)

Zaključki (II): kaj smo se naučili?

- **5x5 + takojšnja op vs CRT + odložena op**
  - podobna učinkovitost glede SP, LK in OS, pozne toksičnosti (Poljska, Trans-Tasmanijska)
  - Downsizing: raje CRT za T4, MRF+, nizko ležeče (?)
  - Morda bo mnenje spremenjeno na kratek režim + odložena op (Stockholm III, Poljska II, Rapido)

Zaključki (III): kako od tu dalje z obema konceptoma?

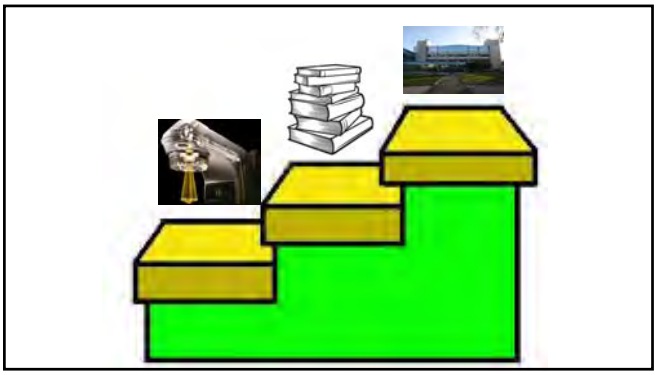
- **T**otalna **N**eoadjuvantna **T**erapija – **O**p odložena ali brez

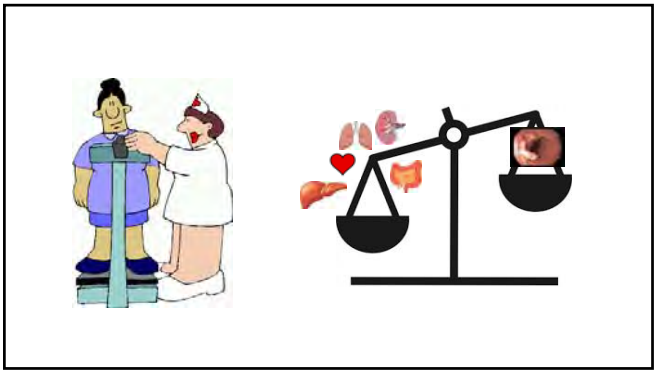


- Selekcija in montoring z modernimi slikovnimi metodami!

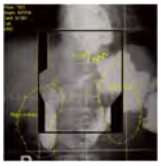
Hvala za pozornost.

Nove tehnike obsevanja tumorjev prebavil

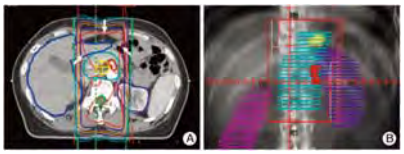




Pogled v preteklost…



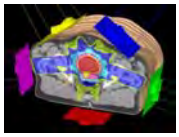
2 D

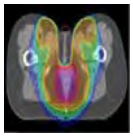


3 D CRT

IMRT (Intensity Modulated RadioTherapy)

- več žarkovnih snopov
- gibanje lističev MLC-spreminjanje intenzitete žarkovnega snopa
- **rezultat:** večji indeks konformonosti
  različni deli tarčnih volumnov so obsevani z različno dozo





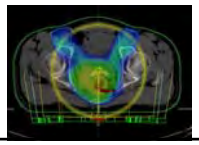
IMRT

- ✓ bolj konformna in homogena porazdelitev doze
- ✓ strm dozni gradient na robu tarče
- ✓ ščitenje kritičnih organov
- ✓ simultani integrirani boost
- ✓ eskalacija doze

- bolj kompleksno planiranje
- daljši čas obsevanja
- več MU
- možnost poddoziranja tarče na robu
- večja celokupna obremenitev telesa s sevanjem

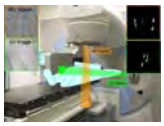
VMAT (Volumetric Modulated Arc Therapy)

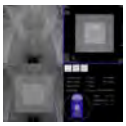
- rotacija glave obsevalnika za 360°
- med proženjem se žarka ves čas spreminja **oblika** obsevalnega polja, **hitrost** izsevane **doze** in **hitrost vrtenja** glave obsevalnika
- **rezultat:** konformnost in zaščita rizičnih organov primerljiva z IMRT (ali še boljša)
  bistveno krajši čas obsevanja
  manjše število monitorskih enot sevanja

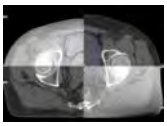


IGRT(Image-Guided Radiation Therapy)

sodobne slikovne metode za zagotavljanje topografske natančnosti obsevanja (primerjamo lego posameznih obsevalnih polj in njihovo obliko, z lego in obliko polj, kot smo ju določili pri planiranju)







Rak požiralnika

Yin et al, 2012: IMRT *vs* VMAT
- V20 in V30 za pljuča nižja pri VMAT, a višja V5 in V10
- V30, V40, V50 za srce nižja pri VMAT
- Dmax medule in Dmean pljuča primerljiva

Kole et al, 2015: Dmean in V30 za srce signifikantno manjša pri IMRT na pram 3D

Lin et al, 2015: -zg.1/3: IMRT: ⇓Dmean in V5 za pljuča
-srednje in spod. 1/3: IMRT ⇓V5 in Dmean za pljuča; ⇑D max medule, Dmean za srce in V20 za pljuča
- pokritost PTV pri zg. in spod 1/3 primerljiv, pri srednji boljši IMRT plan

Nguyen et al, 2011: 3D *vs* tomoterapija:
nižji Dmean za pljuča in srce

Yang et al, 2016: 3D *vs* IMRT *vs* VMAT (cervikalni del):
- ni razlik v 2 yr OS in DFS,
- pri 3D CRT za pljuča večja Dmean in V20, večji Dmax medule, več G1 pneumonitisa

Lin et al, 2015: manj umrljivost zaradi bolezni srca pri IMRT kot pri 3D

Freilich et al, 2015: 3D *vs* IMRT: ni razlik v OS in DFS; manjša izguba teže, manj hospitalizacije

Schroder et al, 2016: IMRT vs VMAT:, ni razlik v pljučnih funkcijskih testih (razen znižane DLCO po 6 tednih pri VMAT)

Rak želodca

Dozimetrične študije: IMRT/VMAT omogočata nižje doze na rizične organe in zagotavljata večji indeks konformnosti in homogenosti.

- **Wieland et al, 2004:** - AP PA *vs* 3D *vs* IMRT
  - IMRT: manjša doza na ledvice (predvsem levo)
- **Zhiping et al, 2013:** - IMRT *vs* VMAT
  - VMAT: višji CI in HI; nižji V13, V18 in Dmean za ledvice
  - IMRT: nižji V30 in Dmean za jetra
- **Zhang et al, 2015:** - 3D *vs* IMRT *vs* VMAT
  - višji CI in HI pri IMRT in VMAT
  - VMAT: najnižja Dmax medule, V30 jeter in V20 ledvic; Dmean pa je za vse enaka
- **Hawrylewicz et al, 2015:** - 3D *vs* IMRT (predop RTKT)
  - največja razlika v dozi na ledvice (predvsem levo!) in medulo

Rak želodca

doprinos v kliničnih rezultatih

?

Minn et al 2010: - ni razlik v 2yr OS in LC
- ni razlik v GI toksičnosti G ⩾2, manjši upad ledvične funkcije, manj prekinitev RT

Suprya et al 2015: -3D *vs* IMRT
- ni razlik v toksičnosti, ne v OS ali LC

Wang et al, 2016: - ni razlik v OS, ni podatkov glede razlik v toksičnosti

Liu ,et al, 2014: 3D (45Gy) *vs* IMRT (50,4Gy):ni razlik v toksičnosti ne v preživetju

Rak danke

3D *vs* IMRT

Tho et al, 2006: nižja Dmean na tanko črevo

Guerrero Urbano et al, 2006: nižja V45 in V50 za tanko črevo

Arbea et al 2010: višji CI, nižja doza na tanko črevo & mehur

Salma et al, 2012: manj G3 toksičnosti, manj prekinitev RT, manj hospitalizacij

Samuelian et al, 2012: manj GI toksičnosti

Parekh et al, 2013: manj GI toksičnosti, manj prekinitev RT

Huan et al 2016: manj GI toksičnosti, boljša LC

Ng et al, 2012: manj diarej G⩾2, manjša GU toksičnost

Še korak dlje v obsevanju rakov danke…

Li et al, 2012: predoperativna RTKT z IMRT (SIB)+ kapecitabin
TD: 41,8 Gy v 22 frakcijah z boostom 50,6Gy

pCR dosežen pri 31%.
G3 diareja pri 9,5%, G3 radiodermatitis pri 3,2%, brez toksičnosti G4

Hernando-Requejo et al, 2014: predoperativna RTKT z IMRT (SIB) +kapecitabin
TD: 46Gy v 23 frakcijah, z integriranim boostom do 57,5 Gy na tumor in patološke bezgavke

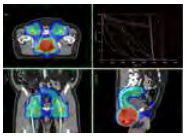
pCR dosežen pri 30,6% .
Zmanjšanje tumorja doseženo pri 73,68% in bezgavk pri 47,2%.
Brez akutnih zapletov G4.

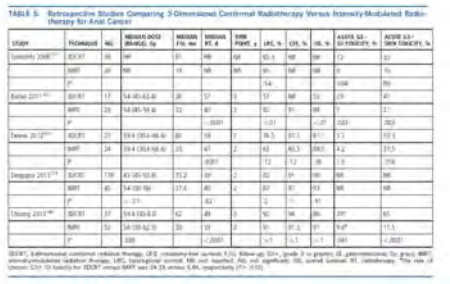
Engels et al, 2014: IMRT s SIB , s TD 46Gy v 23 frakcijah s SIB 55,2Gy
Akutna GI toksičnost G≥3: 9%
Vse kasne toksičnosti G≥3: 13%
5 yr LC: 97%
5 yrPFS: 57%
5 yr OS: 68%G

But-Hadzic, et al. **Acute Toxicity and Tumor Response in Locally Advanced Rectal Cancer After Preoperative Chemoradiation Therapy With Shortening of the Overall Treatment Time Using Intensity-Modulated Radiation Therapy With Simultaneous Integrated Boost: A Phase 2 Trial.** Int J Radiat Oncol Biol Phys. 2016;96:1003-1010.

Rak analnega kanala

- Primarno zdravljenje je radikalna RTKT
- Veliki tarčni volumni
- Bližina rizičnih organov
- Retrospektivne študije: IMRT zmanjša toksičnost, manj prekinitev obsevanj!





Povzeto iz: Shridhar et al, 2015

RTOG 0529

Kachnic LA, Winter K, Myerson RJ, et al. RTOG 0529: a phase 2 evaluation of dose-painted intensity modulated radiation therapy in combination with 5-fluorouracil and mitomycin-C for the reduction of acute morbidity in carcinoma of the anal canal. Int J Radiat Oncol Biol Phys. 2013;86:27-33

- 63 pts, T2-4N0-3 M0, PCC analnega kanala
- elektivne bezgavčne lože: TD: 42-45 Gy
  boost na tumor in prizadete bezgavke:TD: 50,4-54Gy IMRT tehnika s SIB (28-30 x)
- Konkomitantno: 5-FU in mitomycin C

Akutna toksičnost	RTOG 0529 (IMRT)	RTOG 9811 (3D)
Hematološka ⩾ G2	73%	85%
GI ⩾ G3	21%	36%
Dermatološka ⩾ G3	23%	49%

- 2 yr LRC: 80 %
- Kasne posledice?

Obsevanje tumorjev prebavil pri nas…

- Tehnike obsevanja (radikalna RT): 3D CRT, IMRT, VMAT
- Verifikacija obsevalnih polj: MV EPID, KV ortogonalno slikanje, Exac Trac, KV CBCT

- Rak požiralnika: IMRT tehnika (SIB pri različnih doznih nivojih)
- Rak želodca: 3D pri adjuvantnem in IMRT pri predoperativnem zdravljenju
- Rak danke: 3D; pri T4 tumorjih z obsevanimi ložami ob a .iliaci ext. /ingvinami IMRT s SIB
- Rak analnega kanala: IMRT s SIB

Zaključki

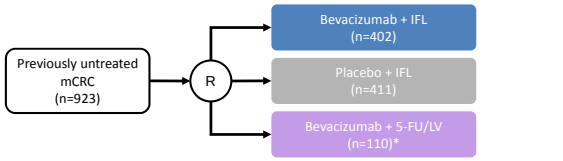
- Hiter in neprestan razvoj novih obsevalnih tehnik v zadnjih desetletjih
- Sočasno se razvija tudi IGRT
- Povečana natančnost obsevanja ima ob vseh dobrobiti tudi svojo ceno

Vloga bioloških zdravil v zdravljenju mCRC

Prof. dr. Janja Ocvirk, dr.med.

AVF2107g: study design and endpoints

Trial started 2000 **NCT00109070**



*Prespecified discontinuation of enrolment in arm 3 when bevacizumab in combination with the bolus-IFL regimen was deemed no more toxic than with 5-FU/LV

Primary endpoint: OS

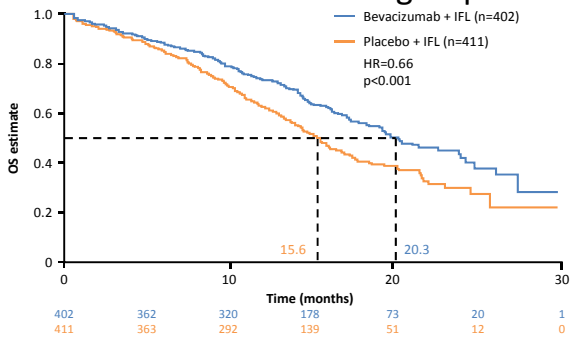
Secondary endpoints: PFS, ORR, duration of response, QoL

Primary endpoint was met

Bevacizumab = 5mg/kg q2w
IFL = irinotecan, 125mg/m²; fluorouracil, 500mg/m2; LV, 20mg/m² once weekly for 4 weeks, cycle repeated every 6 weeks
5-FU/LV = fluorouracil, 500mg/m²; LV, 500mg/m² once weekly for 6 weeks, cycle repeated every 8 weeks

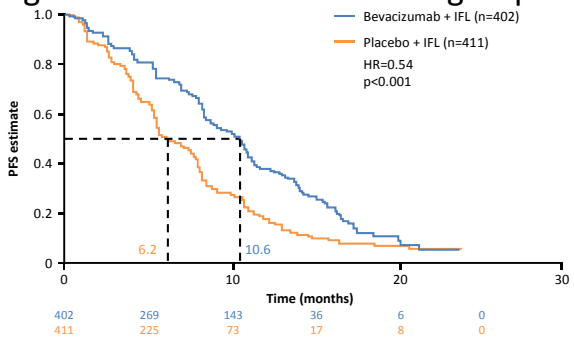
Hurwitz, et al. N Engl J Med 2004

AVF2107g: OS was significantly longer in the bevacizumab + IFL group



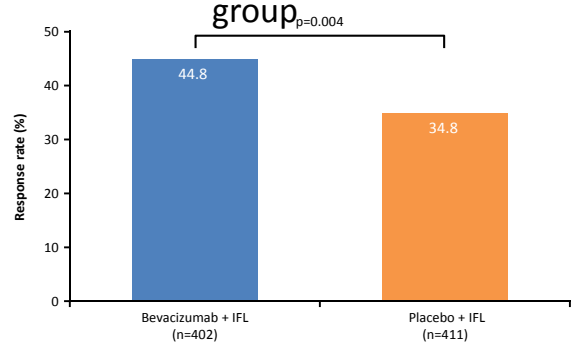
Hurwitz, et al. N Engl J Med 2004

AVF2107g: PFS was also significantly longer in the bevacizumab + IFL group



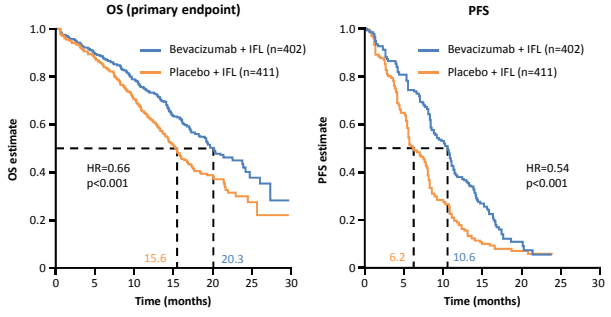
Hurwitz, et al. N Engl J Med 2004

AVF2107g: ORR was significantly increased in the bevacizumab + IFL group$_{p=0.004}$



Hurwitz, et al. N Engl J Med 2004

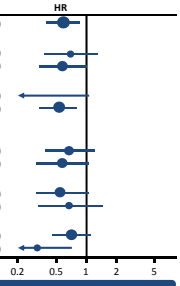
AVF2107g: significant increases in OS and PFS for bevacizumab + IFL in 1L



Hurwitz, et al. N Engl J Med 2004

AVF2107g: survival benefit was independent of BRAF and KRAS mutation status[1]

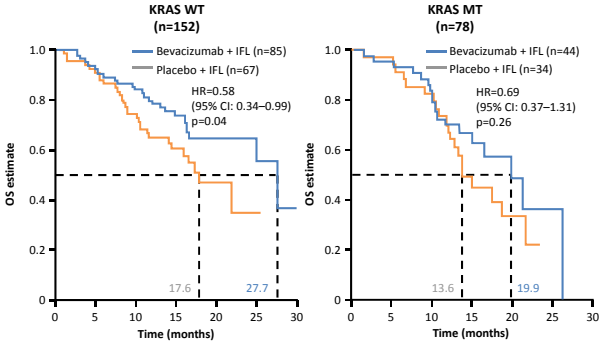
Biomarker	N	Placebo + IFL n	Placebo + IFL Median (months)	Bevacizumab + IFL n	Bevacizumab + IFL Median (months)	HR	(95% CI)
All subjects	267	120	17.5	147	26.4	0.57	(0.39–0.85)
KRAS mutation status							
MT	78	34	13.6	44	19.9	0.69	(0.37–1.31)
WT	152	67	17.6	85	27.7	0.58	(0.34–0.99)
BRAF mutation status							
MT	10	3	8.0	7	15.9	0.11	(0.01–1.06)
WT	217	97	17.5	120	26.4	0.53	(0.34–0.82)
KRAS and BRAF mutation status							
Either MT	88	37	13.6	51	19.9	0.67	(0.37–1.20)
Both WT	125	57	21.7	68	27.7	0.57	(0.31–1.06)
p53 mutation status							
MT	139	63	21.7	76	27.7	0.54	(0.30–0.95)
WT	66	31	16.4	35	NR	0.67	(0.32–1.42)
p53 overexpression							
Positive	191	92	17.5	99	26.4	0.70	(0.45–1.10)
Negative	75	28	16.3	47	25.1	0.32	(0.15–0.70)



Survival benefit also independent of VEGF (plasma and tissue) and thrombospondin-2[2]

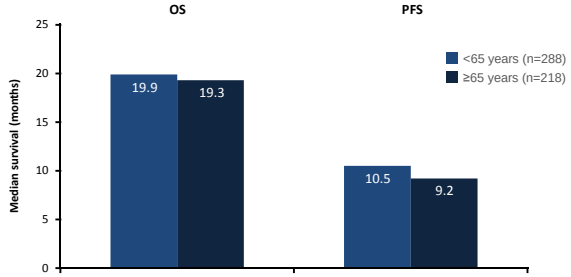
- 1. Ince, et al. J Natl Cancer Inst 2005; 2. Jubb, et al. J Clin Oncol 2006

AVF2107g: OS according to KRAS mutation status



Hurwitz, et al. N Engl J Med 2004

Pooled analysis*: OS and PFS with bevacizumab + chemotherapy were similar in both age subgroups

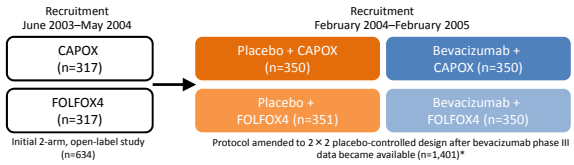


Kabbinavar, et al. J Clin Oncol 2009

*Pooled analysis of AVF2107g and AVF2192g

NO16966: study design and endpoints

Trial started 2003 NCT00069095



Primary endpoint: PFS (non-inferiority of CAPOX vs FOLFOX4; superiority of bevacizumab + CT vs placebo + CT)

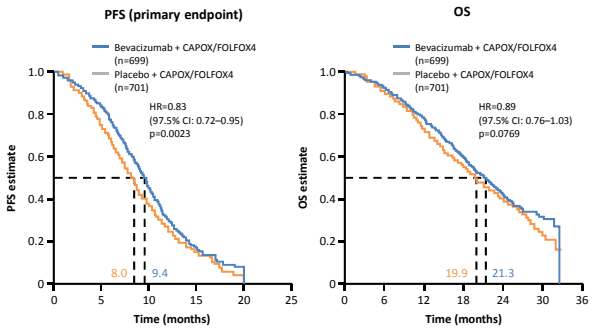
Secondary endpoints: on-treatment PFS (for events that occurred >28 days after the last intake of study medication, the patient was censored back to the date of last known nonprogression), OS, ORR, duration of response, time to treatment failure

Primary endpoint was met

Bevacizumab = 7.5mg/kg d1 q3w with CAPOX; 5mg/kg d1 q2w with FOLFOX4
CAPOX = oxaliplatin, 130mg/m² d1; capecitabine 1,000mg/m² bid d1–14 q3w
FOLFOX4 = oxaliplatin, 85mg/m² d1; LV, 200mg/m² d1; 5-FU 400mg/m² bolus then 600mg/m² continuous infusion over 22h, d1 and d2, q2w

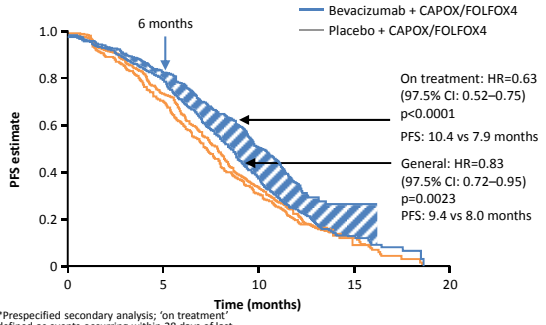
Saltz, et al. ASCO 2007
Saltz, et al. J Clin Oncol 2008

NO16966: PFS, but not OS, was significantly increased with bevacizumab + CAPOX/FOLFOX4



Saltz, et al. J Clin Oncol 2008

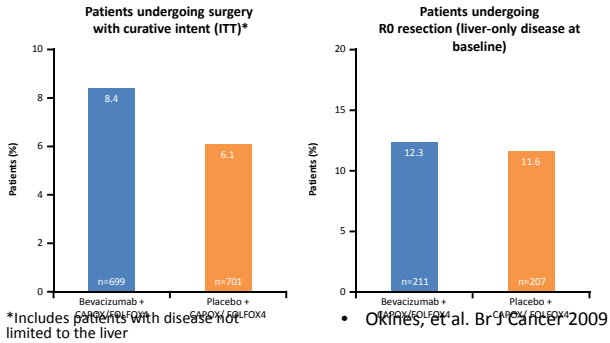
NO16966: clinical benefit in patients 'on treatment'*



- *Prespecified secondary analysis; 'on treatment' defined as events occurring within 28 days of last dose only

Saltz, et al. J Clin Oncol 2008

NO16966: resection rates after oxaliplatin ± bevacizumab-based chemotherapy



- *Includes patients with disease not limited to the liver
- Okines, et al. Br J Cancer 2009

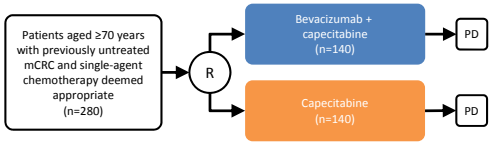
NO16966: updated OS analysis

	FOLFOX4/ placebo + FOLFOX4 (n=668)	CAPOX/ placebo + CAPOX (n=667)	Bevacizumab + FOLFOX4 (n=349)	Bevacizumab + CAPOX (n=350)
No. of events	573	546	274	274
Median OS, months	18.9	19.0	21.0	21.6
HR (97.5% CI)	0.95 (0.83–1.09)		0.95 (0.78–1.15)	

Cassidy, et al. Br J Cancer 2011

AVEX: study design and endpoints

Trial started 2007 NCT00484939



Primary endpoint: PFS

Secondary endpoints: OS, confirmed best overall response, ORR, DCR, duration of response, safety

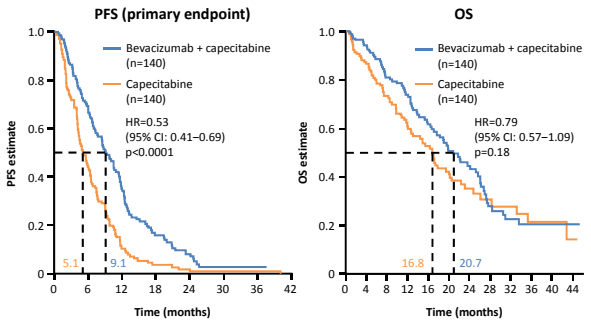
Patients had a median age of 76 (70–87) years

Primary endpoint was met

Bevacizumab = 7.5mg/kg d1 q3w
Capecitabine = 1,000mg/m^2 bid d1–14 q3w

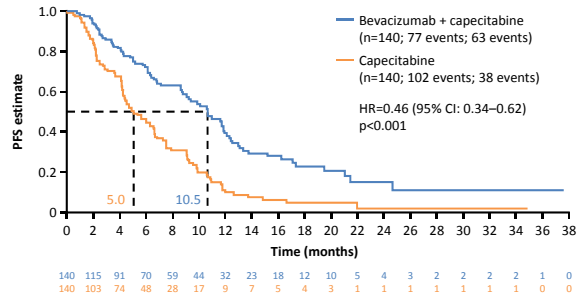
Cunningham, et al. Lancet Oncol 2013

AVEX: PFS and OS



Cunningham, et al. Lancet Oncol 2013

AVEX: significantly improved 'on-treatment' PFS with bevacizumab + capecitabine vs capecitabine in patients aged ≥70 years

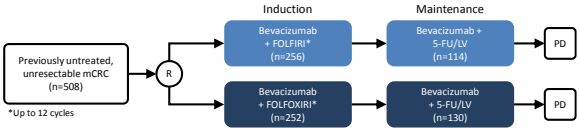


- Saunders, et al. ECC 2013

TRIBE: study design and endpoints

Trial started 2008

NCT00719797



Primary endpoint: PFS

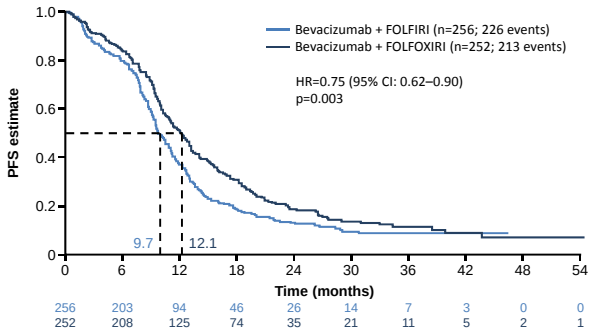
Secondary endpoints: ORR, OS, resection rate of metastases, safety

Primary endpoint was met

Bevacizumab = 5mg/kg d1 q2w
FOLFIRI = irinotecan, 180mg/m² d1; LV, 200mg/m² d1; FU, 400mg/m² bolus then 2,400mg/m² continuous infusion over 46h q2w
FOLFOXIRI = oxaliplatin, 85mg/m² d1; irinotecan, 165mg/m² d1; LV, 200mg/m² d1; FU, 3,200mg/m² over 48h q2w

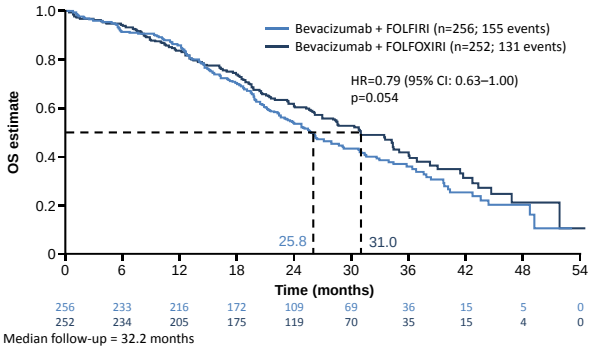
- Loupakis, et al. N Engl J Med 2014

TRIBE: 1L bevacizumab + FOLFOXIRI produces superior PFS to bevacizumab + FOLFIRI



Loupakis, et al. N Engl J Med 2014

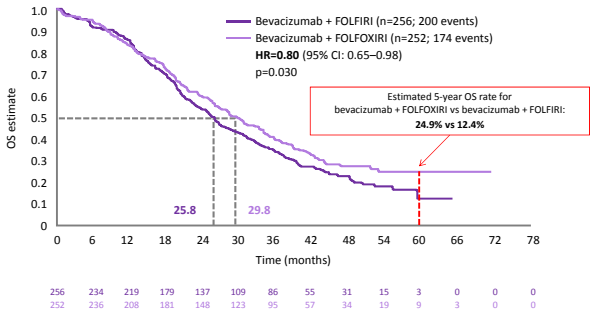
TRIBE: trend towards improved OS with bevacizumab + FOLFOXIRI (data immature)



- Median follow-up = 32.2 months

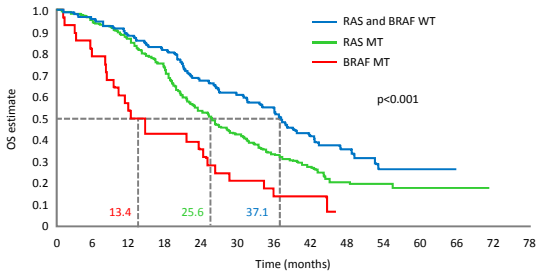
Loupakis, et al. N Engl J Med 2014

TRIBE: updated OS (follow-up of 48.1 months)



- Cremolini, et al. WCGC 2015

TRIBE: patients with BRAF or RAS MT have significantly worse OS compared with RAS/BRAF WT population



Loupakis, et al. ASCO 2015

TRIBE: OS and PFS according to RAS or BRAF status – OS as ASCO 2015, PFS new data at WCGC 2015

		Median OS, months				Median PFS, months			
	n	Bevacizumab + FOLFIRI	Bevacizumab + FOLFOXIRI	HR	P value	Bevacizumab + FOLFIRI	Bevacizumab + FOLFOXIRI	HR	P value
ITT population	508	25.8	29.8	0.80	0.030	9.7	12.3	0.77	0.006
RAS and BRAF evaluable	357	24.9	28.6	0.84	0.159	9.8	12.1	0.80	0.042
RAS and BRAF WT	93	33.5	**41.7**	0.77		12.2	13.7	0.85	
RAS MT	236	23.9	27.3	0.88	0.522*	9.5	12.0	0.78	0.679*
BRAF MT	28	10.7	19.0	0.54		5.5	7.5	0.57	
RAS WT	121	26.8	37.1	0.78	0.658*	11.0	12.8	0.84	0.767*
RAS MT	236	23.9	27.3	0.88		9.5	12.0	0.78	

- A multivariate model accounting for factors significantly associated with shorter OS was developed
  - treatment effect on OS: adjusted HR=0.79 (95% CI: 0.61–1.04), p=0.087
  - effect of BRAF mutation: HR=2.24 (95% CI: 1.32–3.81), p=0.003
  - effect of RAS mutation: HR=1.30 (95% CI: 0.94–1.79), p=0.113

Beneficial effects of bevacizumab + FOLFOXIRI are consistent across all molecular subgroups (KRAS/RAS/BRAF), in particular in the BRAF MT population

Median OS of 41.7 months in the RAS/BRAF WT population is the longest observed to date

TRIBE: early tumour shrinkage (ETS) and deepness of response (DpR) by treatment arm

ETS[1]

Defined as: relative change in the sum of the longest diameters of RECIST target lesions at week 8 compared to baseline. Data cutoff value: 20%[2]

n=443*	Bevacizumab + FOLFIRI (n=222)	Bevacizumab + FOLFOXIRI (n=221)	p value
Range, %	−100 to +56.9	−100 to +54.5	
Median, %	−21.4	−30.2	<0.0001
ETS >20%, n (%)	114 (51)	142 (64)	
ETS ≤20%, n (%)	108 (49)	79 (36)	0.006

*65 patients were not evaluable for ETS

DpR[1]

Defined as: relative change in the sum of the longest diameters of RECIST target lesions at the nadir in the absence of new lesions or progression of non-target lesions compared to baseline. Exploratory cutoff: median DpR in evaluable patients[3]

n=484*	Bevacizumab + FOLFIRI (n=245)	Bevacizumab + FOLFOXIRI (n=239)	p value
Range, %	−100 to +56.9	−100 to +54.5	
Median, %	−33.8	−42.2	0.0009
DpR >38.9%, n (%)	103 (42)	138 (58)	
DpR ≤38.9%, n (%)	142 (58)	101 (42)	0.0008

*24 patients were not evaluable for DpR

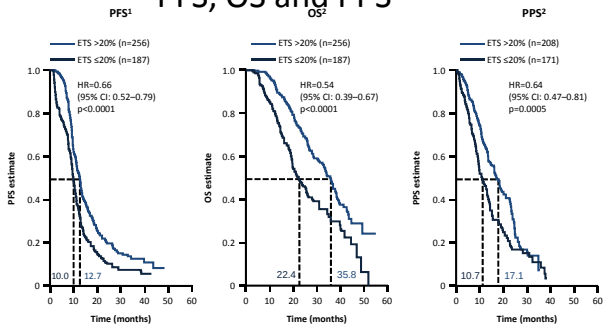
1. Cremolini, et al. ECC 2013
2. Piessevaux, et al. J Clin Oncol 2013
3. Mansmann, et al. ASCO 2013

TRIBE: ETS and DpR correlate with progression-free, post-progression and overall survival

	ETS >20% (n=256)	ETS ≤20% (n=187)	DpR > median* (n=241)	DpR ≤ median* (n=243)
Median PFS, months	12.7	10.0	13.1	9.3
HR (95% CI)	0.66 (0.52–0.79)		0.61 (0.49–0.73)	
p value	**<0.0001**		**<0.0001**	
Median OS, months	35.8	22.4	36.8	21.3
HR (95% CI)	0.54 (0.39–0.67)		0.47 (0.35–0.58)	
p value	**<0.0001**		**<0.0001**	
	(n=208)	**(n=171)**	**(n=201)**	**(n=217)**
Median PPS, months	17.1	10.7	18.4	10.5
HR (95% CI)	0.64 (0.47–0.81)		0.58 (0.44–0.73)	
p value	**0.0005**		**<0.0001**	

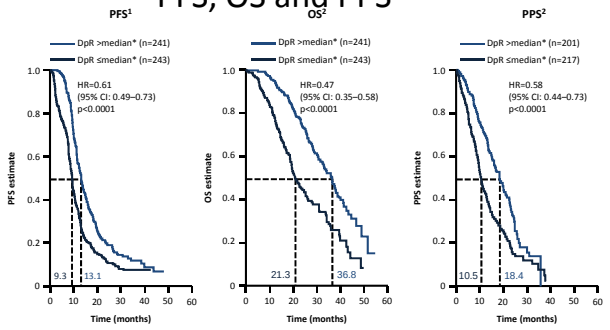
- *Median DpR = 38.9%
- Cremolini, et al. ASCO GI 2014

TRIBE: ETS correlates significantly with PFS, OS and PPS



- 1. Cremolini, et al. ECC 2013
  2. Cremolini, et al. ASCO GI 2014

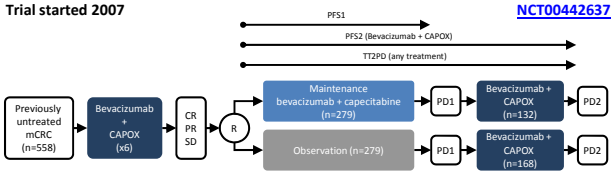
TRIBE: DpR correlates significantly with PFS, OS and PPS



- 1. Cremolini, et al. ECC 2013
  2. Cremolini, et al. ASCO GI 2014

CAIRO3: study design and endpoints

Trial started 2007 NCT00442637



Primary endpoint: PFS2 (PFS after reintroduction of bevacizumab + CAPOX)

Secondary endpoints: PFS1, OS, TT2PD (time to PD2 on any treatment including bevacizumab + CAPOX), QoL, ORR, safety

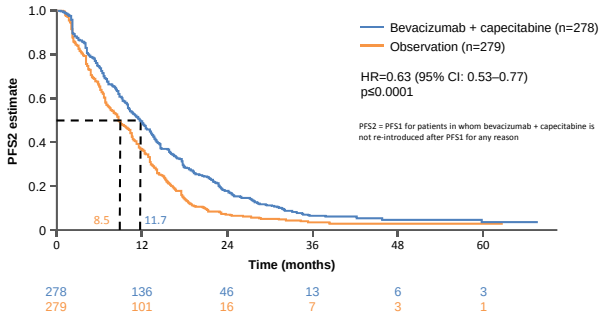
PFS2 was considered to be equal to PFS1 for patients in whom bevacizumab + CAPOX was not reintroduced after PFS1 for any reason

Primary endpoint was met

Bevacizumab = 7.5mg/kg d1 q3w
Capecitabine = 625mg/m² bid
CAPOX = oxaliplatin, 130mg/m² d1; capecitabine, 1,000mg/m² bid d1–d14 q3w

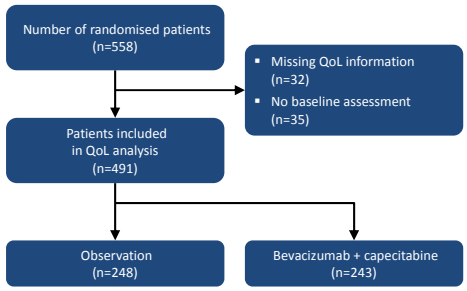
Simkens, et al. Lancet 2015

CAIRO3: PFS2 (primary endpoint) significantly improved with maintenance bevacizumab + capecitabine



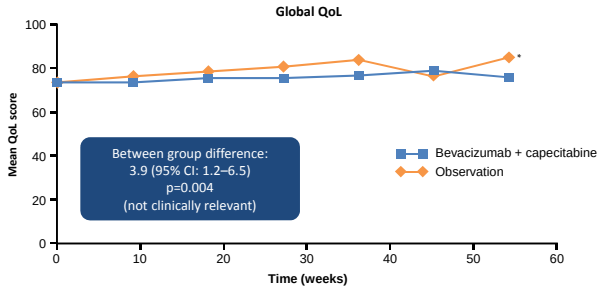
Simkens, et al. Lancet 2015

CAIRO3: QoL analysis



- Punt, et al. ECC 2013

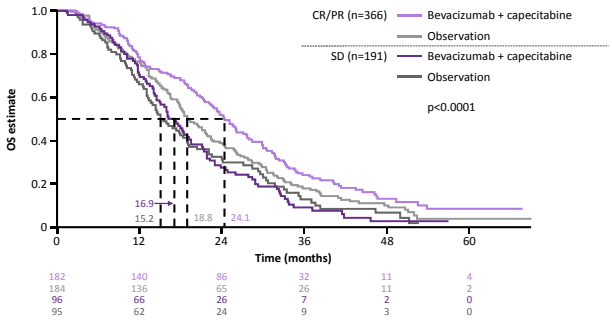
CAIRO3: QoL was higher in the observation group compared with maintenance bevacizumab + capecitabine



- *Significant within group change (p<0.05)

Punt, et al. ECC 2013

CAIRO3: best OS for patients with maintenance therapy after achieving a CR/PR in induction

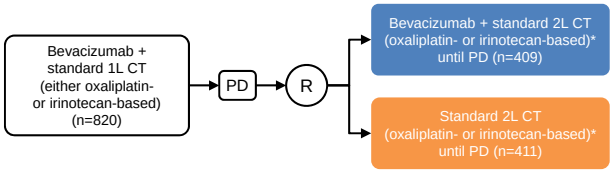


- Induction treatment of six cycles bevacizumab + CAPOX prior to randomisation not included (4–5 months)

- Koopman, et al. ASCO 2014

ML18147: study design and endpoints

Trial started 2006 **NCT00700102**



Primary endpoint: OS from randomisation

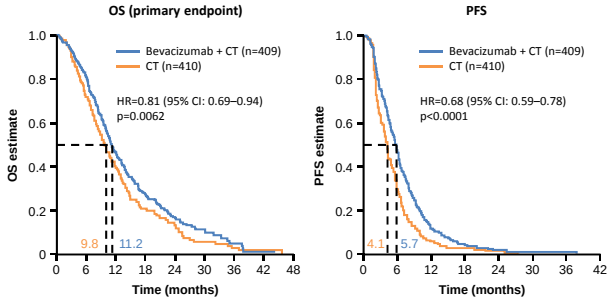
Secondary endpoints: PFS, best overall response, OS from start of 1L therapy, 'on treatment' PFS (i.e. disease progression occurred ≤28 days after the last confirmed dose of study treatment)

Primary endpoint was met

*2L CT was determined by the 1L regimen (i.e. patients given 1L oxaliplatin were switched to 2L irinotecan, and vice versa)
Bevacizumab = 5mg/kg q2w or 7.5mg/kg q3w

Bennouna, et al. Lancet Oncol 2013

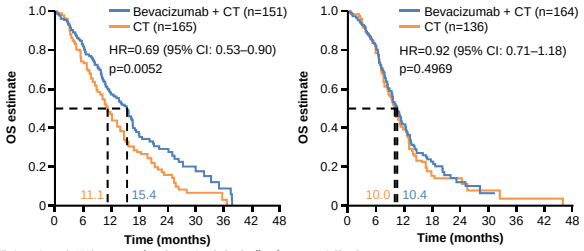
ML18147: OS and PFS from randomisation



Bennouna, et al. Lancet Oncol 2013

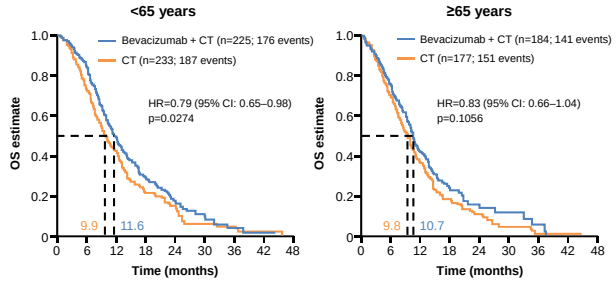
ML18147: OS from randomisation by KRAS mutation status

Interaction test by KRAS status was negative (p=0.1266)*



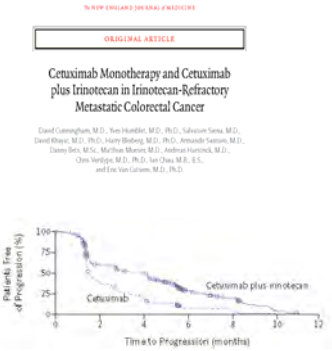
- *The interaction test by KRAS status was performed to examine whether the effect of treatment varied based on whether patients had KRAS MT or WT disease. The interaction test by KRAS status was negative for OS (p=0.1266), indicating that there is no evidence that the treatment effect is dependent on the KRAS mutational status
- Kubicka, et al. Ann Oncol 2013

ML18147: OS from randomisation in patients aged <65 years and ≥65 years



- Bouche, et al. ESMO 2012

BOND


ORIGINAL ARTICLE

Cetuximab Monotherapy and Cetuximab plus Irinotecan in Irinotecan-Refractory Metastatic Colorectal Cancer

David Cunningham, M.D., Wen Humblet, M.D., Ph.D., Salvatore Siena, M.D., David Khayat, M.D., Ph.D., Harry Bleiberg, M.D., Ph.D., Armando Santoro, M.D., Danny Bets, M.Sc., Marlhan Muneer, M.D., Andreas Harstrick, M.D., Chris Verslype, M.D., Ph.D., Ian Chau, M.B., B.S., and Eric Van Cutsem, M.D., Ph.D.

Table 2. Rates of Radiologic Response.*

Subgroup and Variable	Cetuximab plus Irinotecan	Cetuximab	P Value
Intention-to-treat population			
No. of patients	218	111	
Response — no. (%)			
Complete response	0	0	
Partial response	50 (22.9)	12 (10.8)	
Stable disease	71 (32.6)	24 (21.6)	
Progressive disease	68 (31.2)	59 (53.2)	
Could not be evaluated	29 (13.3)	16 (14.4)	
Overall response†	50 (22.9 [17.5–29.1])	12 (10.8 [5.7–18.1])	0.007
Disease control‡	121 (55.5 [48.6–62.2])	36 (32.4 [23.9–42.0])	<0.001
Subgroup with progression during or within 4 wk after prestudy irinotecan			
No. of patients	135	71	
Response — no. (%)	34 (25.2 [18.1–33.4])	10 (14.1 [7.0–24.4])	0.07
Subgroup with prior oxaliplatin therapy			
No. of patients	135	71	
Response — no. (%)	30 (22.2 [15.5–30.2])	6 (8.5 [3.2–17.5])	0.01

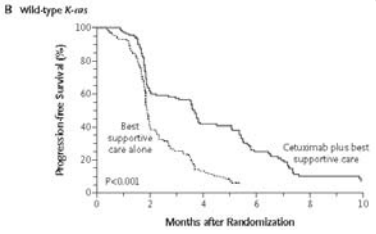
NCIC CTC Co 17


The NEW ENGLAND JOURNAL of MEDICINE

OCTOBER 23, 2008

K-ras Mutations and Benefit from Cetuximab in Advanced Colorectal Cancer

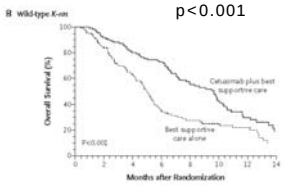
Charles S. Karapetis, M.D., Shimi Khambata-Ford, Ph.D., Derek J. Jonker, M.D., Chris J. O'Callaghan, Ph.D., Dongsheng Tu, Ph.D., Niall C. Tebbutt, Ph.D., R. John Simes, M.D., Hagi Chalchal, M.D., Jeremy D. Shapiro, M.D., Sonia Robitaille, M.Sc., Timothy J. Price, M.D., Lisa Shepherd, M.D.C. M., Heather-Jane Au, M.D., Christiane Langer, M.D., Malcolm J. Moore, M.D., and John R. Zalcberg, M.D., Ph.D.*



- **PFS** 3.7 vs 1.9
  HR=0.40
  p<0.001

NCIC CTC Co 17

- **OS** 9.5 vs 4.8
  HR=0.55
  p<0.001



BSC
RR 13% vs 0

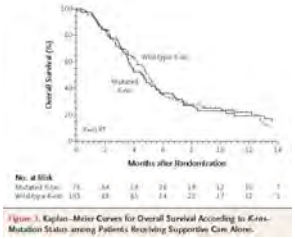
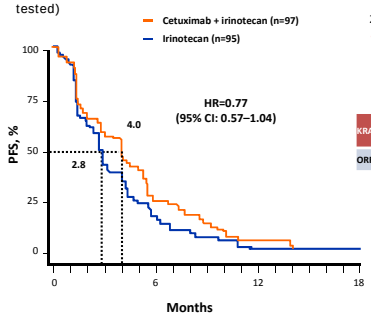


Figure 3. Kaplan–Meier Curves for Overall Survival According to K-ras Mutation Status among Patients Receiving Supportive Care Alone.

2. red zdravljenja

Phase III EPIC study of 2nd line irinotecan ± cetuximab (KRAS exon 2 wt*)[1]

(orig. 1300 pts: 192 KRAS tested)



2nd line cetuximab therapy + CT provides PFS and ORR benefits for patients who missed an opportunity to receive such therapy in 1st line

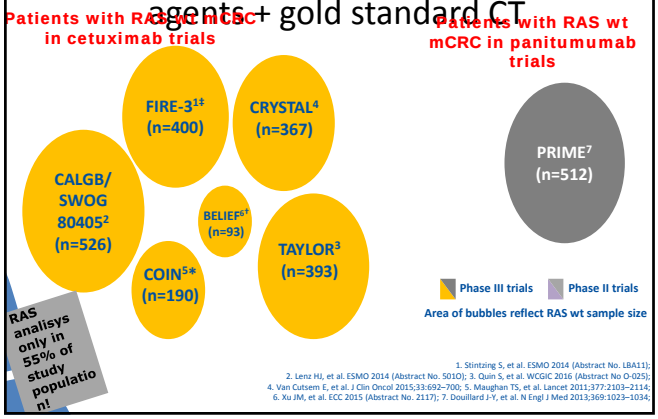
KRAS exon 2 wt*	Cetuximab + irinotecan (n=97)	Irinotecan (n=95)
ORR, %	10.3	7.4

The data are confounded by a high rate of crossover to cetuximab post study[1]

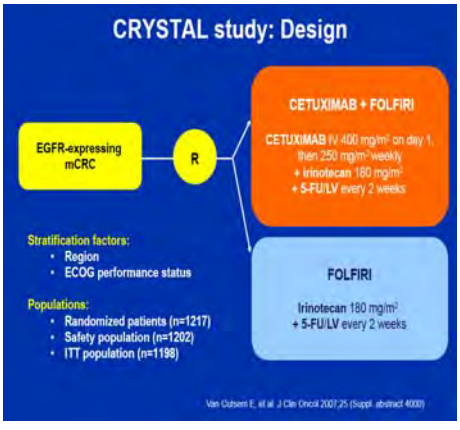
*Cetuximab is approved in patients with RAS wt mCRC.[2] Cetuximab is not indicated for the treatment of patients with mCRC whose tumors have RAS mutations or for whom RAS tumor status is unknown.[2]

1. Langer C, et al. ESMO 2008 (Abstract No. 3853P); 2. Erbitux SmPC June/2014.

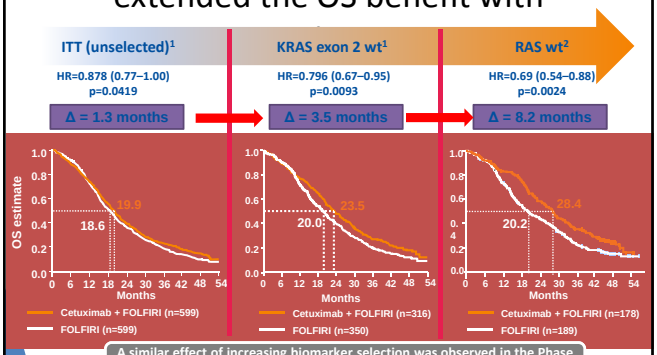
Randomized Phase III trials of anti-EGFR agents + gold standard CT



1. Stintzing S, et al. ESMO 2014 (Abstract No. LBA11); 2. Lenz HJ, et al. ESMO 2014 (Abstract No. 501O); 3. Quin S, et al. WCGIC 2016 (Abstract No O-025); 4. Van Cutsem E, et al. J Clin Oncol 2015;33:692–700; 5. Maughan TS, et al. Lancet 2011;377:2103–2114; 6. Xu JM, et al. ECC 2015 (Abstract No. 2117); 7. Douillard J-Y, et al. N Engl J Med 2013;369:1023–1034;



CRYSTAL: Greater patient selection extended the OS benefit with

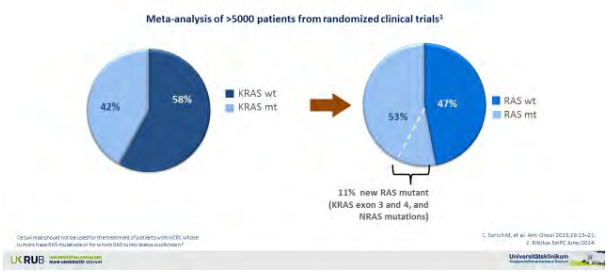


A similar effect of increasing biomarker selection was observed in the Phase III PRIME study of 1st line FOLFOX ± panitumumab[3]

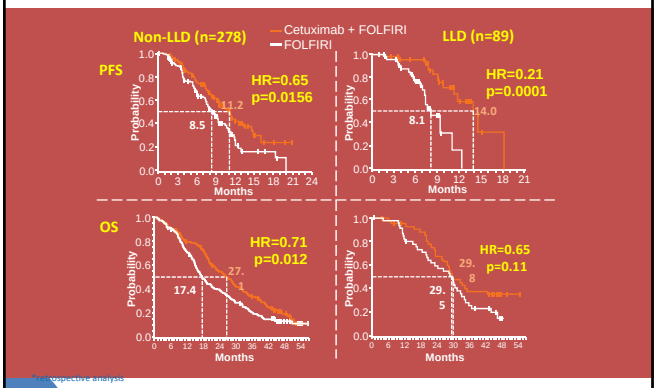
Figure adapted from data from Van Cutsem E, et al.[2]
Cetuximab and panitumumab are approved in patients with RAS wt mCRC.[4,5] Cetuximab and panitumumab are not indicated for the treatment of patients with mCRC whose tumors have RAS mutations or for whom RAS tumor status is unknown.[4,5]

1. Van Cutsem E, et al. J Clin Oncol 2011;29:2011–2019;
2. Van Cutsem E, et al. J Clin Oncol 2015;33:692–700;
3. Douillard J-Y, et al. N Engl J Med 2013;369:1023–1034;
4. Erbitux SmPC June 2014; 5. Vectibix SmPC February 2015.

Extended RAS mutation testing



CRYSTAL: Cetuximab + FOLFIRI vs FOLFIRI increased PFS and OS in both LLD and non-LLD (RAS wt*)[1]



*Retrospective analysis

1. Köhne CH, et al. ESMO 2014 (Abstract No. 5692); adapted from updated information presented at meeting.

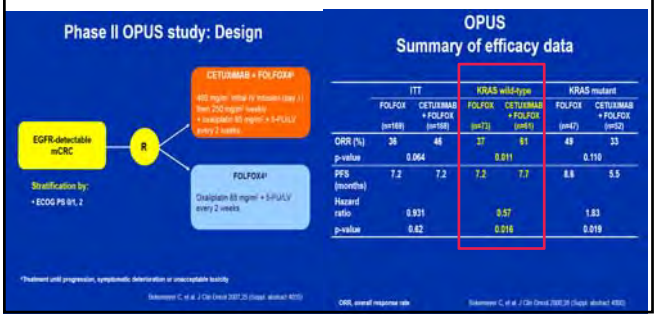
1. red zdravljenja: faza II

Annals of Oncology Advance Access published January 12, 2011

OI original article

Efficacy according to biomarker status of cetuximab plus FOLFOX-4 as first-line treatment for metastatic colorectal cancer: the OPUS study

C. Bokemeyer*, C. Bondarenkoa, L. T. Hartmann, F. G. Hoos, G. Schmidt, A. Zubel, ... Cole, M. Schlichting & E. Kohlewski



OPUS
Summary of efficacy data

	ITT		KRAS wild-type		KRAS mutant	
	FOLFOX (n=168)	CETUXIMAB + FOLFOX (n=168)	FOLFOX (n=72)	CETUXIMAB + FOLFOX (n=61)	FOLFOX (n=47)	CETUXIMAB + FOLFOX (n=52)
ORR (%)	36	46	37	61	49	33
p-value	0.064		0.011		0.110	
PFS (months)	7.2	7.2	7.2	7.7	8.6	5.5
Hazard ratio	0.931		0.57		1.83	
p-value	0.62		0.016		0.019	

1. red zdravljenja: faza III (ERBITUX + FOLFOX vs FOLFOX)

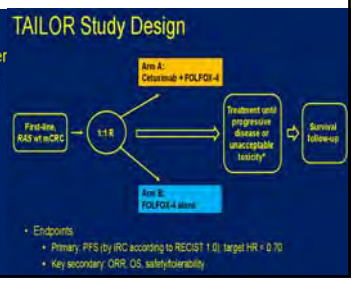
TAYLOR (WCGIC Abstract No.O-025)

First-line FOLFOX-4 ± cetuximab in patients with *RAS* wild-type metastatic colorectal cancer the open-label, randomized phase 3 TAILOR trial

Shukui Qin, Jianmin Xu, Liwei Wang, Ying Cheng, Tianshu Liu*, Jiongjie Chen, S. Peter Eggleton, Joyce Liu, Jin Li

*Zhongshan Hospital affiliated to Fudan University, Shanghai, China

Abstract No. O-025

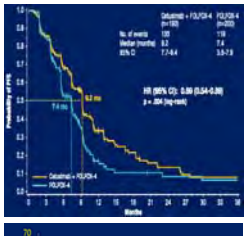


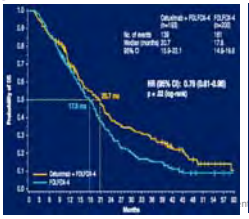
- Endpoints
  - Primary: PFS (by IRC according to RECIST 1.0); target HR = 0.70
  - Key secondary: ORR, OS, safety/tolerability

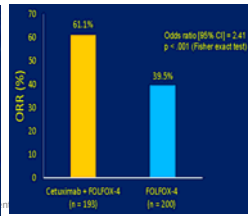
- **Primary: PFS**

ALL ENDPOINTS SIGN. BETTER IN ERBITUX ARM!!!

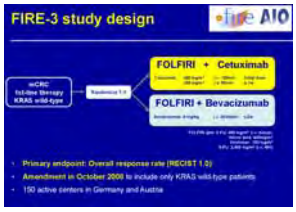
- **Secondary: RR and OS**

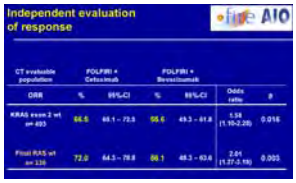






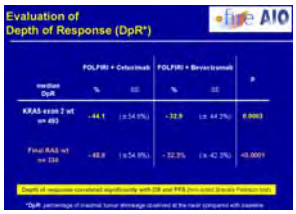
FIRE -3

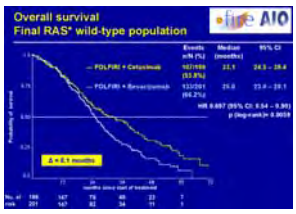




1. Stintzing S, et al. ESMO 2014 (Abstract No. LBA11);
2. Heinemann V, et al. Lancet Oncol 2014;15:1065–1075.

FIRE - 3





1. Stintzing S, et al. ESMO 2014 (Abstract No. LBA11);
2. Heinemann V, et al. Lancet Oncol 2014;15:1065–1075.

FIRE-3: Increased OS benefit with cetuximab in final RAS wt vs KRAS wt population[1,2]

KRAS exon 2 wt population[1,2]

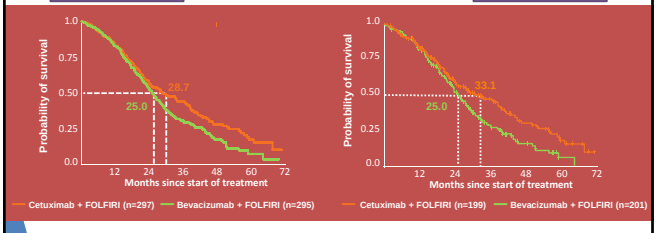
HR=0.77 (0.62–0.96)
p=0.017

Δ = 3.7 months

RAS* wt population[2]

HR=0.697 (0.54–0.90)
p=0.0059

Δ = 8.1 months

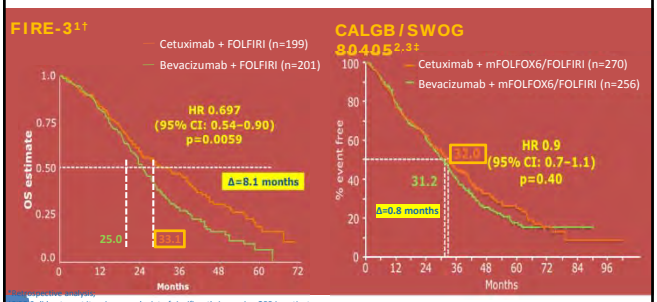


FIRE-3 did not meet its primary endpoint of significantly improving overall response rate (ORR) in patients with KRAS (exon 2) wt mCRC based on investigators' read[1]
Cetuximab is approved in patients with RAS wt mCRC.[3] Cetuximab is not indicated for the treatment of patients with mCRC whose tumors have RAS mutations or for whom RAS tumor status is unknown.[3]
*KRAS and NRAS exon 2, 3 and 4 wild-type.

1. Heinemann V, et al. Lancet Oncol 2014;15:1065–1075;
2. Stintzing S, et al. ESMO 2014 (Abstract No. LBA11), adapted from updated information presented at the meeting;
3. Erbitux SmPC June 2014.

Phase III evidence for anti-EGFRs with gold standard CT (FOLFIRI and FOLFOX):

Randomized Phase III trials of cetuximab + CT vs bevacizumab + CT (RAS wt*)



1. Stintzing S, et al. ESMO 2014 (Abstract No. LBA11);
2. Lenz HJ, et al. ESMO 2014 (Abstract No. 501O);
3. Venook AP, et al. ASCO 2014 (Abstract No. LBA3)
4. Heinemann V, et al. Lancet Oncol 2014;15:1065–1075.

Cetuximab-based therapy in elderly comorbid patients with metastatic colorectal cancer

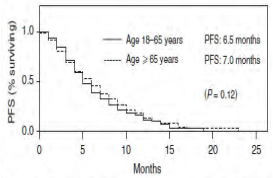


Figure 2 Progression-free survival of pts in age groups 18–65 years vs ⩾65 years clearly showing no difference between both patient subsets.

Best response (% of pts)	Age 18–65 years (n = 309)	Age > 65 years (n = 305)
CR	3	3
PR	35	34
SD	31	34
PD	25	23
NA	7	7

Conclusion: Cetuximab has a similar efficacy and safety profile for pts aged <65 and ≥65 years.

This NIS reports one of the largest mCRC collectives >65 years (305) and reduced performance status (80%),

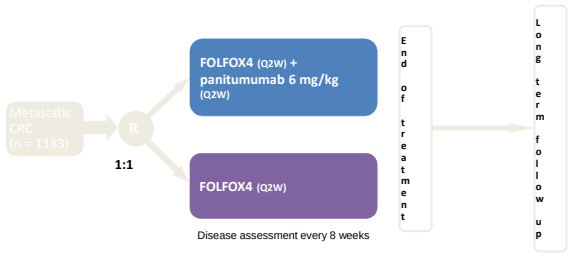
British Journal of Cancer (2012) 106, 274–278. doi:10.1038/bjc.2011.554 www.bjcancer.com

Panitumumab in 1st-line mCRC

Randomised phase 3 study of panitumumab with FOLFOX4 vs. FOLFOX4 alone as 1st-line treatment in mCRC patients: the PRIME trial

PRIME study

FOLFOX4 ± panitumumab in 1st-line treatment of metastatic CRC



- Study endpoints: PFS (1°); OS, ORR, safety, HRQoL
- KRAS status was prospectively analysed

www.amgentrials.com; protocol ID: 20050203; ClinicalTrials.gov identifier: NCT00364013.

HRQoL, health-related quality of life

PRIME study

Key eligibility criteria

- ≥18 years of age
- Previously untreated metastatic adenocarcinoma of the colon/rectum
- Adjuvant 5-FU-based therapy allowed if disease progression occurred >6 months after completion; prior oxaliplatin not allowed
- Measurable disease
- Paraffin-embedded tumour tissue from primary tumour or metastasis available for central biomarker testing
- EGFR expression and *KRAS* status not required at entry
- ECOG performance status 0-2

Douillard JY, et al. J Clin Oncol 2010; 28:4697-705.

PRIME study

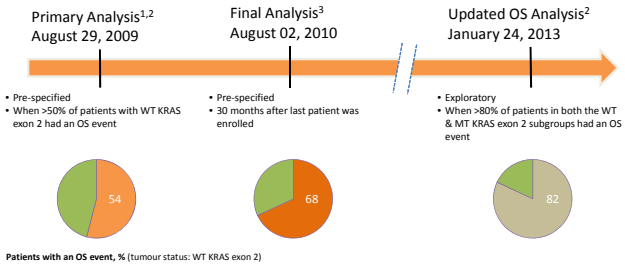
Prospective *KRAS* analysis

- First randomised study in 1st-line prospectively analysed by *KRAS* mutation status
- *KRAS* status determined by blinded, independent central testing*
  - Identification of seven somatic mutations located in *KRAS* exon 2 (codons 12 and 13)[1]
- High ascertainment rate of 93%
- 60% WT *KRAS* exon 2 in both arms

Douillard JY, et al. J Clin Oncol 2010; 28:4697-705;
1. Amado RG, et al. J Clin Oncol 2008; 26:1626-34.

*KRAS testing was performed using allele-specific polymerase chain reaction (DxS, Manchester, UK)

PRIME study
Statistical considerations



Patients with an OS event, % (tumour status: WT KRAS exon 2)

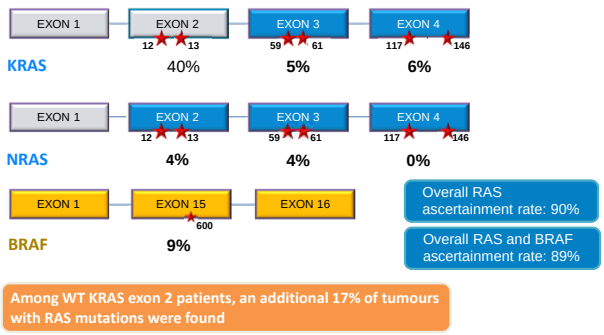
1. Douillard JY, et al. J Clin Oncol 2010; 28:4697-705;
2. Douillard JY, et al. N Engl J Med 2013; 369:1023-34;
3. Douillard JY, et al. J Clin Oncol 2011; 29(suppl):abstract 3510 (and oral presentation).

WT *KRAS*, WT *KRAS* in codons 12/13

Panitumumab in 1st-line mCRC

The PRIME study: Panitumumab + FOLFOX4 treatment in WT *RAS* mCRC

PRIME study *RAS* analysis
KRAS, *NRAS* and *BRAF* mutation hotspots



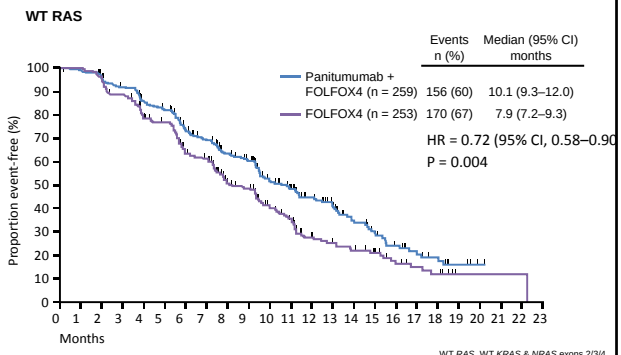
Among WT KRAS exon 2 patients, an additional 17% of tumours with RAS mutations were found

Based on Douillard JY, et al. N Engl J Med 2013; 369:1023-34;
Oliner KS, et al. EJC 2013; 49 (suppl 3):abstract 2275 (and poster).

Percentages have been rounded; 7 patients harboured either *KRAS* or *NRAS* codon 59 mutations

PRIME study *RAS* analysis

PFS (primary analysis)

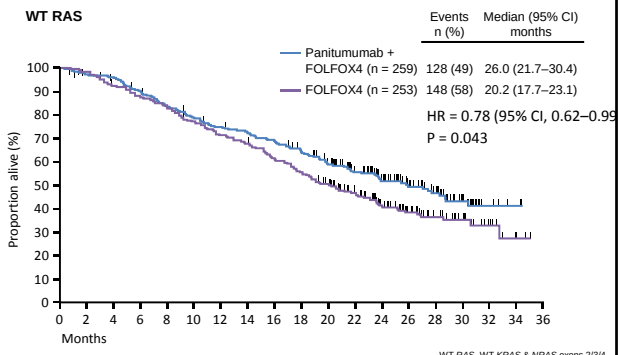


WT *RAS*, WT *KRAS* & *NRAS* exons 2/3/4 (includes 7 patients harbouring *KRAS/NRAS* codon 59 mutations)

Douillard JY, et al. N Engl J Med 2013; 369:1023-34.

PRIME study *RAS* analysis

OS (primary analysis)

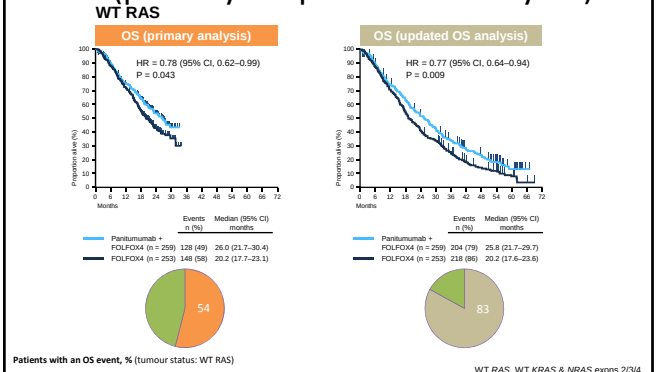


WT *RAS*, WT *KRAS* & *NRAS* exons 2/3/4 (includes 7 patients harbouring *KRAS/NRAS* codon 59 mutations)

Douillard JY, et al. N Engl J Med 2013; 369:1023-34.

PRIME study *RAS* analysis

OS (primary & updated OS analyses)



Patients with an OS event, % (tumour status: WT RAS)

WT *RAS*, WT *KRAS* & *NRAS* exons 2/3/4 (includes 7 patients harbouring *KRAS/NRAS* codon 59 mutations)

1. Douillard JY, et al. N Engl J Med 2013; 369:1023-34.

PRIME study *RAS* analysis

Summary of adverse events (primary analysis)

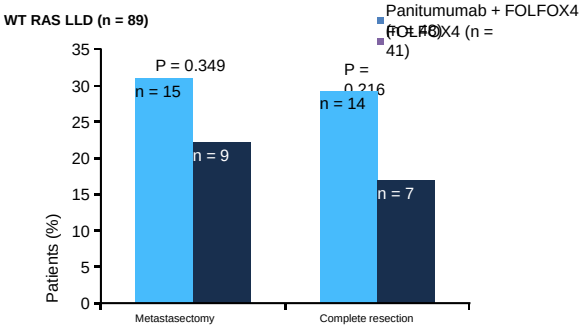
Adverse event	WT *RAS*			MT *RAS*		
	Panitumumab + FOLFOX4 (n = 256)	FOLFOX4 (n = 250)	Total (n = 506)	Panitumumab + FOLFOX4 (n = 268)	FOLFOX4 (n = 275)	Total (n = 543)
Patients with any AE, n (%)	256 (100)	248 (99)	504 (100)	266 (99)	273 (99)	539 (99)
Worst grade of 3	146 (57)	124 (50)	270 (53)	153 (57)	146 (53)	299 (55)
Worst grade of 4	71 (28)	51 (20)	122 (24)	63 (24)	55 (20)	118 (22)
Worst grade of 5	14 (5)	16 (6)	30 (6)	19 (7)	10 (4)	29 (5)
Any serious AE	110 (43)	92 (37)	202 (40)	121 (45)	84 (31)	205 (38)
AE leading to permanent discontinuation of any study drug	65 (25)	40 (16)	105 (21)	60 (22)	37 (13)	97 (18)
Not serious	48 (19)	28 (11)	76 (15)	50 (19)	24 (9)	74 (14)
Serious	24 (9)	15 (6)	39 (8)	17 (6)	14 (5)	31 (6)

WT *RAS*, WT *KRAS* & *NRAS* exons 2/3/4 (includes 7 patients harbouring *KRAS/NRAS* codon 59 mutations); AE, adverse event

Douillard JY, et al. N Engl J Med 2013; 369:1023-34.

PRIME study *RAS* analysis

Metastasectomy and complete resection rates (LLD patients, updated analysis)

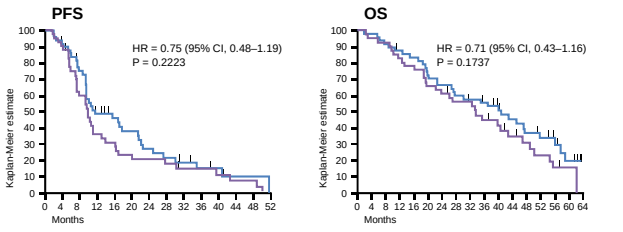


Peeters M, et al. EJC 2013; 49 (suppl 4):abstract MC13-0022 (and poster).

LLD, liver-limited disease

PRIME study *RAS* analysis

PFS, OS (LLD patients, updated analysis)



	Events n (%)	Median, months (95% CI)
Panitumumab + FOLFOX4 (n = 48)	38 (79)	11.3
FOLFOX4 (n = 41)	37 (90)	9.9

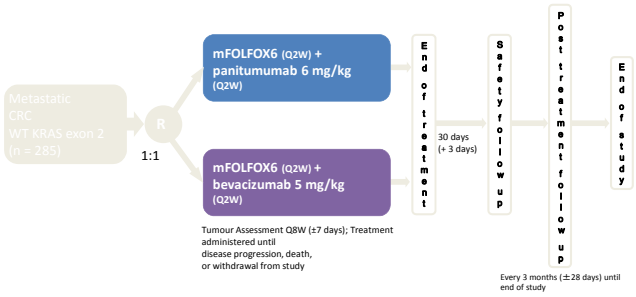
	Events n (%)	Median, months (95% CI)
Panitumumab + FOLFOX4 (n = 48)	32 (67)	40.7
FOLFOX4 (n = 41)	31 (76)	33.4

Peeters M, et al. EJC 2013; 49 (suppl 4):abstract MC13-0022 (and poster).

LLD, liver-limited disease

PEAK study

mFOLFOX6 + panitumumab or bevacizumab in 1st-line treatment of WT *KRAS* exon 2 mCRC



- Study endpoints: PFS (1°); OS, ORR, safety, exploratory biomarker analysis
- No formal hypothesis testing was planned

Karthaus M, et al. EJC 2013; 49 (suppl 3):abstract 2262 (and poster);
Protocol ID: 20070509; ClinicalTrials.gov identifier: NCT00819780.

ORR, objective response rate; mFOLFOX6, modified FOLFOX6

PEAK study *RAS* analysis

Biomarker testing methodology

- Banked patient tumour specimens characterized as WT *KRAS* exon 2 were selected for analysis:
  - *KRAS* exon 2 (codons 12/13), exon 3 (codons 59/61) & exon 4 (codons 117/146)
  - *NRAS* exon 2 (codons 12/13), exon 3 (codons 59/61) & exon 4 (codons 117/146)
- Analytical methods were qualified and the testing lab blinded to treatment assignment and patient outcome

Karthaus M, et al. EJC 2013; 49 (suppl 3):abstract 2262 (and poster).

PEAK study *RAS* analysis

KRAS, NRAS and *BRAF* mutation hotspots

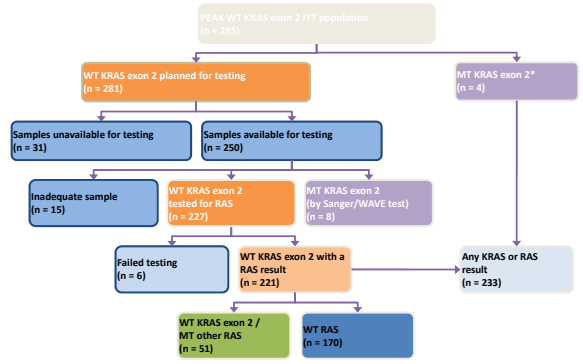
Overall RAS ascertainment rate: 82%

1. Schwartzberg L, et al. J Clin Oncol 2013; 31 (suppl):abstract 3631 (and poster);
2. Karthaus M, et al. EJC 2013; 49 (suppl 3):abstract 2262 (and poster).

Percentages have been rounded; #WT *KRAS* exon 2 tumour status was defined in the trial eligibility criteria; N/A, not applicable

PEAK study *RAS* analysis

RAS testing

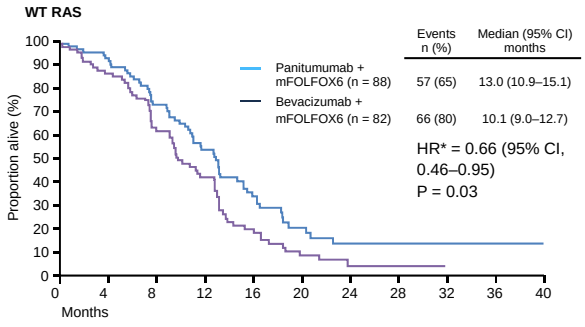


Karthaus M, et al. EJC 2013; 49 (suppl 3):abstract 2262 (and poster).

ITT, intent-to-treat

PEAK study *RAS* analysis

PFS (longer follow-up analysis)

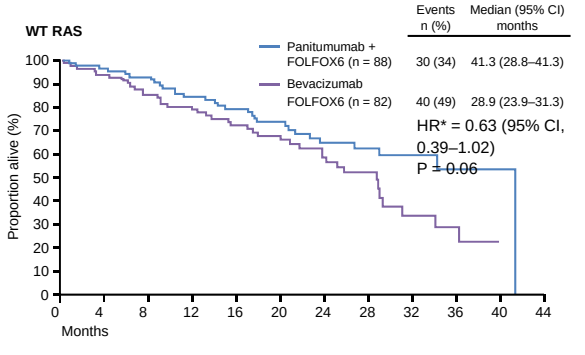


Karthaus M, et al. EJC 2013; 49 (suppl 3):abstract 2262 (and poster).

*Stratified Cox proportional hazards model; No formal hypothesis testing was planned; WT *RAS*, WT *KRAS* & *NRAS* exons 2/3/4

PEAK study *RAS* analysis

OS (longer follow-up analysis)



Karthaus M, et al. EJC 2013; 49 (suppl 3):abstract 2262 (and poster).

*Stratified Cox proportional hazards model; No formal hypothesis testing was planned; WT *RAS*, WT *KRAS* & *NRAS* exons 2/3/4; NR, not reached

PEAK study *RAS* analysis

Efficacy data (longer follow-up analysis)

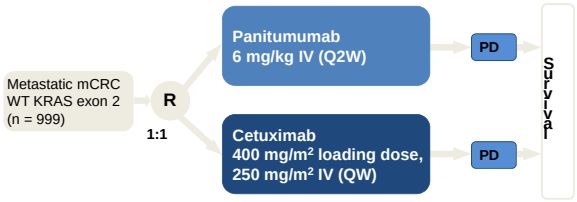
	WT *KRAS* exon 2[1]		WT *RAS*[2]	
	Panitumumab + mFOLFOX6 (n = 142)	Bevacizumab + mFOLFOX6 (n = 143)	Panitumumab + mFOLFOX6 (n = 88)	Bevacizumab + mFOLFOX6 (n = 82)
Median PFS, months (95% CI)	10.9 (9.7–12.8)	10.1 (9.0–12.0)	13.0 (10.9–15.1)	10.1 (9.0–12.7)
Hazard ratio (95% CI)	0.84 (0.64–1.11) P = 0.22		0.66 (0.46–0.95) P = 0.03	
Median OS, months (95% CI)	34.2 (26.6–NR)	24.3 (21.0–29.2)	41.3 (28.8–41.3)	28.9 (23.9–31.3)
Hazard ratio (95% CI)	0.62 (0.44–0.89) P = 0.009		0.63 (0.39–1.02) P = 0.06	

1. Schwartzberg L, et al. J Clin Oncol 2013; 31 (suppl):abstract 3631 (and poster);
2. Karthaus M, et al. EJC 2013; 49 (suppl 3):abstract 2262 (and poster).

WT *RAS*, WT *KRAS* and *NRAS* exons 2/3/4

ASPECCT study

Panitumumab vs. cetuximab in 3rd-line treatment of WT *KRAS* exon 2 mCRC (open-label, phase 3)



- Study endpoints: OS (1°); PFS, ORR, safety
- Crossover between arms during study treatment was not allowed

Price T, et al. EJC 2013; 49 (suppl 3):LBA 18 (and oral presentation);
Protocol ID: 20080763; ClinicalTrials.gov identifier: NCT01001377.

WT *KRAS*, WT *KRAS* in codons 12/13

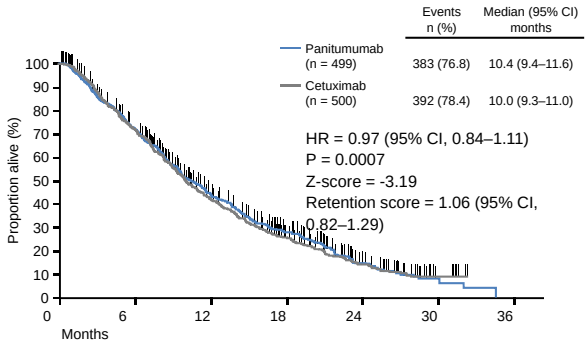
ASPECCT study

Key eligibility criteria

- ≥18 years
- Metastatic adenocarcinoma of the colon or rectum
- WT *KRAS* exon 2 tumour status
- No prior anti-EGFR therapy
- Disease progression or intolerability on irinotecan-, oxaliplatin- and fluorouracil-based therapy for mCRC
- Measurable or non-measurable disease
- Adequate hematologic, renal, hepatic, metabolic function
- No symptomatic brain metastases
- Signed informed consent

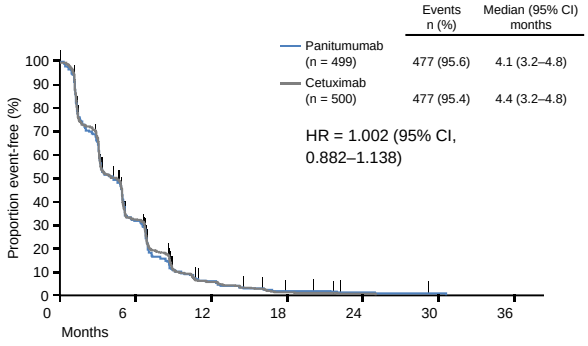
Price T, et al. EJC 2013; 49 (suppl 3):LBA 18 (and oral presentation);
Protocol ID: 20080763; ClinicalTrials.gov identifier: NCT01001377.

ASPECCT study
OS (primary analysis)



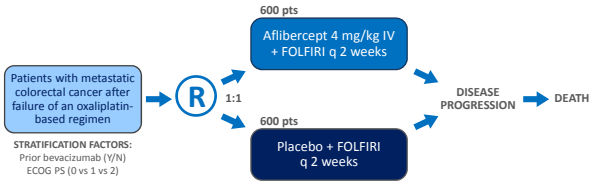
Price T, et al. EJC 2013; 49 (suppl 3):LBA 18 (and oral presentation).

ASPECCT study
PFS (primary analysis)



Price T, et al. EJC 2013; 49 (suppl 3):LBA 18 (and oral presentation).

VELOUR: Aflibercept Phase III Trial in Previously Treated mCRC

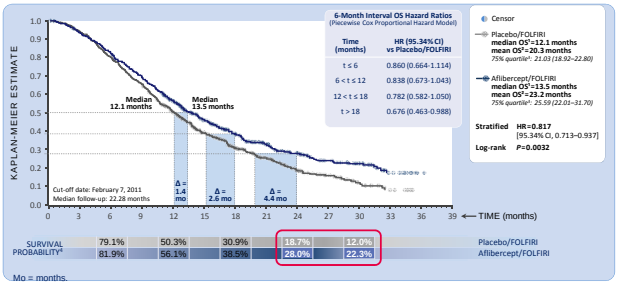


FIRST PATIENT IN: November 2007
ENROLLMENT COMPLETED:
1226 randomized, 1216 treated
Final analysis at 863 OS events

PRIMARY ENDPOINT: OS
SECONDARY ENDPOINTS:
ORR, PFS, safety, **PK**

Van Cutsem E, et al. JCO 2012;30:3499-506

VELOUR: OS results



Van Cutsem E, et al. JCO 2012;30:3499-506

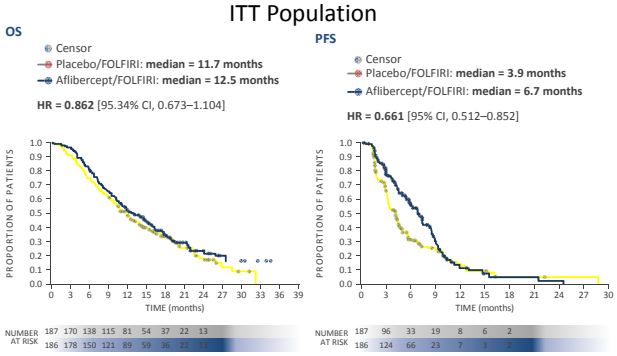
VELOUR: response

EVALUABLE POPULATION* (%)	PLACEBO (N=530)	AFLIBERCEPT (N=531)
BEST OVERALL RESPONSE		
Complete response	0.4	0
Partial response	10.8	19.8
Stable disease	64.9	65.9
Progressive disease	21.5	10.4
Not evaluable	2.5	4.0
OVERALL RESPONSE RATE		
CR or PR	11.1	19.8
95% CI	8.5–13.8	16.4–23.2
P-value**	0.0001	

*Evaluable population: Patients with measurable target lesions that have agreed for third party review.
**Stratified, Cochran Mantel test.

Van Cutsem E, et al. JCO 2012;30:3499-506

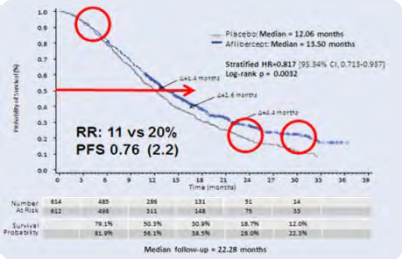
VELOUR: Efficacy data stratified by Prior Bevacizumab – ITT Population



Not powered for direct comparisons (stratification factor)

Allegra, et al. JCO 2012;30(suppl): Abstract 3505.

VELOUR ITT Population: Overall Survival



Modest benefit for all on prior oxaliplatin-based regimen

Large benefit for some

EXPERIMENTAL ARM	12 MONTHS	18 MONTHS	24 MONTHS	30 MONTHS
Absolute OS increase, %*	~6%	~8%	~9%	~10%
Proportional OS increase, %*	~12%	~25%	~50%	~86%

SOURCES: Ruff et al. Eur J Cancer. 2015 Jan;51(1):18-26. Van Cutsem et al. J Clin Oncol. 2012;30:3499-3506.

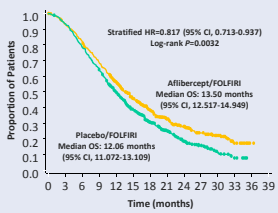
Baseline Characteristics: VELOUR ITT Population vs Better Responders

	BETTER RESPONDERS		ITT POPULATION	
	PLACEBO/ FOLFIRI (n=406)	AFLIBERCEPT/ FOLFIRI (n=404)	PLACEBO/ FOLFIRI (n=614)	AFLIBERCEPT/ FOLFIRI (n=612)
No. metastatic organs involved, %				
0	0.5	0.5	1.0	0.3
1	58.4	56.9	44.1	41.8
>1	41.1	42.6	54.9	57.8
Metastatic sites, %				
Liver	69.7	72.8	70.2	75.0
Lung	39.4	37.6	45.1	44.3
Lymph	21.7	24.8	29.5	28.3
Liver only	33.0	34.9	23.8	25.0
ECOG status, %				
0	77.3	78.5	57.0	57.0
1	22.7	21.5	40.7	40.8
2	0	0	2.3	2.1
Prior bevacizumab, %				
Yes	32.8	32.7	30.5	30.4
No	67.2	67.3	69.5	69.6

SOURCE: Chau et al. BMC Cancer. 2014;14:605.

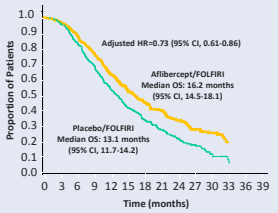
Results: OS in VELOUR ITT Population and Better Responders Subgroup

ITT POPULATION[1]



Median OS difference: 1.4 months

BETTER RESPONDERS[2]



Median OS difference: 3.1 months

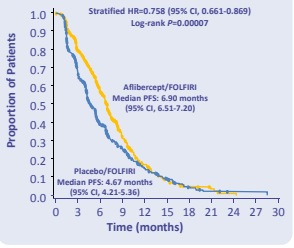
Probability of survival (%) (95% CI)

Placebo/FOLFIRI	83	54	34	22	12
Aflibercept/FOLFIRI	88	64	46	35	27

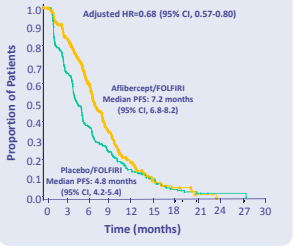
1. Van Cutsem et al. J Clin Oncol. 2012;30:3499-3506. **2.** Chau et al. BMC Cancer. 2014;14:605.

Results: PFS in VELOUR ITT Population and Better Responders Subgroup

ITT POPULATION[1]

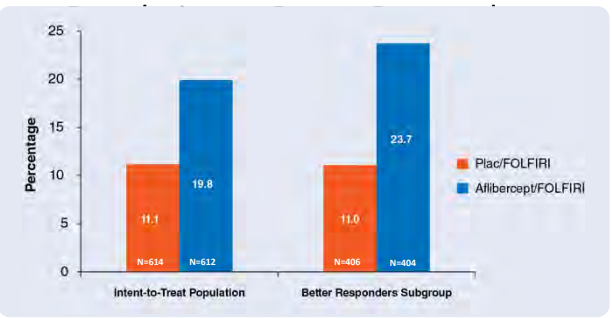


BETTER RESPONDERS[2]



1. Van Cutsem et al. J Clin Oncol. 2012;30:3499-3506. 2. Chau et al. BMC Cancer. 2014;14:605.

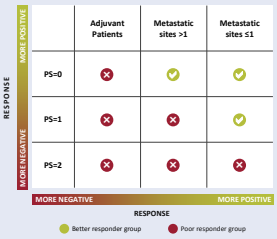
Results: ORR* in VELOUR ITT



*ORR = complete response + partial response.
SOURCE: Chau et al. BMC Cancer. 2014;14:605.

Summary: Good Responder Patient Group Derived Greater Benefit in VELOUR

- Overall survival was improved in the patient subgroup that excluded the adjuvant-only patients and included only those patients with PS 0 or PS 1 with ≤1 metastatic site.
- The probability of survival in the GRP group at 6 months was 83% in the placebo + FOLFIRI group compared with 88% in the aflibercept + FOLFIRI group; over time the difference between the two groups increased:
  - The probability of survival at 12 months was 54% vs. 64%, respectively
  - At 24 months it was 22% vs. 35%, respectively
  - At 30 months, the probability of survival was more than double in the aflibercept + FOLFIRI group (12% vs. 27%, respectively)



SURVIVAL BENEFIT FOR BETTER RESPONDER PATIENTS COMPARED TO POOR RESPONDER PATIENTS IN VELOUR[1]

MEDIAN OS (months)	PLACEBO + FOLFIRI	AFLIBERCEPT + FOLFIRI	Δ MEDIAN OS
BRP group	13.11	16.23	3.12
PRP group	10.35	9.63	-0.72

SOURCE: Chau et al. BMC Cancer. 2014 Aug 20;14:605.

Summary: Efficacy Results in the Better Responders Sub-group of VELOUR - by Prior Bevacizumab Use

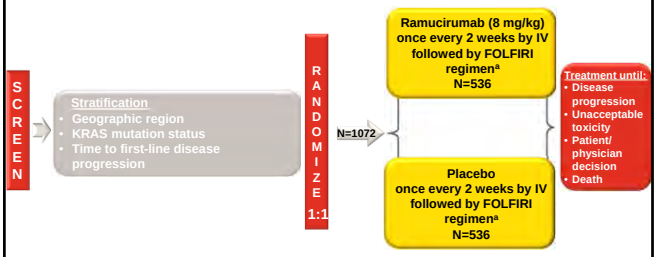
GOOD RESPONDER PATIENTS	PLACEBO + FOLFIRI (N=406) [95% CI]	AFLIBERCEPT + FOLFIRI (N=404) [95% CI]	Δ	HR
Median OS (months)	13.11 [11.70; 14.19]	16.23 [14.49; 18.14]	3.12	0.718 [0.605; 0.851]
Mean OS (months)	18.62	24.83	6.21	-
Median PFS (months)	4.76 [4.24; 5.42]	7.16 [6.77; 8.21]	2.4	0.678 [0.572; 0.803]
	WITH PRIOR BEV (N=133)	**WITH PRIOR BEV (N=132)**		
Median OS (months)	12.29 [10.32; 14.26]	15.47 [13.80; 18.79]	3.18	0.744 [0.551; 1.005]
Mean OS (months)	18.71	22.47	3.76	-
Median PFS (months)	4.17 [3.15; 5.42]	6.93 [5.85; 8.57]	2.76	0.646 [0.475; 0.879]
	WITHOUT PRIOR BEV (N=273)	**WITHOUT PRIOR BEV (N=272)**		
Median OS (months)	13.54 [11.70; 14.72]	16.85 [14.29; 18.76]	3.31	0.707 [0.575; 0.869]
Mean OS (months)	18.53	25.90	7.37	-
Median PFS (months)	5.32 [4.37 ; 5.55]	7.20 [6.80 ; 8.28]	1.88	0.693 [0.566; 0.850]

Consistent with improved OS benefit observed in better responders group, there was also an increase in the incremental benefit in survival when analyzed by prior bevacizumab use.

SOURCE: Chau et al. BMC Cancer. 2014 Aug 20;14:605.

88

RAISE: Study Design

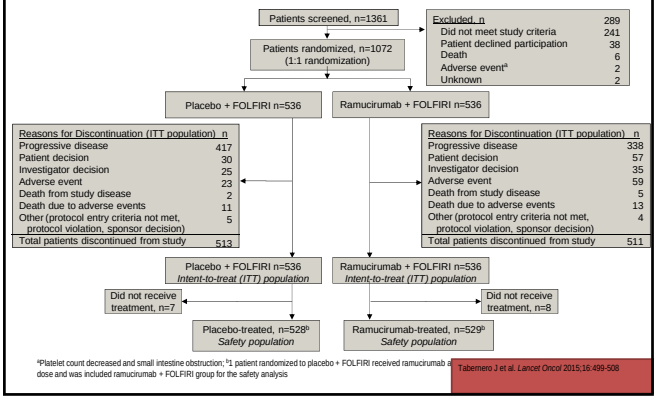


Study Design	Global, placebo-controlled, randomized, double-blind Phase 3 study comparing the efficacy and safety of ramucirumab + FOLFIRI vs. placebo + FOLFIRI as second-line therapy in patients with mCRC whose disease had progressed during or after first-line treatment including bevacizumab
Primary Endpoint	Overall survival

[a]Irinotecan (180 mg/m², 90-minute IV), followed by or concurrent with folinic acid (400 mg/m², 120-minute IV); followed by 5-fluorouracil (400 mg/m² IV bolus over 2-4 minutes); then 5-FU (2400 mg/m² continuous 48-hour infusion)

Tabernero J et al. *Lancet Oncol* 2015;16:499-508

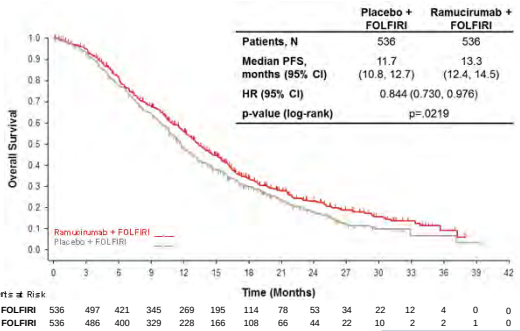
RAISE: Patient Disposition



[a]Platelet count decreased and small intestine obstruction; [b]1 patient randomized to placebo + FOLFIRI received ramucirumab at dose and was included ramucirumab + FOLFIRI group for the safety analysis

Tabernero J et al. *Lancet Oncol* 2015;16:499-508

RAISE: Primary Endpoint – Overall Survival of ITT Population



	Placebo + FOLFIRI	Ramucirumab + FOLFIRI
Patients, N	536	536
Median PFS, months (95% CI)	11.7 (10.8, 12.7)	13.3 (12.4, 14.5)
HR (95% CI)	0.844 (0.730, 0.976)	
p-value (log-rank)	p=.0219	

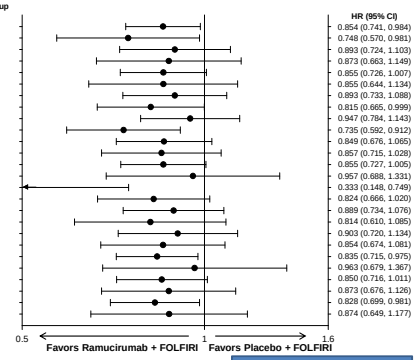
Patients at Risk

Ramucirumab + FOLFIRI	536	497	421	345	269	195	114	78	53	34	22	12	4	0	0
Placebo + FOLFIRI	536	486	400	329	228	166	108	66	44	22	10	2	2	1	0

Tabernero J et al. *Lancet Oncol* 2015;16:499-508

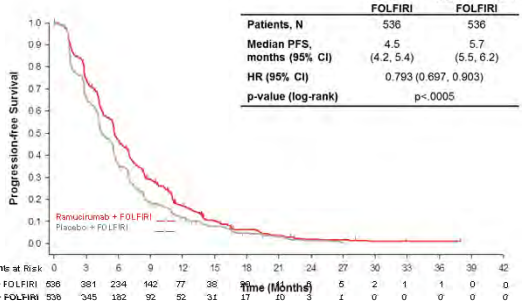
RAISE: Forest Plot – Overall Survival

		PBO Group N	RAM Group N	HR (95% CI)
Overall		536	536	0.854 (0.741, 0.984)
Region	N America	143	143	0.748 (0.570, 0.981)
	Europe	235	235	0.893 (0.724, 1.103)
	Other	158	158	0.873 (0.663, 1.149)
PD from 1st line	≥6 months	407	411	0.855 (0.726, 1.007)
	<6 months	129	125	0.855 (0.644, 1.134)
KRAS status	Mutant	261	269	0.893 (0.733, 1.088)
	Wild-Type	275	267	0.815 (0.665, 0.999)
Sex	Male	326	289	0.947 (0.784, 1.143)
	Female	210	247	0.735 (0.592, 0.912)
Age (years)	≥65	215	212	0.849 (0.676, 1.065)
	<65	321	324	0.857 (0.715, 1.028)
Race	White	410	405	0.855 (0.727, 1.005)
	Asian	103	111	0.957 (0.688, 1.331)
	Other	18	18	0.333 (0.148, 0.749)
ECOG PS	0	259	263	0.824 (0.666, 1.020)
	1+	275	269	0.889 (0.734, 1.076)
# metastatic sites	1	157	171	0.814 (0.610, 1.085)
	≥3	182	157	0.854 (0.674, 1.081)
Liver only metastases	No	441	444	0.835 (0.715, 0.975)
	Yes	95	92	0.963 (0.679, 1.367)
Site of primary tumor	Colon	358	358	0.850 (0.716, 1.011)
	Rectum	171	174	0.873 (0.676, 1.126)
CEA	<200µg/L	393	389	0.828 (0.699, 0.981)
	≥200µg/L	107	108	0.874 (0.649, 1.177)



Tabernero J et al. *Lancet Oncol* 2015;16:499-508

RAISE: Secondary Endpoint – PFS of ITT Population



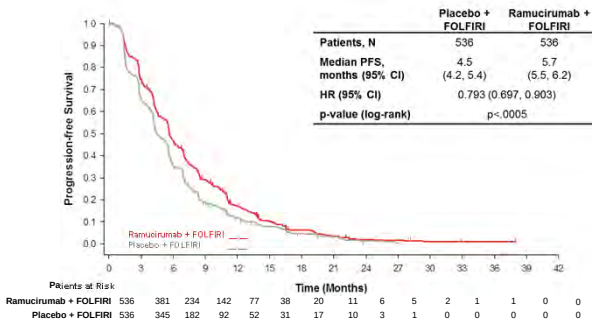
	Placebo + FOLFIRI	Ramucirumab + FOLFIRI
Patients, N	536	536
Median PFS, months (95% CI)	4.5 (4.2, 5.4)	5.7 (5.5, 6.2)
HR (95% CI)	0.793 (0.697, 0.903)	
p-value (log-rank)	p<.0005	

Patients at Risk

Ramucirumab + FOLFIRI	536	381	234	142	77	38	20	14	5	5	2	1	1	0	0
Placebo + FOLFIRI	536	345	182	92	52	31	17	10	3	1	0	0	0	0	0

Tabernero J et al. *Lancet Oncol* 2015;16:499-508

RAISE: Secondary Endpoint – PFS of ITT Population



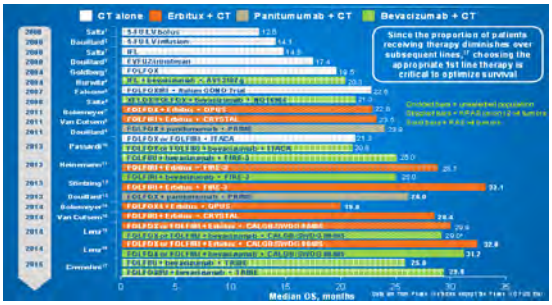
	Placebo + FOLFIRI	Ramucirumab + FOLFIRI
Patients, N	536	536
Median PFS, months (95% CI)	4.5 (4.2, 5.4)	5.7 (5.5, 6.2)
HR (95% CI)	0.793 (0.697, 0.903)	
p-value (log-rank)	p<.0005	

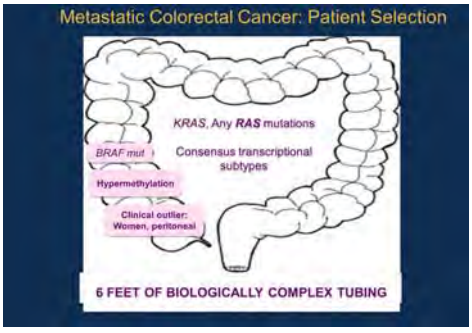
Patients at Risk

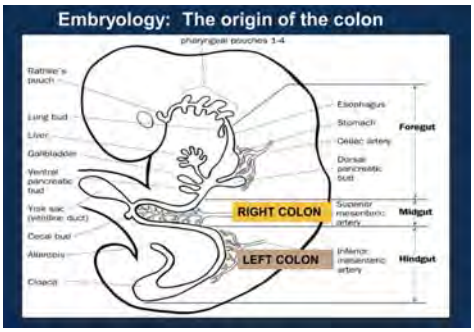
Ramucirumab + FOLFIRI	536	381	234	142	77	38	20	11	6	5	2	1	1	0	0
Placebo + FOLFIRI	536	345	182	92	52	31	17	10	3	1	0	0	0	0	0

Tabernero J et al. *Lancet Oncol* 2015;16:499-508

Podatki iz randomiziranih raziskav 1. reda zdravljenja







mCRC – je stran pomembna?

PUBLICATION (Study)	Patients N	Molecular Selection	Treatment	OUTCOME	RIGHT	LEFT
O'Dwyer JCO, 2001 (E2290)	N = 1120	NONE	5FU VARIATIONS	OS (MOS)	10.9	15.8
Brule, Eur J Can, 2015 (CO.17)	N =399	*KRAS* wt	BSC v. BSC + CET	PFS (MOS)	1.9 1.8	1.9 5.4
Loupakis, JNCI, 2015	N = 2053	NONE	FOLFIRI/BEV FUOX/BEV IFL/BEV	OS (MOS)	24.8 18.0 14.6	42.0 23.0 24.0

Venook A, ASCO 2016

Lokacija je prognostični dejavnik za OS

KRAS wt N = 1025	Right 1° Median OS (mos)	Left 1° Median OS (mos)	Hazard Ratio 95% CI (adjusted*)	P (adjusted*)
All pts	19.4	33.3	1.55 (1.32,1.82)	P < 0.0001
Cet	16.7	36.0	1.87 (1.48, 2.32)	P < 0.0001
Bev	24.2	31.4	1.32 (1.05, 1.65)	P = 0.01

19,3 meseca je velika razlika v OS!

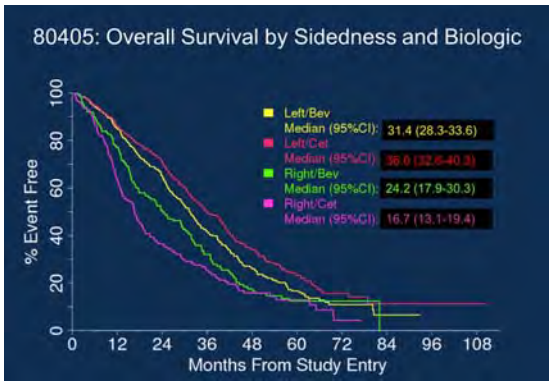
Venook A, ASCO 2016

Median OS by Sidedness: 80405 and FIRE-3*

		Right 1° Median OS (mos)	Left 1° Median OS (mos)	P (adjusted)
		N = 293	N = 732	
KRAS wt N=1025	Cet	16.7	36.0	P < 0.0001
	Bev	24.2	31.4	P = 0.01
		FIRE-3		
		N = 88	N = 306	
All RAS wt N=394	Cet	18.3	38.3	P < 0.00001
	Bev	23.0	28.0	P = 0.038

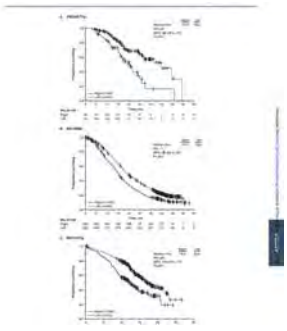
* Sebastian Stintzing,MD, personal communication
Heinemann, et al, ASCO, 2014

Venook A, ASCO 2016



Venook A, ASCO 2016

Primary Tumor Location as a Prognostic Factor in Metastatic Colorectal Cancer

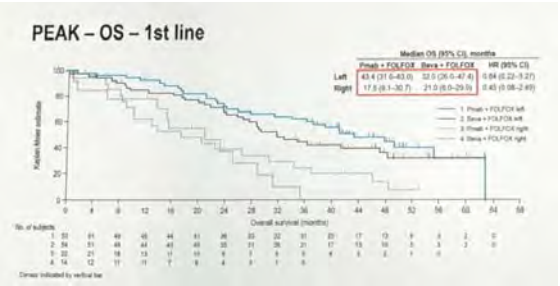


Loupakis F, JNCI 2015

Results – distribution and patients

	RAS WT, n	TS ascertainment, n (%)	Patients/side, n (%)		Treatment, n (%)		
			Left	Right		Left	Right
PRIME (1st line)	512	416 (81)	328 (79)	88 (21)	Pmab + FOLFOX	169 (81)	39 (19)
					FOLFOX	159 (76)	49 (24)
PEAK (1st line)	170	143 (84)	107 (75)	36 (25)	Pmab + FOLFOX	53 (71)	22 (29)
					Beva + FOLFOX	54 (79)	14 (21)
181 (2nd line)	421	368 (87)	298 (81)	70 (19)	Pmab + FOLFIRI	150 (83)	31 (17)
					FOLFIRI	148 (79)	39 (21)

PEAK – OS – 1st line



Bolniki s sistemsko razširjeno boleznijo in dobrim stanjem zmogljivosti naj bi bili deležni zdravljenja s sistemsko terapijo – **kemoterapijo in tarčnimi zdravili**. Srednja preživetja tako zdravljenih bolnikov presegajo **30 mesecev** .

Sistemsko zdravljenje mCRC je čedalje bolj zapleteno, saj imamo na voljo več zdravil in njihovih kombinacij, z različno učinkovitostjo in neželenimi učinki, kar moramo upoštevati pri odločitvi o zdravljenju, kakor tudi biologijo tumorja, zato le-to sodi samo v roke izkušenega internista onkologa, načrtovanje celotnega zdravljenja teh bolnikov pa potrebuje multidiscilinarno obravnavo.

TOKSIČNI SOPOJAVI FLUOROPIRIMIDINOV (KAPECITABIN, 5-FU)

Marko Boc, dr.med.
ONKOLOŠKI INŠTITUT LJUBLJANA
Maja Ravnik, dr.med.
UKC MARIBOR

ŠOLA CRC
LJUBLJANA, NOVEMBER 2016

VSEBINA

- NAJBOLJ POGOSTI TOKSIČNI SOPOJAVI FLUOROPIRIMIDINOV
- UKREPI
- KARDIOTOKSIČNOST
- DPD in DPDd
- KLINIČNI PRIMER BOLNIKA Z HUDO TOKSIČNOSTJO OB KAPECITABINU

NAJBOLJ POGOSTI TOKSIČNI SOPOJAVI KAPECITABINA IN 5-FU

X-ACT

Event	All Grades of Events		Grade 3 or 4 Events (Severe)	
	Capecitabine (N=995)	Fluorouracil plus Leucovorin (N=974)	Capecitabine (N=995)	Fluorouracil plus Leucovorin (N=974)
	percent			
Diarrhea	46†	64	11	13
Nausea or vomiting	36†	51	3	3
Stomatitis	22†	60	2†	14
Hand–foot syndrome	60†	9	17†	<1
Fatigue or asthenia	23	23	1	2
Abdominal pain	10	13	2	1
Alopecia	6†	22	0‡	<1
Lethargy	10	9	<1	<1
Anorexia	9	10	<1	<1
Neutropenia§	32†	63	2†	26
Hyperbilirubinemia§	50†	20	20†	6

Twelves et al. N Engl J Med 2005

KOŽNA TOKSIČNOST (Sindrom roka-noga)

- Kapecitabin, 5-fluorouracil,
- Srednji čas do pojava je 79 dni (11-360),
  - 92,9% znotraj prvih dveh ciklusov [1,2]
- Po prekinitvi KT izboljšanje po 1-2 tednih[2]
- Gradiranje[3]

	ZNAK	SIMPTOM
Gradus 1	eritem	parastezije disestezija
Gradus 2	1+edem	diskomfort bolečina +
Gradus 3	2+razpoke	bolečina ++, oteklina, paronihija
Gradus 4	3+mehurji	bolečina +++, deskvamacija, ulceracija

1. Cassidy J. Clin Colorectal Cancer 2005; 5 (Suppl. 1): 47-50.
2. Abushullaih S et all. Cancer Invest 2002; 20: 3-10.
3. Gressett et al. J Oncol Pharm Pract. 2006; 12: 131-141.

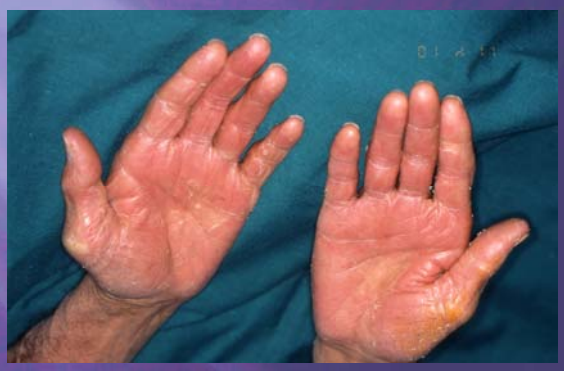
KOŽNA TOKSIČNOST (Sindrom roka-noga)
Prekinitev zdravljenja oz. prilagajanje odmerkov*

	Nadaljevanje th.	Prilagoditev odmerka?
Gradus 1	nadaljevanje z enakim odmerkom	nadaljevanje z enakim odmerkom
Gradus 2		
1. manifestacija	prekinitev do G 0-1	100%
2. manifestacija	prekinitev do G 0-1	75%
3. manifestacija	prekinitev do G 0-1	50%
4. manifestacija	prenehanje zdravljenja	-
Gradus 3		
1. manifestacija	prekinitev do G 0-1	75%
2. manifestacija	prekinitev do G 0-1	50%
3. manifestacija	prenehanje zdravljenja	-
Gradus 4		
1. manifestacija	prenehati oz. če predvidevamo veliko dobrobit zdravljenja prekinitev do G 0-1	50%

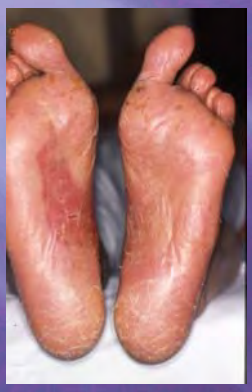
*Gressett et al. J Oncol Pharm Pract. 2006; 12: 131-141.

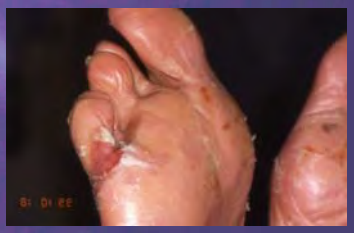
KOŽNA TOKSIČNOST (Sindrom roka-noga)
Primeri 1/4 – STOPNJA 1

KOŽNA TOKSIČNOST (Sindrom roka-noga)
Primer 2/4 – STOPNJA 2-3

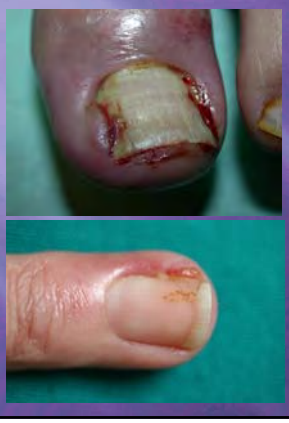


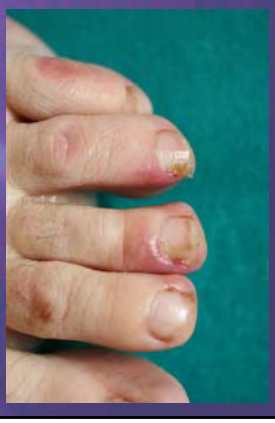
KOŽNA TOKSIČNOST (Sindrom roka-noga)
Primeri 3/4 – STOPNJA 3-4





KOŽNA TOKSIČNOST
Primeri 4/4 – PARONIHIJA





KOŽNA TOKSIČNOST (Sindrom roka-noga) Priporočila glede obvladovanja

- nefarmakološki pristop
  - + dvignjene noge in roke
  - + hlajenje dlani in stopal (hladne kopeli)
  - + izogibanje izpostavljanja kože topli vodi
  - + ohlapna oblačila in obutev
  - + blaga mila
  - + skrbeti za stalno vlažnost in oljnost kože
  - - drgniti kože z brisačo, temveč pivnati
  - - aktivnost, kjer je koža izpostavljena velikemu pritisku in trenju
  - - uporaba gumijastih rokavic
  - - izpostavljanje soncu in vročini
- farmakološki pristop
  - Kreme z vsebnostjo uree
  - Vitamin B_6
  - topični kortikosteroidi
  - pri paronihijah (okužba)
    - antibiotična mazila
    - peroralni AB

*Cancer chemotherapy an Hand-Foot syndrome. http://www.xeloda.com.

DRISKA

- Srednji čas do pojava G_{2-4} je 34 dni[1,2]
- Pogostnost odvajanj presega število, ki je za bolnika običajno
- >5x dnevno ➔ kontakt z zdravnikom

- Svetujemo
  - Uživanje zadostne količine tekočine
  - Rehidracijske raztopine
  - Nega zadnjika (umivanje s hladno vodo, uporaba hladilnih mazil)
  - Dieta (izogibanje mastni in z vlakninami bogati hrani)
  - Ne sveže iztisnjenih sadnih sokov
  - Loperamid hydrochlorid

1. Cassidy J. Clin Colorectal Cancer 2005; 5 (Sippl. 1): 47-50.
2. Abushullaih S et all. Cancer Invest 2002; 20: 3-10.

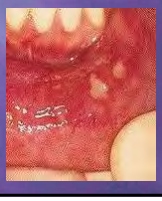
SLABOST, BRUHANJE, IZGUBA TEKA

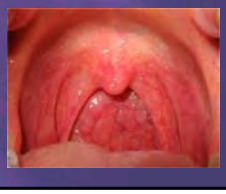
- 2 ali večkrat v obdobju 24 ur

- Svetujemo
  - Uporabo antiemetikov (metoclopramide ali tietilperazin)
  - Več manjših obrokov
  - Izogibanje mastni in ocvrti hrani
  - Pitje nesladkanih, hladnih in bistrih sokov
  - Pitje pred ali po in ne med obrokom
  - Uživanje hrane brez motečega vonja, ki bi lahko sprožil slabost
  - Izogibanje vonjem, ki motijo

STOMATITIS, MUKOZITIS

- Redna nega ustne votline
  - Uporabljanje mehkejše zobne ščetke
  - Izpiranje z žajbljevim ali kamiličnim čajem
- Pitje zadostne količine tekočin (vsaj 2L)
- Uživanje pasirane oz. tekoče hrane





KARDIOTOKSIČNOST FLUOROPIRIMIDINOV 1/2

Opisane vrste kardiotoksičnosti:

1. Angina pektoris
2. Miokardni infarkt
3. Kongestivna odpoved srca
4. Kardiomiopatija
5. VT
6. SVT
7. Podaljšanje QT
8. Nenadna smrt
9. Kardiogeni šok
10. Koronarna disekcija

Možni mehanizmi:

1. Koronarni vazospazem
2. AI poškodba miokarda
3. Poškodba endotelija
4. Trombogeni efekt
5. Direktna miokardna toksičnost zaradi nekroze
6. Globalna disfunkcija
7. Akumulacija metabolitov

Incidenca: 1.2-18%

Odvisna od odmerka.

Bolus: 1.6-3%
Podaljšana inf.: 7.6-18%

BOLNIKI Z ŽE ZNANO KMP!!!

Tsibiribi et al. Bull Cancer, 2006; 93: 27-30.

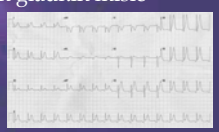
1350 bolnikov brez kardialnih bolezni

1.2% kardiotoksičnosti (MI, KVS, AP)

Sorrentino MF, et al. Cardiol J, 2012; 19(5):453-8.

KARDIOTOKSIČNOST FLUOROPIRIMIDINOV 2/2

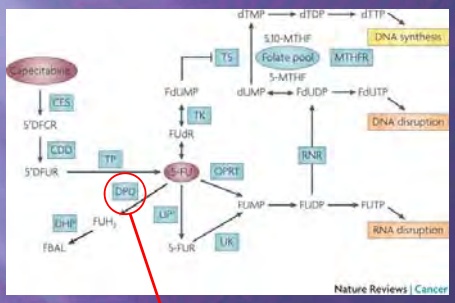
- KVS/AP – najbolj pogost kardialni simptom[1]
  - 19%, lahko traja še 12 ur po ustavitvi inf.[2]
  - bolečina za prsnico v mirovanju z spremembami ST spojnice v EKG, +/- troponin
  - ponavadi so že prisotne aterosklerozne spremembe na koronarnem žilju (ni pa nujno[3])
  - mehanizem: konstrikcija vaskularnih gladkih mišic preko aktivacije protein kinaze C



- prenehanje zdravljenja
  - reindukcija
    - ponovitev v 82-100%[4]
    - 18% smrtnost[5]

1. Meydan N, et al. Jpn J Clin Oncol, 2005; 35: 265-70.
2. Wacker A, et al. Oncology 2003; 65: 108-12.
3. Sorrentino MF, et al. Cardiol J, 2012; 19(5): 453-8.
4. Becker K, et al. Abstract. Drugs, 1999; 57: 475-484.
5. Saif M, et al. Expert Opin Drug Saf, 2009; 8: 191-202.

DPD (dihidropirimidin dehidrogenaza)



Prvi od treh encimov pri metabolizmu 5-fluoropirimidinov

Zadolžen za 80-90% metabolizma

Walther A, et al. Nature Reviews Cancer 9 (July 2009), 489-499.

DPD deficienca (DPDd) 1/4

Avtosomno recesivno dedovanje

- Znanih preko 40 mutacij in polimorfizmov dihidropirimidin dehidrogenaznega gena (DPYD), ki vodijo v zmanjšano aktivnost DPD

Bolniki na 5-FU s hudo toksičnostjo: 30-57% zaradi DPDd[2,3]

- Prevalenca[1]:
  - delno pomanjkanje: 3 - 5% bolnikov z rakom
  - popolno pomanjkanje: 0,5% bolnikov z rakom
  - pogojeno z raso in spolom,
    - najnižja incidenca pri belcih,
    - večja pri ženskah (2x)

DPD aktivnost < 95 percentila N

N=0.182-0.688 nmol/min/mg proteina

DPD aktivnost < 99 percentila N oz. nedetektibilno

1. Law L, et al. J Adv Pract Oncol. 2014 May-Jun; 5(3): 205–210.
2. Morel A, et al. Cancer Therapeutics, 2006, 5 (11), 2895-2904.
3. van Kuilenburg AB, et al. International Journal of Cancer, 2002, 101 (3), 253-258.

DPD deficienca (DPDd) 2/4

- Popolno ali delno pomanjkanje aktivnosti vodi v hudo toksičnost
  - Akumulacija toksičnih produktov in prolongirana izpostavljenost 5-FU

Hud mukozitis
H-F Sy
Huda diareja
Nevtropenija
Cerebelarna ataksija
Cerebelarna disfunkcija

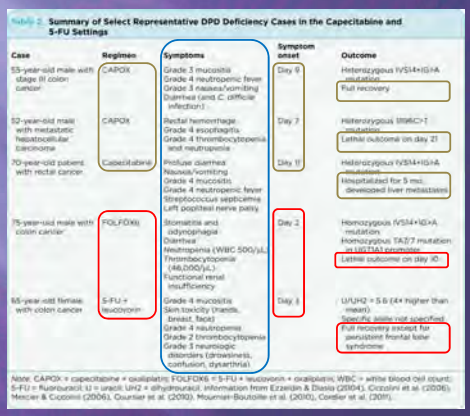
Smrt (100%) pri 100% DPDd

G3-4 Kepecitabin

G3-4 5-FU

Law L, et al. J Adv Pract Oncol. 2014 May-Jun; 5(3): 205–210.

DPD deficienca (DPDd) 3/4



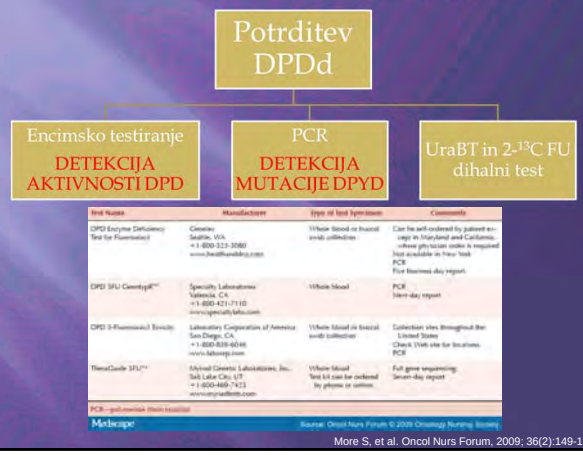
Summary of Select Representative DPD Deficiency Cases in the Capecitabine and 5-FU Settings

Case	Regimen	Symptoms	Symptom onset	Outcome
55-year-old male with stage III colon cancer	CAPOX	Grade 3 mucositis Grade 4 neutropenic fever Grade 3 nausea/vomiting Diarrhea (and *C. difficile* infection)	Day 9	Heterozygous IVS14+1G>A mutation Full recovery
52-year-old male with metastatic hepatocellular carcinoma	CAPOX	Rectal hemorrhage Grade 4 esophagitis Grade 4 thrombocytopenia and neutropenia	Day 7	Heterozygous 1896C>T mutation Lethal outcome on day 21
70-year-old patient with rectal cancer	Capecitabine	Profuse diarrhea Nausea/vomiting Grade 4 mucositis Grade 4 neutropenic fever Streptococcus septicemia Left popliteal nerve palsy	Day 11	Heterozygous IVS14+1G>A mutation Hospitalized for 5 mo; developed liver metastases
75-year-old male with colon cancer	FOLFOX6	Stomatitis and odynophagia Diarrhea Neutropenia (WBC 500/μL) Thrombocytopenia (46,000/μL) Functional renal insufficiency	Day 2	Homozygous IVS14+1G>A mutation Homozygous TA7/7 mutation in UGT1A1 promoter Lethal outcome on day 10
65-year-old female with colon cancer	5-FU + leucovorin	Grade 4 mucositis Skin toxicity (hands, breast, face) Grade 4 neutropenia Grade 2 thrombocytopenia Grade 3 neurologic disorders (drowsiness, confusion, dysarthria)	Day 8	U/UH2 = 5.6 (4× higher than mean) Specific allele not specified Full recovery except for persistent frontal lobe syndrome

Note: CAPOX = capecitabine + oxaliplatin; FOLFOX6 = 5-FU + leucovorin + oxaliplatin; WBC = white blood cell count; 5-FU = fluorouracil; U = uracil; UH2 = dihydrouracil. Information from Ezzeldin & Diasio (2004), Cizzolini et al. (2006), Mercier & Cuzzolini (2006), Courtier et al. (2010), Mourmat-Boutoille et al. (2010), Cortier et al. (2011).

Law L, et al. J Adv Pract Oncol. 2014 May-Jun; 5(3): 205–210.

DPD deficienca (DPDd) 4/4



More S, et al. Oncol Nurs Forum. 2009; 36(2):149-152.

KLINIČNI PRIMER 1/8

- 04/2013
- 63-letni bolnik
- Stanje po R0 resekciji adenokarcinoma sigme
  - pT3N0(0/25)M0 ➔ stadij IIA
  - VI+
- 26.04.2013
  - Začne dopolnilno terapijo z kapecitabinom
  - Odmerek 2000mg/12^{h}

KLINIČNI PRIMER 2/8

- 09.05.2013 (14 dni)
- Sprejem v dežurstvu
- Kapecitabin je jemal 7 dni
  - Vnetje v ustih
  - Težave z hranjenjem in pitjem tekočin
  - Driska
  - Pekoče in pordele dlani in podplati
- Ob sprejemu
  - WHO 3
  - Mukozitis
  - Huda oslabelost
  - HFsy 1-2 stopnje

Laboratorij ob sprejemu:

L 4,59
N 3,26
Hb 134
TR 88
CRP 22

KLINIČNI PRIMER 3/8

- 10.-17.05.2013
  - Postane febrilen
  - Prejme AB in AM
  - Parenteralna prehrana
  - Parenteralna hidracija
  - Iz HK E. colli ➔ G- sepsa
  - Menjan AB po antibiogramu
  - Transfuzija E in T
- 17.05.2014 pljučni edem

Laboratorij 4 dan hospitalizacije

L 0,23
Hb 103
TR 11
CRP 126

Laboratorij 6 dan hospitalizacije

L 0,27
Hb 87
TR 10
CRP 221
pCT 9,1

KLINIČNI PRIMER 4/8

- 20.05.2013
- Hemodinamsko nestabilen
- Premestitev na INT. ODD.
  - Respiratorna insuficienca
  - ARDS – intubacija
  - Hidrokortizon
  - Hemodinamska podpora z NA
  - Poslabšanje enterokolitisa
    - Paralitični ileus
  - Poslabšanje kožne toksičnosti
    - epidermoliza
  - Maksimalna AB in AM th.
    - Conet, Vankomicin, Anidulafungin, Tavanic
  - Krvavitev iz sluznic
  - Transfuzije T in E
  - Prejme rastni dejavnik

Laboratorij 11 dan ob premestitvi na INT.

L 0,49
Hb 81
TR 7
CRP 214
pCT 32
Bill 116/102
AST 5,7
ALT 1,58
Kreatinin 122
Sečnina 32
PČ/INR 0,23/2,79

KLINIČNI PRIMER 8/8

- Dokazana invazivna okužba z Aspergillus-om
- Multiorganska odpoved

- 22.05.2013
- 13. dan po sprejemu bolnik umre kljub **MAKSIMALNI PODPORNI TERAPIJI**

Laboratorij 13 dan hospitalizacije

L 0,31
Hb 69
TR 7
CRP 221
pCT 9,1
PČ/INR 0,18/3,96
Kreatinin 210
Sečnina 28,6
D-dimer 10840
Bill 161/138
AST 19,4
ALT 7,99
LDH 30
CRP 158
PCT 30

HVALA ZA POZORNOST

LAČN SM FUL DRUGAČN!

Toksičnost tarčnih zdravil pri zdravljenju tumorjev prebavil

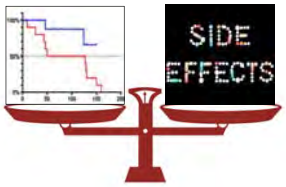
Maja Ebert Moltara
Onkološki inštitut Ljubljana

30. november 2016

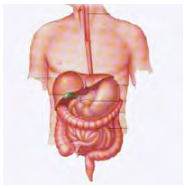
Definicija:
Tarčna zdravila so tista, katerih mehanizem delovanja v razvoju/rasti rakave celice, je natančno poznan.

Delujejo lahko preko znanih tarčnih molekul ali v posameznih stopnjah v celičnem razvoju.

Namen uporabe zdravil v obravnavi raka prebavil:
- ozdravitev
- **preživetje**
- **zmanjšanje simptomov**



Uporaba tarčnih zdravil - ESMO/NCCN guidelines



požiralnik	herceptin (HER2+) ramicirumab
želodec	herceptin (HER2+) ramicirumab
debelo črevesja/	bevacizumab aflibercept cetuksimab panitumumab regorafenib
trebušna slinavka	/
jetra	sorafenib
žolčni vodi	/

KARDIOTOKSIČNOST

GASTROINTESTINALNA TOKSIČNOST

LEDVIČNA TOKSIČNOST

KOŽNA TOKSIČNOST

KARDIOTOKSIČNOST

ARTERIJSKA HIPERTENZIJA
DIASTOLNA DISFUNKCIJA
PODALJŠANJE QTc DOBE
TROMEMBOLIČNI ZAPLETI

KARDIOTOKSIČNOST

ARTERIJSKA HIPERTENZIJA

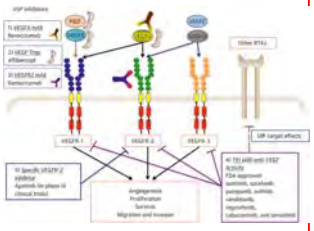
DIASTOLNA DISFUNKCIJA

PODALJŠANJE QTc DOBE

TROMEMBOLIČNI ZAPLETI

ARTERIJSKA HIPERTENZIJA

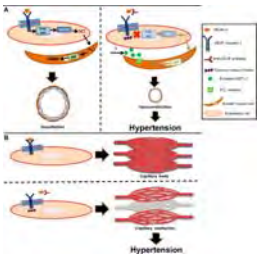
- Najpogosteje pri zdravilih, ki delujejo na nivoju VEGF liganda ali njegovega receptorja VEGFR
- Zdravila:
  - monoklonska protitelesa, ki se vežejo na VEGF ligand (bevacizumab)
  - fuzijska molekular VEGFR, ki vežejo VEGF ligand (aflibercept)
  - monoklonsko telo, ki se veže na VEGFR-2 in blokira njegovo aktivacijo (ramicirumab)
  - TKI male molekule (sorafenib, regorafenib,...)



ARTERIJSKA HIPERTENZIJA

MEHANIZEM:

- VEGF zvišuje delovanje endotelijske NO sitetaze in s tem nivo dušikovega oksida (NO), ki je vazodilatator. Anti-VEGF zdravila zato znižujejo nivo endogenega NO v stenah ožilja, kar vodi v vazokonstrikcijo in zvišan krvi tlak.
- VEGF inhibicija moti zaznavo baroreceptorjev in zvišuje tonus žilja.
- Zmanjšan razvoj arteriol in kapilar, „otrdelost" ožilja zvišuje periferni odpor
- Zmanšanje izločanje Na in s tem povečanje srčnega afterloada



ARTERIJSKA HIPERTENZIJA

Definicija:

Gradus 1	Prehipertenzivno stanje	**systolic BP 120 - 139 mm Hg** or **diastolic BP 80 - 89 mm Hg**
Gradus 2	Stopnja 1 hipertenzije	**systolic BP 140 - 159 mm Hg** or **diastolic BP 90 - 99 mm Hg**; medical intervention indicated; recurrent or persistent (>=24 hrs); symptomatic increase by >20 mm Hg (diastolic) or to >140/90 mm Hg if previously WNL; monotherapy indicated
Gradus 3	Stopnja 2 hipertenzije	**systolic BP >=160 mm Hg** or **diastolic BP >=100 mm Hg**; medical intervention indicated; more than one drug or more intensive therapy than previously used indicated
Gradus 4	Življenje ogrožujoča hipertenzija	malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis; urgentintervention indicated

CTCAE4.02

ARTERIJSKA HIPERTENZIJA

POGOSTOST (SMPC):

	vsi gradusi	gradus 3/4	opombe
bevacizumab	42%	do 17% (do 1%)	brez JO25567
aflibercept	41%	do 19% (0,2%)	mCRC bolniki
regorafenib	30%	7,6% (0%)	mCRC bolniki
ramucirumab	25%	14%	RAINBOW
sorafenib	16%	1,8%	Yan Li et al. A Systematic Review and Meta-Analysis

ARTERIJSKA HIPERTENZIJA

OBRAVNAVA:

- natančna anamneza in ocena tveganja za kardiovaskularne zaplete
- individualno odločanje – tveganje/dobrobit
- bolniki primerni za pričetek zdravljenja RR pod 140/90, bolniki s SB ali ledvično insuficienco pod 130/80
- nato reden nadzor krvnega tlaka, sprva tedensko (2 ciklusa), nato na 2-3 tedne

ZDRAVLJENJE:
- nefarmakološko (gibanje, prehrana, sol?)
- farmakološko

Kdaj pričeti s terapijo:
- tlak nad 140/90
- sistolični nad 160 mmHg
- diastolični nad 100 mmHg
- porast diastoličnega za 20mmHg

ARTERIJSKA HIPERTENZIJA

Class of drug	Cancer-specific cautions or reasons to avoid	Basis for preferred selection	General cautions and contraindications
Angiotensin-converting enzyme inhibitors	Coadministration/titration with renal clearance–dependent agents (eg, cisplatin and pemetrexed); hyperkalemia	Left ventricular systolic dysfunction; diabetic nephropathy	Renovascular disease; peripheral vascular disease; renal impairment
Angiotensin II receptor blockers	Coadministration/titration with renal clearance–dependent agents (eg, cisplatin and pemetrexed); hyperkalemia	Intolerance of other agents, especially ACE inhibitors; left ventricular systolic dysfunction; diabetic nephropathy	Renovascular disease; peripheral vascular disease; renal impairment
Beta blockers	Asthenia; malaise; fatigue; QT interval prolonging drugs	Angina; history of myocardial infarction; anxiety	Bradycardia/heart block; diabetes (risk for hypoglycemia); asthma/ chronic obstructive pulmonary disease (wheezing); decompensated heart failure
Calcium channel blockers (eg, dihydropyridines)	Lower extremity swelling	Elderly patients; isolated systolic hypertension	Preexisting edema; slow onset of action
Thiazide diuretics	Gout; hypercalcemia; hypokalemia; young patients (age ≤45 yr); QT interval prolonging drugs	Elderly patients; isolated systolic hypertension; secondary stroke prevention; typically least expensive	Gout; documented sulfa allergy

KARDIOTOKSIČNOST

ARTERIJSKA HIPERTENZIJA
DIASTOLNA DISFUNKCIJA
PODALJŠANJE QTc DOBE
TROMEMBOLIČNI ZAPLETI

TROMEMBOLIČNI ZAPLETI (TEZ)

PROTOTIP: BEVACIZUMAB

- Arterijski tromembolični zapleti
  - možganski infarkt, TIA, srčni infarkt, angina pektoris
- Venski tromembolični zapleti
  - globoka venska tromboza, pljučna embolija, tromboflebitis

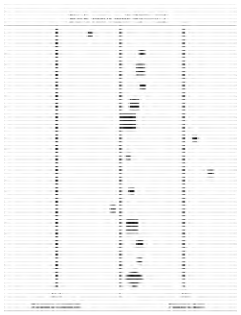
TROMEMBOLIČNI ZAPLETI (TEZ)

PROTOTIP: BEVACIZUMAB

- Arterijski tromembolični dogodki
  - pri bolnikih, ki prejemajo bevacizumab (SMPC) se ugotavlja
    TEZ v 3,8% vs 2,1%
    zapleti s smrtjo 0,8 vs. 0,5%
    TIA 2,7 vs 0,5%
    miokardni infarkt 1,4 vs 0,7%
  - pri bolnikih na bevacizumabu, ki so
    že imeli srčni infarkt je verjetno ponovitve 5x večja
    stari nad 65 let 3x večja
    imajo arterijsko hipertenzijo 2x večja

Bolniku, ki utrpi arterijsko TEZ, je potrebno prekiniti zdravljenje z bevacizumabom.

TROMEMBOLIČNI ZAPLETI (TEZ) - BEVACIZUMAB



Meta-analiza 22 RCT
- 13285 bolnikov mCRC

Incidenca ATE: 2.3% vs 1,1%

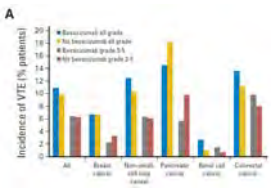
Tveganje (RR): 1,627 (P .005)

62% ↑ tveganje za ATE

Abdullah K. Et al. **Thromboembolic Events Associated with Bevacizumab plus Chemotherapy for Patients with Colorectal Cancer: A Meta-Analysis of RandomizedControlled Trials**

TROMEMBOLIČNI ZAPLETI (TEZ) - BEVACIZUMAB

- Venski trombembolični dogodki (SMPC)
  - incidenca 2,8% – 17,3% (grade 3-5: 7,8 vs 4,9%)

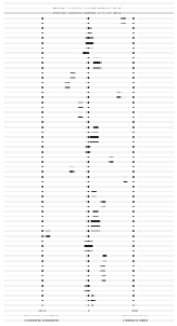


Pooled anlysis 10 RCT
6055 bolnikov

Incidenca any G: 10,9% vs 9,8%
G3-5: 6,4 vs 6,3%

Herbert I. Hurwitz et al. Venous Thromboembolic Events With Chemotherapy Plus Bevacizumab: A Pooled Analysis of Patients in Randomized Phase II and III Studies

TROMEMBOLIČNI ZAPLETI (TEZ) - BEVACIZUMAB



Meta-analiza 22 RCT
- 13285 bolnikov mCRC

Incidenca VTE: 8% vs 6,5%

Tveganje (RR): 1,244 (P .001)

24% ↑ tveganje za VTE

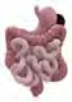
Abdullah K. Et al. **Thromboembolic Events Associated with Bevacizumab plus Chemotherapy for Patients with Colorectal Cancer: A Meta-Analysis of RandomizedControlled Trials**

TROMEMBOLIČNI ZAPLETI (TEZ)

	all TE	ATE	VTE	opombe
bevacizumab	10%	2,3%	8% (G3-4: 6%)	
aflibercept	13%	2,6% (G3-4: 1,8%)	9,3% (G3-4: 7,9%)	
regorafenib	12%	=	=	CORRECT
ramucirumab	NP			
sorafenib	4%	1,4%	3,2%	
cetuksimab	5,7% (vs. 3,9%)			
panitumumab	6,1% (vs. 4,8%)			

TK Choueiri e al. **Risk of arterial thromboembolic events with sunitinib and sorafenib: a systematic review and meta-analysis of clinical trials**

GASTROINTESTINALNA TOKSIČNOST



DRISKA

GIT KRVAVITVE/PERFORACIJE

CELJENJE RAN

HEPATOTOKSIČNOST

DVIG ENCIMOV TREBUČNE SLINAVKE

GASTROINTESTINALNA TOKSIČNOST

Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by frequent and watery bowel movements					
Intra-abdominal hemorrhage	-	Medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding in the abdominal cavity.					
Colonic perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a rupture in the colonic wall.					
Alkaline phosphatase increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Definition: A finding based on laboratory test results that indicate an increase in the level of alkaline phosphatase in a blood specimen.					
Aspartate aminotransferase increased	>ULN - 3.0 x ULN	Asymptomatic with AST >3.0 - 5.0 x ULN; >3 x ULN with the appearance of worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia	>5.0 - 20.0 x ULN; >5 x ULN for >2 weeks	>20.0 x ULN	-

GASTROINTESTINALNA TOKSIČNOST

DRISKA

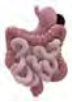
GIT KRVAVITVE/PERFORACIJE

CELJENJE RAN

HEPATOTOKSIČNOST

DVIG ENCIMOV TREBUČNE SLINAVKE

GASTROINTESTINALNA TOKSIČNOST - DRISKA

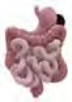


MEHANIZEM:
- driska ob zdravlenju z EGFR inhibitorji se pojavi po 2 tednih
- Korelira z odmerki zdravila (ne s serumsko koncentracijo)

- EGFR je močno izražen na celicah normalne sluznice, ki uravnava sekrecijo Cl in absorbcijo Na
- Inhibicija EGFR zato vodi v sekrecijsko drisko

INCIDENCA
- monoklonskih EGFR: 20 – 28%, le redko G3-4 (1-2%)
- TKI: 50-60%, G3-4: 5% (dose limiting)
  - Sorafenib: 39%, 8% G3
- Anti VEGF
  - Bevacizumab 12%, 0 G3-4

GASTROINTESTINALNA TOKSIČNOST - DRISKA



OBRAVNAVA:

- izključi druge možnosti driske (okužbe,...)
- izključi uporabo odvajal
- standardni postopki: hidracija, prilagoditev prehrane
- terapija izbora: loperamid
  (opiatni agonist brez prehajanja v CŽS in učinka na bolečino)
- razmisli o prilagoditvi odmerka (zlasi pri TKI)
- ob hudih driskah – nadzor bolnika?

GASTROINTESTINALNA TOKSIČNOST

DRISKA

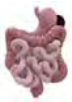
GIT KRVAVITVE/PERFORACIJE

CELJENJE RAN

HEPATOTOKSIČNOST

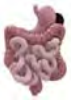
DVIG ENCIMOV TREBUČNE SLINAVKE

GASTROINTESTINALNA TOKSIČNOST – CELJENJE/PERFORACIJE



- Najpogosteje pri zdravilih, ki delujejo na nivoju VEGF, saj je le ta pomembni del v kompleksnem mehanizmu angioneogenezi.
- BEVACIZUMAB je povezan z 4,5% zapleti ob celjenju posoperativnih ran.
- elektivne operacije se odsvetujejo 28 - 48 dni po aplikaciji zdravila
- po večjih operacijah se svetuje, da se z aplikacijami ne prične prej kot po 28 dneh
- razpolovni čas BEVACIZUMABA je 21 dni

GASTROINTESTINALNA TOKSIČNOST – CELJENJE/PERFORACIJE

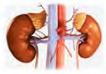


- **INCIDENCA** GI PERFORACIJ: 2,4%
- Pri tem gre za življenje ogrožajoče stanje – smrtnost 30%
- Prepozavanje:
  - abdominalne bolečine, zaprtje, bruhanje

MEHANIZEM: neznan

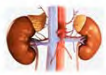
- regres tumorskega tkiva
- perforacija na mestu operacije
- Infekt, abces, divertukul, fistula

LEDVIČNA TOKSIČNOST

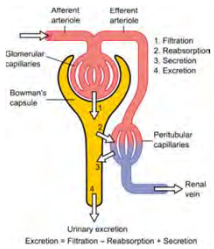


- poškodbe na nivoju nefrona
  - poškodbe glomerulov (glomerulonefritis, proteinurija)
  - poškodbe tubulov tubularna acidoza, motnje v distalnih tubulih)
  - intersticijske poškodbe
    (alergični intersticijski nefritisi)
- poškodbe zaradi motenj v prekrvavitvi
  (trombotična mikroangiopatija)

LEDVIČNA TOKSIČNOST



- Najpogosteje pri zdravilih, ki delujejo na nivoju VEGF liganda ali njegovega receptorja VEGFR

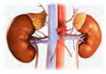


MEHANIZEM:
VEGF ima pomembno vlogo v delovanju glomerulov in peritubularnem žilju.
Anti-VEGF tako motijo prekrvavitev glomerulov vpliv na permeabilnost) in posledično proteniurijo.

LEDVIČNA TOKSIČNOST

Monoklonska protitelesa	
BEVACIZUMAB	Proteinurija
	Nefrontski sindrom
	Glomerulonefritis
	Intersticijski nefritis
	Trombotična mikroangiopatija
CETUKSIMAB	Hipomagnesemija
PANITUMUMAB	Hipomagnesemija
TKI	
SORAFENIB	Intersticijski nefritis

LEDVIČNA TOKSIČNOST



Klasifikacija:

- poškodbe na nivoju nefrona
  - poškodbe glomerulov
    (glomerulonefritis, **proteinurija**)
  - poškodbe tubulov
    (Fanconijev sindrom, tubularna acidoza, motnje v distalnih tubulih)
  - intersticijske poškodbe
    (alergični intersticijski nefritisi)
- poškodbe zaradi motenj v prekrvavitvi
  (trombotična mikroangiopatija)

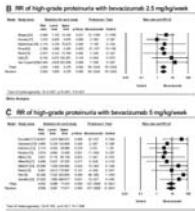
LEDVIČNA TOKSIČNOST - PROTEINURIJA

	Grade				
Adverse Event	1	2	3	4	5
Proteinuria	1+ proteinuria; urinary protein <1.0 g/24 hrs	Adults: 2+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs; Pediatric: urine P/C (Protein/Creatinine) ratio 0.5 - 1.9	Adults: urinary protein >3.5 g/24 hrs; Pediatric: urine P/C >1.9	-	-

Definition: A disorder characterized by laboratory test results that indicate the presence of excessive protein in the urine. It is predominantly albumin, but also globulin.

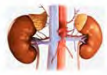
PROTOTIP: BEVACIZUMAB
Meta-analiza 16 RTC: 12568 pts

Low dose 2,5mg/teden: tveganje 1,4
High dose 5mg/teden: tveganje 2,2



Shenhong Wu et al. Bevacizumab Increases Risk for Severe Proteinuria in Cancer Patients

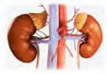
LEDVIČNA TOKSIČNOST - PROTEINURIJA



	incidenca	Gradus 3(4)	opombe
bevacizumab	0,7 -54,7%	8,1% (1,4%)	SMPC
aflibercept	62,2%	7,9% (0,5%)	SMPC
regorafenib	7,4%	1,4	SMPC, Meta-analiza TKI: 6882 pts
ramucirumab	5,8-17%	2%	Meta-analiza: 5694 pts
sorafenib	11, 6 (18,7% TKI)	0,9% (TKI 2,4%)	Meta-analiza TKI: 6882 pts
cetuksimab	/	/	SMPC
panitumumab	/	/	SMPC

Abdel-Rahman O et al. **Proteinuria in Patients with Solid Tumors Treated with Ramucirumab: A Systematic Review and Meta-Analysis**
Ze-Feng Zhang. **Risks of Proteinuria Associated with Vascular Endothelial Growth Factor Receptor Tyrosine Kinase Inhibitors in Cancer Patients: A Systematic Review and Meta-Analysis**

LEDVIČNA TOKSIČNOST - PROTEINURIJA

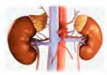


OBRAVNAVA PROTEINURIJE:

Pred vsako aplikacijo BEVACIZUMABA/AFLIBERCEPT je potrebno določiti proteinurijo.

Če je v urinu več kot 2g/24H urinu je potrebno z zdravilom prekiniti, do izboljšanja ledvične funkcije.

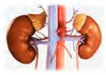
LEDVIČNA TOKSIČNOST



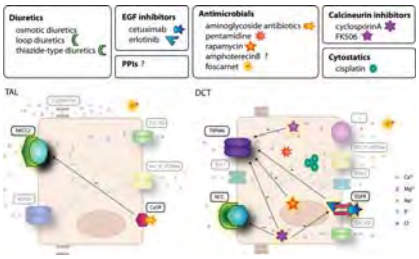
Klasifikacija:

- poškodbe na nivoju nefrona
  - poškodbe glomerulov
    (glomerulonefritis, proteinurija)
  - poškodbe tubulov
    (Fanconijev sindrom, **tubularna acidoza**, motnje v distalnih tubulih)
  - intersticijske poškodbe
    (alergični intersticijski nefritisi)
- poškodbe zaradi motenj v prekrvavitvi
  (trombotična mikroangiopatija)

LEDVIČNA TOKSIČNOST – TUBULARNA ACIDOZA

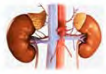


- Najpogosteje pri zdravilih, ki delujejo na nivoju EGFR
- ZNAČILNOST: znižan Mg



Anke L. LAMERIS et al. Drug-induced alterations in Mg2+ homoeostasis.

LEDVIČNA TOKSIČNOST – TUBULARNA ACIDOZA



OBRAVNAVA HIPOMAGNEZEMIJE:

- Ob uporabi zdravil, ki delujejo na EGFR
  konrola Mg v serumu, zlasti če je prisotna utrujenost in hipokalcemija.
- Nadomeščanje.

KOŽNA TOKSIČNOST

TOKSIČNOST EGFR ZDRAVIL

TOKSIČNOST TKI ZDRAVIL

KOŽNA TOKSIČNOST

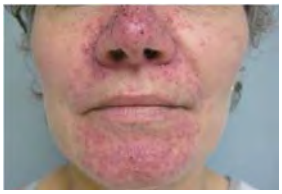
TOKSIČNOST EGFR ZDRAVIL

TOKSIČNOST TKI ZDRAVIL

KOŽNA TOKSIČNOST – EGFR ZDRAVILA

Kožne spremembe:

- Akneformni izpuščaj
- Suha koža
- Ekcem
- Fisure
- Spremembe na nohtih
- Spremembe na laseh, obrveh
- Teleangiektazije
- hiperpigmentacija



KOŽNA TOKSIČNOST

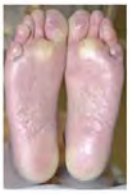
TOKSIČNOST EGFR ZDRAVIL

TOKSIČNOST TKI ZDRAVIL

KOŽNA TOKSIČNOST – TKI ZDRAVILA

Kožne spremembe:

- Hand-foot-skin reaction
- Asimptomatske krvavitve pod nohti
- Suha koža in sluznice



HVALA!

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MRI IN PET-CT PRI NAČRTOVANJU OBSEVANJA TUMORJEV PREBAVIL

mag. Franc Anderluh, dr.med.

5. šola tumorjev prebavil
Onkološki inštitut
30.11.2016

Uporabnost modernih slikovnih preiskav (CT, MRI, PET-CT) v onkologiji:

1. **Diagnostika**
2. **Spremljanje odgovora na zdravljenje – med in po zaključenem zdravljenju**
3. **Načrtovanje obsevanja**

CT

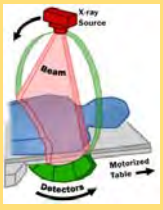
Snemanje večjega števila rentgenskih posnetkov pod različnimi koti okoli ene osi rotacije

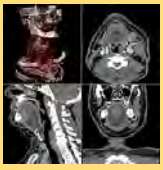
↓

Digitalno geometrijsko procesiranje iz večjega števila 2-D rentgenskih slik

↓

Tomografski posnetki („virtualne rezine“) struktur v notranjosti telesa z možnostjo prikaza v različnih ravninah in 3-D rekonstrukcijo





CT

- v uporabi od 1970 dalje
- uporaba v medicini, industriji, arheologiji
- problem izpostavljenosti ionizirajočemu sevanju
- danes večinoma spiralni CT-ji z večrezinskimi („multi-slice“) detektorji → hitrejša preiskava in nižja izpostavljenost sevanju

MRI

- slikanje z magnetno resonanco je tehnika, s katero lahko prostorsko odvisnost obnašanja atomskih jeder v magnetnem polju prikažemo kot dvo ali tridimenzionalno sliko
- za slikanje uporabljamo pojav jedrske magnetne resonance, kjer magnetni momenti atomskih jeder v zunanjem magnetnem polju procesirajo okrog smeri zunanjega magnetnega polja

MRI

Bolnik leži na premični mizi, ki jo lahko premaknemo v močno magnetno polje, ki ga generira cirkularni magnet.

↓

V magnetnem polju pride do poravnavanja protonov vodikovih atomov v molekulah (voda in maščoba!), ki jih nato izpostavimo snopu radijskih valov.

↓

To povzroči zasuk protonov, ki ga detektorji zaznajo v obliki šibkega signala. Jakost signala je povezana z gostoto protonov v tkivu.

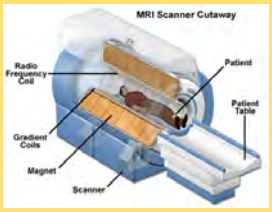
↓

Digitalno geometrijsko procesiranje.

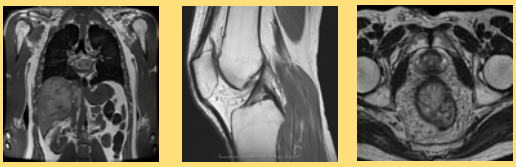
↓

Tomografski posnetki („virtualne rezine“) struktur v notranjosti telesa z možnostjo prikaza v različnih ravninah in 3-D rekonstrukcijo.

MRI



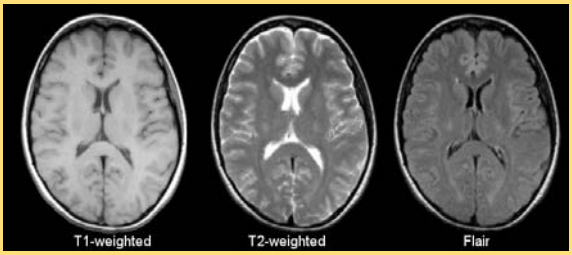
Digitalno geometrijsko procesiranje



MRI sekvenca

Vnaprej programirani seti spremenljivih radiofrekvenčnih pulzov in magnetnih gradientov, ki rezultirajo v setu slik določenega izgleda.

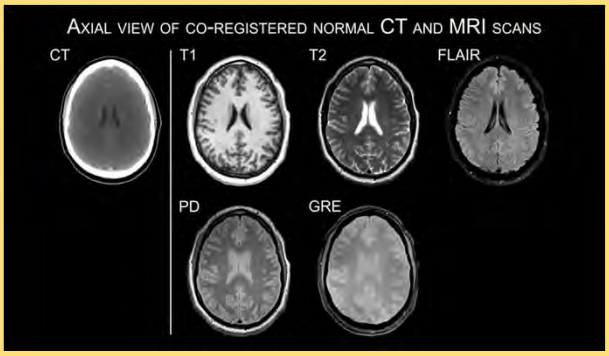
Vsaka sekvenca vsebuje različno število parametrov, več sekvenc pa združujemo v MRI protokole za posamezne anatomske lokalizacije.



MRI

- v uporabi od 1980 dalje
- ni problema izpostavljenosti ionizirajočemu sevanju, je pa preiskava bistveno daljša kot CT preiskava
- v primerjavi s CT boljša metoda za ugotavljanje razlik na mehkih tkivih!!!

MRI



PET-CT

Kombinacija: PET (pozitronske emisijske tomografije) in CT (računalniške tomografije)

S preiskavo pridobimo informacijo o:

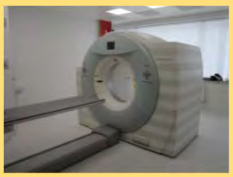
→ anatomiji (CT)

→ prostorski razporeditvi metabolne oz. biokemične aktivnosti v telesu (PET)

PET-CT

Kombinacija: PET (pozitronske emisijske tomografije) in CT (računalniške tomografije)

1. Detektor sevanja ⟶ PET skener in CT



2. Radiofarmak:

- ^{18}F-FDG
- drugi radiofarmaki označeni z ^{18}F: holin, timidin,...
- drugi pozitronski sevalci: ^{11}C, ^{13}N, ^{15}O, ^{68}Ga,...

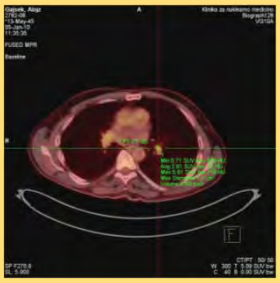
PET-CT

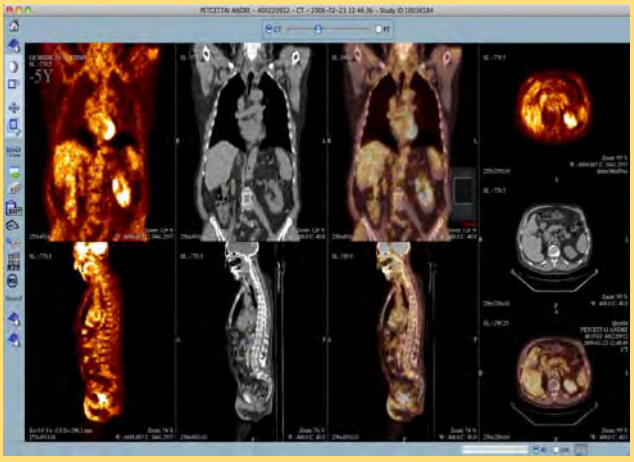
- **^{18}F-FDG** (2-deoksi-2-[18F]fluoro-D-glukoza) se v telesu obnaša enako kot glukoza
- **^{18}F-FDG-6-fosfat** (FDG-6-P) je metabolit ^{18}F-FDG, ki se kopiči v celicah in prikaže porabo glukoze v organih in tkivih telesa (maligne celice imajo povečano izražanje glukoznega prenašalca GLUT-1)
- **^{18}F**
  - pozitronski sevalec
  - $t_{1/2}$ 110 min
  - aktivnost 250 - 370 MBq
- sevanje zaznavajo detektorji PET skenerja

PET-CT

Pri evaluaciji rezultatov je potrebno biti pozoren na to, da gre za semikvantitativno preiskavo!

SUV – standardized uptake value





Uporabnost PET-CT

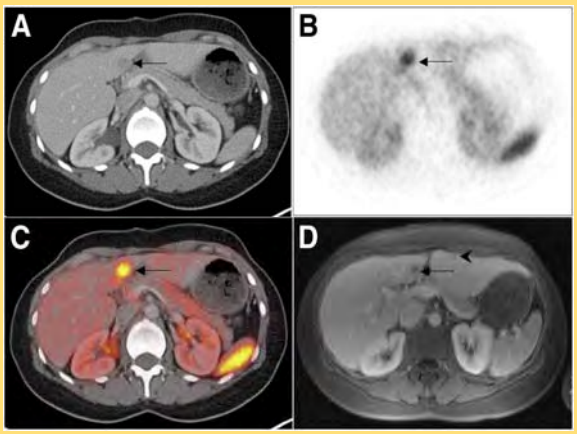
1. <u>onkologija:</u>
- → postavitev diagnoze (redko)
- → staging
- → ocena učinkovitosti zdravljenja
- → sledenje

POZOR!
- **pri bolnikih po OP, KT, RT**
  → zaradi sprememb v tkivih po specifičnem onkološkem zdravljenju (vnetje, edem, nekroza,..) so rezultati lahko zavajajoči
  → ne prej kot 8-12 tednov po zdr.
- **pri bolnikih s sladkorno boleznijo**

2. <u>infektologija</u>:
→ prikaz vnetja, vročina neznanega izvora, kronična vnetna bolezen črevesja (aktivnost, razširjenost)

3. <u>nevrologija:</u>
→ opredeljevanje demenc, določitev mesta epileptogenega žarišča,...

4. <u>kardiologija:</u>
→ ocena viabilnosti miokarda



NAČRTOVANJE OBSEVANJA

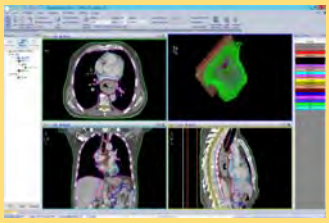
Zaporedje postopkov, s katerimi bolnika pripravimo na obsevanje

1. Postavitev indikacije za obsevanje
↓
2. Simulacija obsevanja

Multidisciplinarni konzilij
↓
CT simulator (radiološki inženir v sodelovanju z radioterapevtom)
⇣
1. pravilna namestitev bolnika z uporabo fiksacijskih pripomočkov
2. po potrebi aplikacija kontrastnega sredstva (po, iv ali intrakavitarno)
3. preslikava določenega dela telesa

NAČRTOVANJE OBSEVANJA

3. Vrisovanje tarčnih struktur



Vrisovalnica (radioterapevt, po potrebi v sodelovanju z radiologom)

1. tarčnih volumnov:
   - GTV
   - CTV
   - PTV

2. zdravih tkiv (= rizičnih organov), ki se nahajajo znotraj tarčnih volumnov ali na poti obsevalnih žarkov

NAČRTOVANJE OBSEVANJA

4. Izdelava obsevalnega načrta

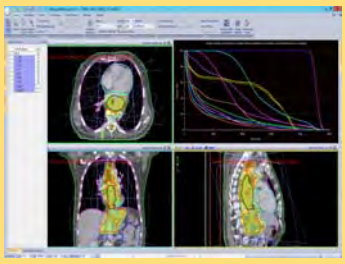
Planirnica (medicinski fizik/ dozimetrist, po potrebi v sodelovanju z radioterapevtom)

1. določitev števila, vstopnih kotov in energije žarkov ter postavitev zaščit za zdrava tkiva

2. evaluacija izdelanega obsevalnega načrta:
→ ustrezna doza in pokritost tarčnih volumnov
→ ocena doze znotraj rizičnih organov

NAČRTOVANJE OBSEVANJA

5. Pregled in potrditev obsevalnega načrta



Vrisovalnica in/ali planirnica (radioterapevt v sodelovanju z medicinskim fizikom/ dozimetristom)

Evaluacija izdelanega obsevalnega načrta glede na namen obsevanja in klinično sliko:
→ ustrezna absorbirana doza znotraj vrisanih tarčnih volumnov
→ ne presežena tolerančna doza v zdravih tkivih

NAČRTOVANJE OBSEVANJA

(korekcija obsevalnega plana)

(reevaluacija obsevalnega plana)

(naris izocentra)

(planirnica)
(medicinski fizik/dozimetrist v sodelovanju z radioterapevtom)

(vrisovalnica in/ali planirnica)
(radioterapevt v sodelovanju z medicinskim fizikom/dozimetristom)

(CT simulator)
(radiološki inženir: korekcija oznak na koži glede na izdelan obsevalni načrt)

NAČRTOVANJE OBSEVANJA

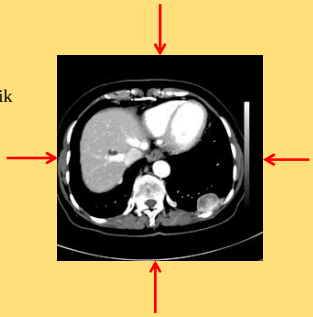
6. Obsevanje

Linearni pospeševalnik
(radiološki inženir, po potrebi v sodelovanju z radioterapevtom in medicinskim fizikom

NAČRTOVANJE OBSEVANJA – računanje absorbirane doze

Kompleksni računalniški algoritmi, ki absorbirano dozo računajo na osnovi gostote tkiv

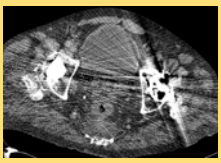
→ informacije pridobljene iz seta CT slik



NAČRTOVANJE OBSEVANJA – računanje absorbirane doze

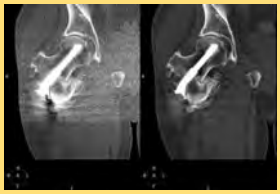
Težave pri:

1. CT slikah z veliko artefakti



↓

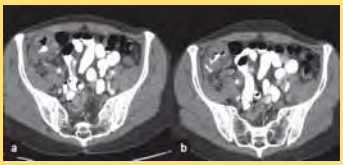
MAR – „metal artifact reduction“



NAČRTOVANJE OBSEVANJA – računanje absorbirane doze

Težave pri:

2. Veliki količini apliciranega kontrastnega sredstva
(praviloma sredstva z veliko elektronsko gostoto, ki jih planirni sistemi zaznavajo kot tkiva, v katerih je absorbcija žarkov navidezno večja kot v resnici)



↓

Ustvarimo nov volumen z gostoto vode

NAČRTOVANJE OBSEVANJA S POMOČJO PET-CT in/ali MRI

Zakaj?

- **s pomočjo informacije iz PET in MRI slik pridobiti dodatne informacije o obsegu bolezni**

  → natančnejša določitev obsega bolezni in velikosti tarčnih volumnov
  → boljše ščitenje zdravih tkiv znotraj obsevalnih polj ali v njihovi neposredni bližini

↓

Spremembe v volumnu vrisanih struktur!!!

NAČRTOVANJE OBSEVANJA S POMOČJO PET-CT in/ali MRI

Zakaj?

- **na področju prebavil problem zlasti pri:**

  → tumorjih, ki ležijo nizko v mali medenici
  (npr. ploščatocelični karcinomi analnega kanala in adenokarcinomi spodnje 1/3 rektuma)

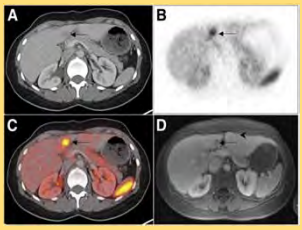
  → tumorjih, katerih obseg je težje določljiv zaradi njihovih patofizioloških lastnosti
  (npr. ploščatocelični karcinom požiralnika, ki se lahko širi submukozno)

NAČRTOVANJE OBSEVANJA S POMOČJO PET-CT

Bolnik pripravo na obsevanje namesto na CT simulatorju opravi na PET-CT aparatu!

1. seti CT slik, ki služijo izdelavi obsevalnega načrta

2. seti PET slik, ki nam dajo dodatno informacijo o obsegu bolezni in fizioloških značilnostih tumorja



NAČRTOVANJE OBSEVANJA S POMOČJO PET-CT

Problemi:

1. aparat je potrebno za potrebe načrtovanja obsevanja ustrezno dodatno opremiti oz. prilagoditi:
   → ravna miza, fiksacijski pripomočki, sistem laserjev

2. dostopnost do preiskave (aparat in radioizotop)

3. pazljivost pri določanju ustreznih SUV vrednosti pri interpretaciji PET slik
   → lažno prevelika ali premajhna področja kopičenja radiofarmaka v tumorju

NAČRTOVANJE OBSEVANJA S POMOČJO PET-CT

V procesu vrisovanja tarčnih volumnov lahko poleg GTV generiramo tudi strukturo, ki kopiči na PET (GTV-PET)

→ proces je lahko ročen ali v popolnosti avtomatiziran

→ pazljivo pri nastavitvah vrednosti SUV (lažno prevelika ali premajhna področja kopičenja radiofarmaka v tumorju)

„Fully automated contouring can sometimes be 100% reproducible but 100 % wrong.“

„Do it right, or don't do it at all.“

NAČRTOVANJE OBSEVANJA S POMOČJO MRI

Bolnik mora pripravo na obsevanje opraviti tako na CT simulatorju kot MRI aparatu!

1. seti CT slik, ki služijo izdelavi obsevalnega načrta in na katere se vrisujejo tarčni volumni

2. seti MRI slik, ki nam dajo dodatno informacijo o obsegu bolezni (boljša ločljivost mehkih tkiv!!!)

↓

Za potrebe načrtovanja obsevanja posnamemo le določene sekvence (postopek je krajši od diagnostičnega MRI)

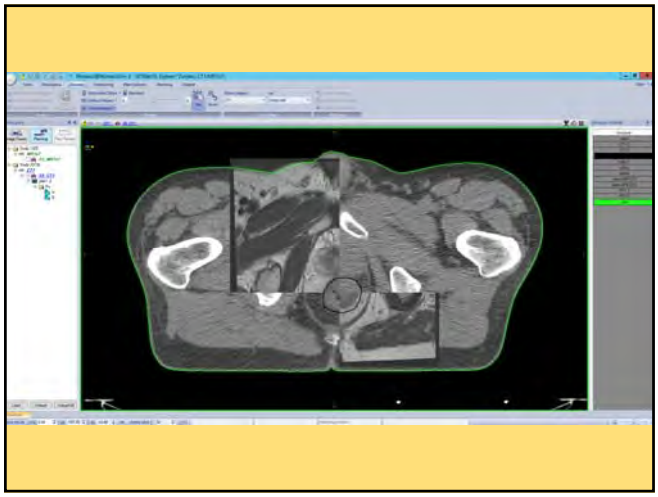
NAČRTOVANJE OBSEVANJA S POMOČJO MRI

Problemi:

1. aparat je potrebno za potrebe načrtovanja obsevanja ustrezno dodatno opremiti oz. prilagoditi:
   → ravna miza, fiksacijski pripomočki, sistem laserjev

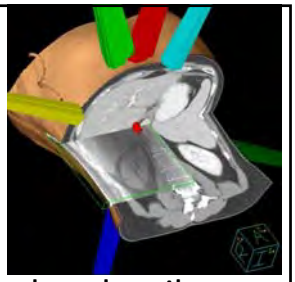
(2. dostopnost do preiskave)

3. pazljivost pri zlivanju slik
   → ob neustrezni registraciji je informacija lahko napačna!



NAČRTOVANJE OBSEVANJA S POMOČJO PET-CT in/ali MRI na OIL

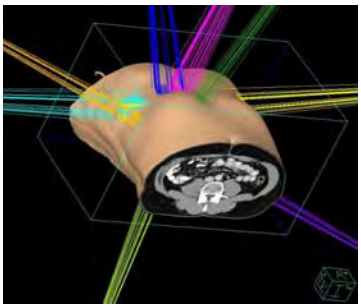
	MRI	PET-CT
GIT	Spodnja 1/3 rektuma	Analni kanal, požiralnik, kardija želodca
GUT	TRT: prostata, mehur, (cervix) BRT: prostata, cervix, nožnica	/
Pljuča	(Pancoastovi tumorji)	Pljuča
Glava&vrat	Obnosne votline, žrelo	/
LPS	Možgani, hrbtenica (sarkomi)	
Dojka	/	/



SBRT primarnih in sekundarnih tumorjev jeter

Irena Oblak

SBRT (stereotaktična radioterapija ali stereotaktična radioablacija) je novejša tehnika RT, ki omogoča precizno posredovanje visoke D obsevanja na TU z minimalno D obremenitvijo sosednjih zdravih tkiv.



SBRT

- ↑ D na TU v eni ali nekaj frakcijah;
- ↑tumoriciden učinek (↑ kot pri konvencionalni frakcionaciji);
- <u>Predpogoj:</u>

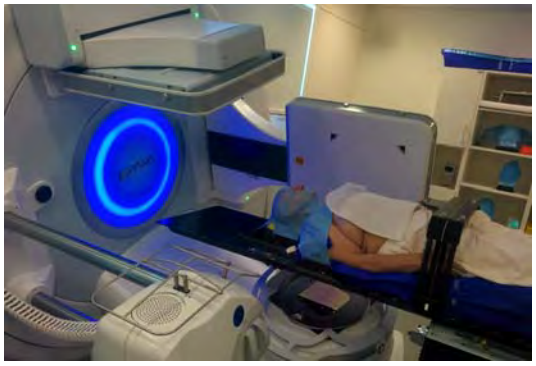
a) Linearni akceleratorji novejše generacije, ki omogočajo tehniko SBRT (IGRT);

b) Kontrola respiratorne gibljivosti med RT;

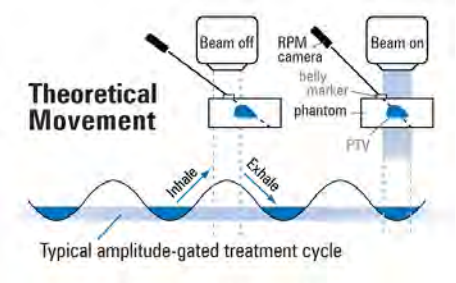
c) Natančna imobilizacija bolnika.

Linearni akcelerator (aparat 8)

SBRT hrbtenice na novem aparatu 4

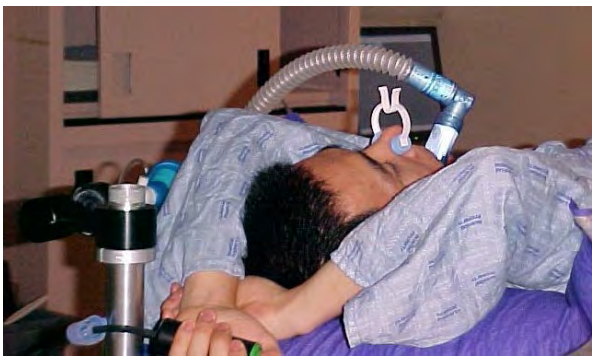


Dihalno proženje



RPM = Real-time Position Management

Kontrola respiratorne gibljivosti



Stereotaktična radioterapija

- Moderna tehnika obsevanja;
- Omogoča ↑ D na TU (ablativno);
- 1 do nekaj frakcij (↓OTT);
- Neinvazivna metoda (brez anestezije, bolečin,..);
- Ambulantno zdravljenje;
- Odlična lokalna kontrola primarnega TU ali M+;
- Zadovoljiv toksični profil.

Indikacije za SBRT

- Standardno zdravljenje zgodnjega pljučnega raka, ki ni za OP: LC_3 90%;
- Standardno zdravljenje HCC, ki ni za OP *(NCCN smernice, Wang et al, 2015);*
- Za izbrane bolnike z rakom prostate *(Alongi et al, 2015);*
- Za že obsevane bolnike z rakom prostate *(Arcangeli et al, 2015);*
- Recidivi v področju lobanjske baze *(Krengly et al, 2014);*
- Ponovno obsevanje lokalnega recidiva pljučnega raka *(Amendola et al, 2015);*

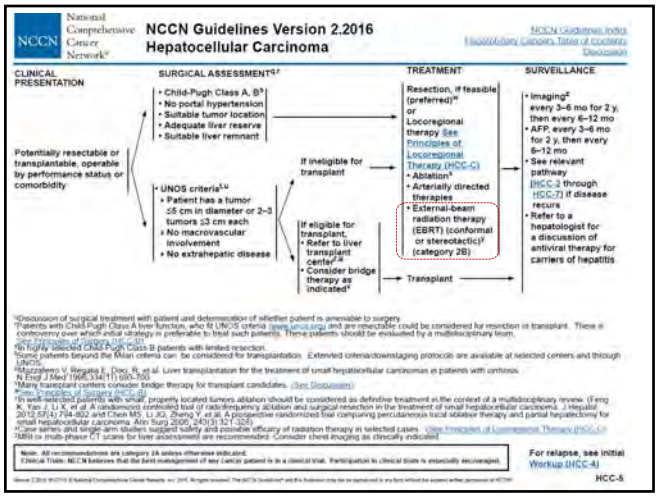
Indikacije za SBRT

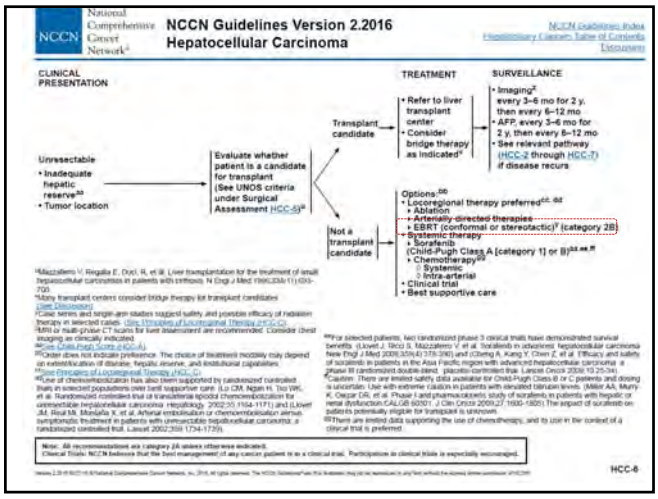
- Pljučni zasevki raka dojke *(Navarria et al, 2015);*
- Zasevki v hrbtenici *(Greco et al, 2015);*
- Jetrni zasevki različnih rakov, ki niso primerni za OP *(Comito et al, 2014);*
- Izbrani bolniki z recidivom v bezgavkah *(Jereczek-Fossa et al, 2015);*
- Zasevek v nadledvičnici *(Ippolito et al, 2015);*
- Paliativno ali predoperativno pri raku trebušne slinavke *(Hajj and Goodman et al, 2015);*
- ….

SBRT pri HCC

- Za izbrane bolnike, kjer OP ni možna;
- Za 1-3 lezije;
- Velikost lezije pogojuje volumen zdravega jetrnega tkiva,
- Kot premostitveno TH pri bolnikih, ki čakajo transplantacijo;
- Ob 2 letih po SBRT:LC 95%, OS 69%

  (Kwon JH, 2010)





NCCN Guidelines Version 2.2016
Hepatocellular Carcinoma

CLINICAL PRESENTATION

Unresectable
- Inadequate hepatic reserve[a,b]
- Tumor location

Evaluate whether patient is a candidate for transplant (See UNOS criteria under Surgical Assessment HCC-5)[a]

Transplant candidate
- Refer to liver transplant center
- Consider bridge therapy as indicated[b]

Not a transplant candidate

TREATMENT

Options:[bb]
- Locoregional therapy preferred[cc, dd]
  - Ablation
  - Arterially-directed therapies
  - EBRT (conformal or stereotactic)[f] (category 2B)
- Systemic therapy
  - Sorafenib (Child-Pugh Class A [category 1] or B)[aa, ee, ff]
  - Chemotherapy[gg]
    - Systemic
    - Intra-arterial
- Clinical trial
- Best supportive care

SURVEILLANCE

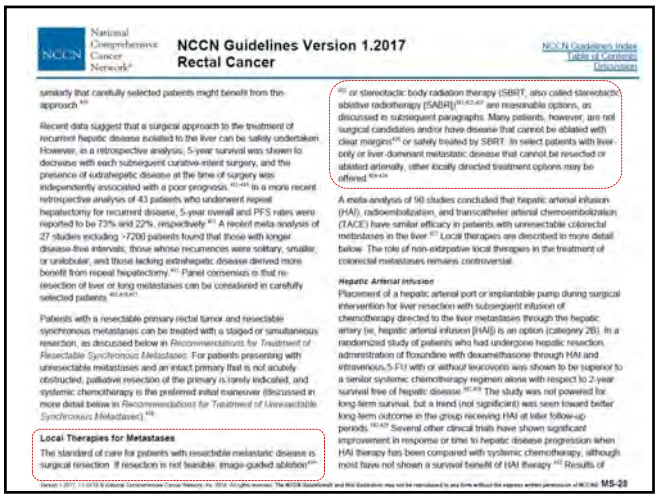
- Imaging[c] every 3–6 mo for 2 y, then every 6–12 mo
- AFP, every 3–6 mo for 2 y, then every 6–12 mo
- See relevant pathway (HCC-2 through HCC-7) if disease recurs

[a] Mazzaferro V, Regalia E, Doci, R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334(11):693-700.
[b] Many transplant centers consider bridge therapy for transplant candidates (See Discussion)
[c] Case series and single-arm studies suggest safety and possible efficacy of radiation therapy in selected cases. (See Principles of Locoregional Therapy (HCC-C))
[d] MRI is multi-phase CT scans for liver assessment are recommended. Consider chest imaging as clinically indicated.
[e] (See Child-Pugh Score (HCC-A))
[f] Order does not indicate preference. The choice of treatment modality may depend on extent/location of disease, hepatic reserve, and institutional capabilities.
[g] (See Principles of Locoregional Therapy (HCC-C))
[h] Use of chemoembolization has also been supported by randomized controlled trials in selected populations (see best supportive care: Lo CM, Ngan H, Tso WK, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 2002;35:1164-1171) and (Llovet JM, Real MI, Montaña X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet 2002;359:1734-1739).

Misc. All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

[aa] For selected patients, two randomized phase 3 clinical trials have demonstrated survival benefits (Llovet J, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. New Engl J Med 2008;359(4):378-390) and (Cheng A, Kang Y, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomized double-blind, placebo-controlled trial. Lancet Oncol 2009;10:25-34).
[bb] Caution: There are limited safety data available for Child-Pugh Class B or C patients and dosing is uncertain. Use with extreme caution in patients with elevated bilirubin levels. (Miller AA, Murry K, Oaczar DR, et al. Phase I and pharmacokinetic study of sorafenib in patients with hepatic or renal dysfunction: CALGB 60301. J Clin Oncol 2009;27:1800-1805) The impact of sorafenib on patient is potentially eligible for transplant is unknown.
[cc] There are limited data supporting the use of chemotherapy, and its use in the context of a clinical trial is preferred.

HCC-6



NCCN Guidelines Version 1.2017
Rectal Cancer

similarly that carefully selected patients might benefit from this approach.[435]

Recent data suggest that a surgical approach to the treatment of recurrent hepatic disease isolated to the liver can be safely undertaken. However, in a retrospective analysis, 5-year survival was shown to decrease with each subsequent curative-intent surgery, and the presence of extrahepatic disease at the time of surgery was independently associated with a poor prognosis.[431-435] In a more recent retrospective analysis of 43 patients who underwent repeat hepatectomy for recurrent disease, 5-year overall and PFS rates were reported to be 73% and 22%, respectively.[431] A recent meta-analysis of 27 studies including >7200 patients found that those with longer disease-free intervals, those whose recurrences were solitary, smaller, or unilobular, and those lacking extrahepatic disease derived more benefit from repeat hepatectomy.[432] Panel consensus is that re-resection of liver or lung metastases can be considered in carefully selected patients.[431,433,437]

Patients with a resectable primary rectal tumor and resectable synchronous metastases can be treated with a staged or simultaneous resection, as discussed below in *Recommendations for Treatment of Resectable Synchronous Metastases*. For patients presenting with unresectable metastases and an intact primary that is not acutely obstructed, palliative resection of the primary is rarely indicated, and systemic chemotherapy is the preferred initial maneuver (discussed in more detail below in *Recommendations for Treatment of Unresectable Synchronous Metastases*).[438]

Local Therapies for Metastases

The standard of care for patients with resectable metastatic disease is surgical resection. If resection is not feasible, image-guided ablation[439] or stereotactic body radiation therapy (SBRT, also called stereotactic ablative radiotherapy [SABR])[431,432,437] are reasonable options, as discussed in subsequent paragraphs. Many patients, however, are not surgical candidates and/or have disease that cannot be ablated with clear margins[439] or safely treated by SBRT. In select patients with liver-only or liver-dominant metastatic disease that cannot be resected or ablated arterially, other locally directed treatment options may be offered.[439,439]

A meta-analysis of 90 studies concluded that hepatic arterial infusion (HAI), radioembolization, and transcatheter arterial chemoembolization (TACE) have similar efficacy in patients with unresectable colorectal metastases in the liver.[427] Local therapies are described in more detail below. The role of non-extirpative local therapies in the treatment of colorectal metastases remains controversial.

Hepatic Arterial Infusion

Placement of a hepatic arterial port or implantable pump during surgical intervention for liver resection with subsequent infusion of chemotherapy directed to the liver metastases through the hepatic artery (ie, hepatic arterial infusion [HAI]) is an option (category 2B). In a randomized study of patients who had undergone hepatic resection, administration of floxuridine with dexamethasone through HAI and intravenous 5-FU with or without leucovorin was shown to be superior to a similar systemic chemotherapy regimen alone with respect to 2-year survival free of hepatic disease.[427,428] The study was not powered for long-term survival, but a trend (not significant) was seen toward better long-term outcome in the group receiving HAI at later follow-up periods.[427,428] Several other clinical trials have shown significant improvement in response or time to hepatic disease progression when HAI therapy has been compared with systemic chemotherapy, although most have not shown a survival benefit of HAI therapy.[427] Results of

MS-28

Raziskave faze I-II SBRT jetrnih zasevkov

Study	No. Pts	Primary Cancer (No. Patients)	Tumor Size	Dose (No. #)	Local Control	Survival
Herfarth 2001	35	NR	1-132 cc	14-26 Gy (1)	1 yr 71%	NR
Mendez-Romero 2006	17	CRC (14) Other (3))	1.1-322 cc	30-37.5 Gy (3)	1 yr 100% 2 yr 82%	1 yr 85% 2 yr 62%
Hoyer 2006	44	CRC (44)	1-8.8 cm	45 Gy (3)	NR	NR
Lee 2009	68	CRC (40) Breast (12) Other (16)	1.2 – 3090 cc	27.7-60 Gy (6)	1 yr 71%	Med surv 17.6 mo
Rusthoven 2009	47	CRC (15) Lung (10) Other (22)	0.8-98.0 cc	60 Gy (3)	1 yr 95% 2 yr 92%	Med surv 20.5 mo
Goodman 2010	22 47	CRC (5) Other (17)	7.5-146 cc	18-36 Gy (1)	1 yr 77%	Med surv 28.6 mo
Rule 2011	27	CRC (12) Other (15)	1-135 cc	30-60 Gy (5)	1 yr 100% (60Gy)	Med surv 37 mo

Prospektivna raziskava faze II SBRT za jetrne zasevke (januar 2010- avgust 2011)

VKLJUČITVENI KRITERIJI:

- Inoperabilni zasevki
- Max. TU diameter < 6cm
- ≤ 3 lezije
- PS 0-2

CILJI:

- PRIMARNI: LC
- SEKUNDARNI: toksičnost, PFS, OS

Scorsetti, 2013

Predpisane doze in restrikcije za RT jeter

	Doza/fr	Št. fr	Srednja doza
Standardna D	25Gy	3	75 Gy
Zmanjšanje D 10%	22.5 Gy	3	67.5 Gy
Zmanjšanje D 20%	20. 63 Gy	3	61.89 Gy
Zmanjšanje D 30%	18.75 Gy	3	56.25 Gy

ORGAN	Dose-Volume omejitve	Drugo
Zdrava jetra	> 700 cc pri < 15 Gy v 3 fr	Volumen zdravih jeter> 1000 cc
Hrbtenjača	< 18 Gy v 3 fr	
Ledvica (R+L)	V15 Gy < 35%	
želodec, duodenum, tanko črevo	< 21 Gy v 3 fr	Bolniki z GTV < 3 mm od srca, želodca, duodenuma in tankega črevesa s so izključeni
Srce	<30 Gy v 3fr	

Prospektivna raziskava faze II SBRT za jeterne zasevke (januar 2010- avgust 2011)

Bolniki	
Št. bolnikov	57
Starost	67 (39 – 85) let
Spol (M:Ž)	35:22

Št. lezij	77
Št.lezij na bolnika	1 pri 43 bolnikih (74%) 2 pri 11 bolnikih (19 %) 3 pri 4 bolnikih (7%)
Preiskava za definiranje TU	57 CT 32 CT-PET 2 MRI

Predpisana D	Št. lezij
75 Gy	63 (82%)
67,5 Gy	5 (7%)
61,89 Gy	5 (7%)
56,25 Gy	4 (4%)
Skupaj	77 (100%)

Rezultati

Mediani čas sledenja 7 mesecev
43 evaluabilnih bolnikov (48 lezij)

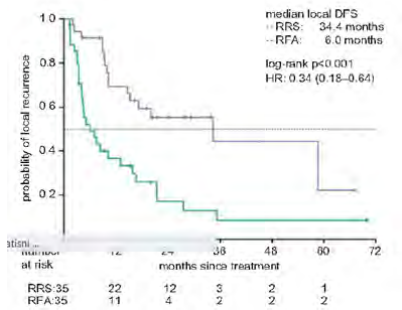
Odgovor	Lezije (št/%)
CR	25 (52%)
PR	15 (31%)
SD	5 (11%)
PD	3 (6%)
Total	48 (100%)

AKUTNA TOKSIČNOST:

- **4 bolniki: G2 slabost, bruhanje**
- **3 bolniki: G2 toksičnost mehkih tkiv** (kožni eritem in bolečina)

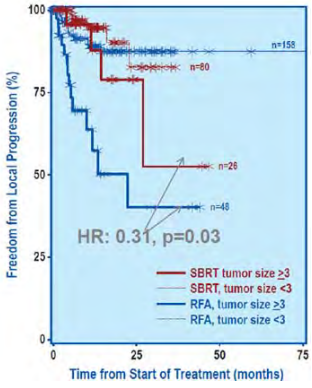
LC 94%

Primerjava SBRT v 1 fr (24-26 Gy) z RFA



Stintzing, 2013:

SBRT vs RFA



SBRT > RFA pri TU ≥ 3 cm

Michigan, 2013

Kriteriji za SBRT

- Velikost: ≤6 cm
- Št. lezij: ≤5
- Brez aktivne ekstrahepatične bolezni
- >700 cc zdravih jeter
- Fokalni TU
- >5mm od lumna črevesja

Ugotovitve nekaterih raziskovalcev

- **Lee, 2009:** 68 bolnikov z neresektabilnimi zasevki v jetrih CRC raka, raka dojke, žolčnika,…

rak dojke ima daljše preživetje v primerjavi z ostalimi raki

- **Swaminath, 2011:**

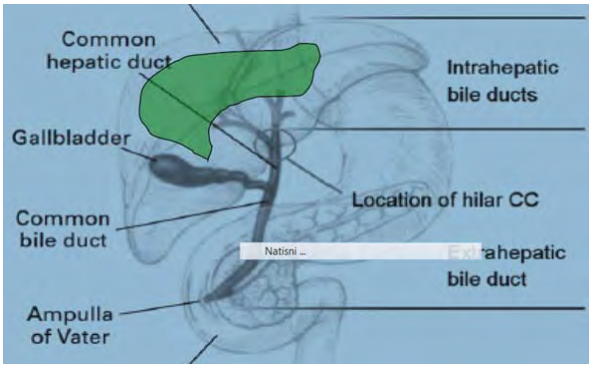
nekateri bolniki z 1-5 zasevkov v jetrih po SBRT živijo 5-10 let brez bolezni

- **Scorsetti, 2013:** 57 bolnikov z 77 zasevki v jetrih CRC raka dojke, 36% bolnikov stabilno extrahepatično bolezen

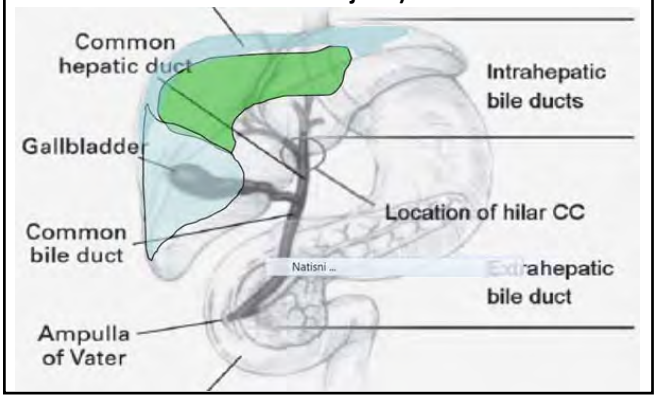
LC 94%, mediano preživetje 19 mesecev

Najnižja stopnja tveganja za SBRT

(**centralno:** stran od črevesja, reber, biliarnega trakta)

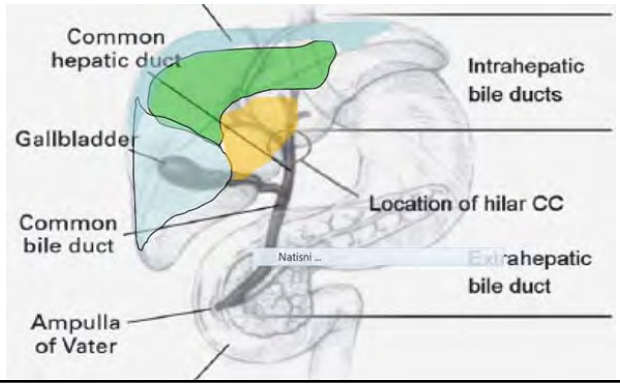


Nizka stopnja tveganja za SBRT (**zgornja lateralna jetra**)

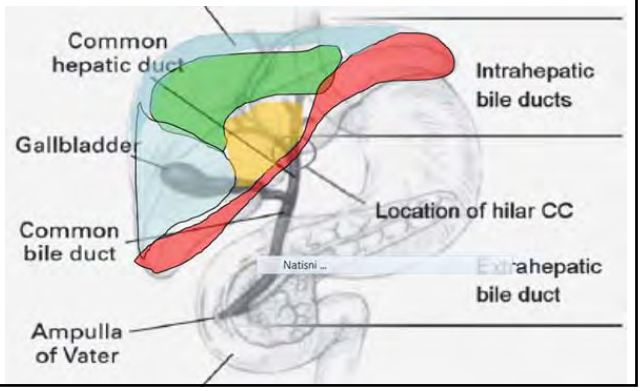


Srednja stopnja tveganja za SBRT

(**centralne lezije, ob biliarnem traktu**)



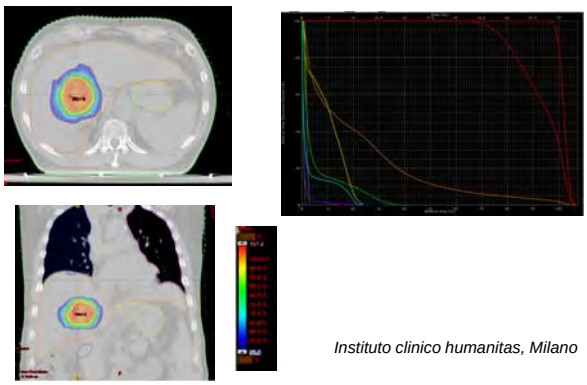
Visoka stopnja tveganja za SBRT (**bližina želodca, črevesja**)



PAZLJIVOST

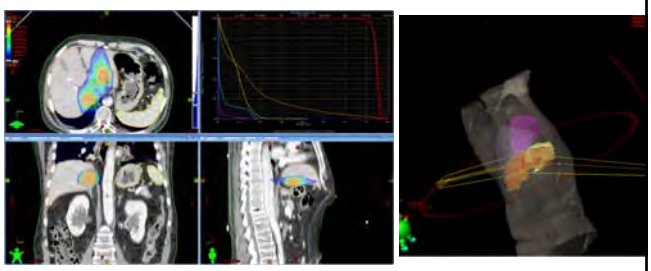
- Centralne lezije: večja toksičnost
- Prehodno prekini sistemsko terapijo
- Pazljivost pri antiangiogenski terapiji

SBRT JETER : 25Gy x 3;



Instituto clinico humanitas, Milano

SBRT JETER: 25Gy x 3

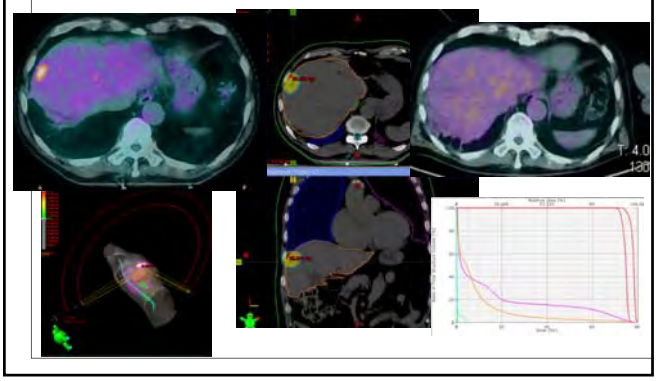


Instituto clinico humanitas, Milano

SBRT JETER: 25Gy x 3

PET pred zdravljenjem

PET po 6 mesecih



SBRT INOPERABILNEGA CA PANKREASA

2013

RADIATION ONCOLOGY

RESEARCH Open Access

SBRT in unresectable advanced pancreatic cancer: preliminary results of a mono-institutional experience

- Januarjem 2010 - oktober 2011
- **30 bolnikov** z **inoperabilnim ali recidivivnim adenocarcinomom pancreasa**
- KT z gemcitabinom pred SBRT
- predpisana doza **45Gy v 6 frakcijah po 7.5Gy**

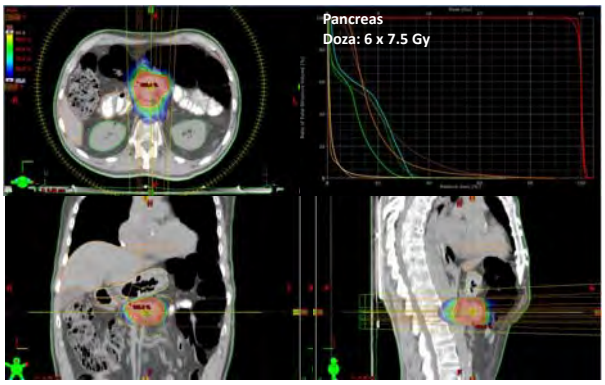
Rezultati:

- **Srednji čas sledenja 11 mesecev (2–28 mesecev)**
- **LC 91% pri 6 mesecih, 85% pri 1 letu.**

Restrikcije

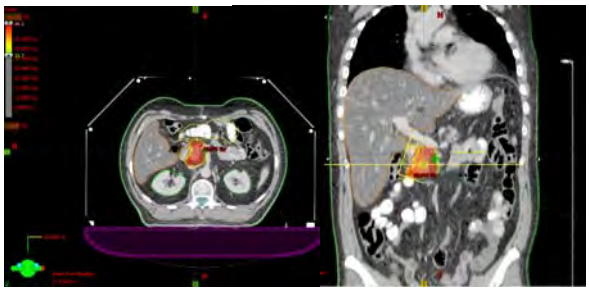
MEDULA	D1cc<18 Gy
LEDVICA	V15Gy <35%
DUODENUM	V36Gy<1cc
ŽELODEC	V36Gy<1cc
TANKO ČREVO	V36Gy<3cc
JETRA	(Vcela jetra – V21Gy)>700cc

SBRT KARCINOMA PANCREASA



SBRT KARCINOMA PANCREASA

Bolnik: 56 let. Neresektabilni adenokarcinom pankreasa;
GEM + FOLFIRI in RT (**45Gy v 6 frakcijah**) -> OP (R0).



ZAKLJUČEK

- SBRT za neoperabilne HCC in jeterne zasevke;
- najboljši rezultati pri zasevkih velikosti < 6cm in številu <5.

Citoreduktivna kirurgija (CRS) in hipertermična intraperitonealna kemoterapija (HIPEC)

Rok Petrič

- Peritonej = organ
- Peritonealni zasevki = lokoregionalna bolezen
- CRS + HIPEC
- Preživetje podobno kot pri jetrnih zasevkih

Hipertermija in intraop. KT

- poveča prehod kemoterapevtika v tkiva
- poveča citotoksičnost kemoterapevtika
- anti tumorski učinek
- dosežemo večjo lokalno koncentracijo KT
- manjša sistemska toksičnost KT

Indikacije

standardno zdravljenje:

- peritonealni psevdomiksom
- peritonealni mezoteliom
- kolorektalni rak z omejeno karcinozo

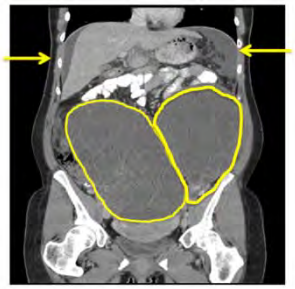
v fazi raziskovanja:

- ovarijski karcinom
- rak želodca

Elias et al. EJC, 2014

Diagnostika

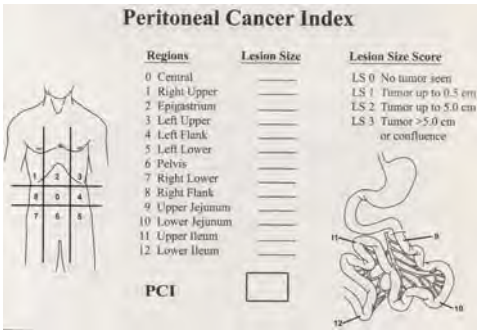
- CT trebuha
- CT toraksa
- PET-CT
- MR trebuha



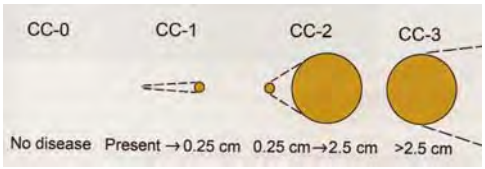
Kvantitativni prognostični kazalci

- PCI
- CCS
- PSS

Indeks peritonealne karcinomatoze (PCI)



Completeness of Cytoreduction after surgery (CC Score)



Odstranitev vseh zasevkov > 2,5 mm (CC-0 ali 1)

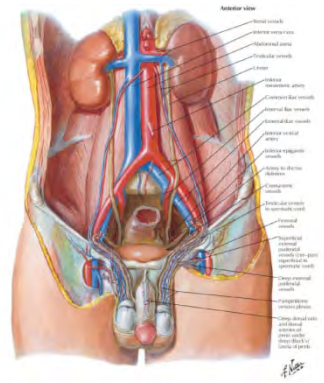
Prior Surgical Score (PSS)

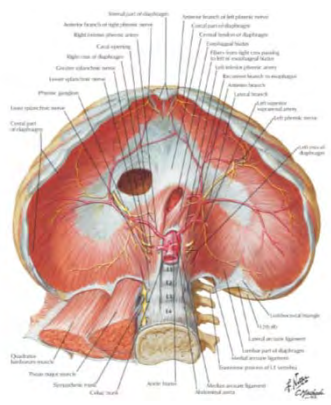
Opredeli obseg kirurških posegov pred kompletno CRS in HIPEC-om.

- PSS 0 – 1 regija
- PSS 1 – 2 do 5 regij
- PSS 2 – 5 ali več regij
- PSS 3 – kompletna CRS brez HIPEC

Posegi pri CRS

Peritonektomija	Resekcije
• Anteriorna parietalna peritonektomija • Peritonektomija L zg. kvadranta • Peritonektomija D zg. kvadranta • Pelvična peritonektomija • Omentalna bursektomija	• Kožna brazgotina, epigastrično maščevje • Omentektomija in splenektomija • Kapsulektomija jeter • Histerektomija z ovariektomijo • Resekcija rektosigmoidnega kolona • Holecistektomija





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- kolorektalni rak z omejeno karcinozo

v fazi raziskovanja:

- ovarijski karcinom
- rak želodca

Elias et al. EJC, 2014

Indikacije

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v fazi raziskovanja:

- ovarijski karcinom
- rak želodca

Elias et al. EJC, 2014

Psevdomiksom peritoneja

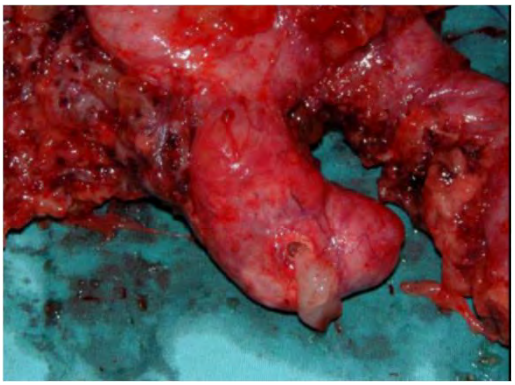
- 1-2/1000000
- > 90 % tumorji slepiča (ovarij, kolon, pankreas)
- low in high grade
- citoredukcija: 88 % relaps, 21 % 10 letno preživetje
- CCRS + HIPEC: srednje preživetje 16 let, 63 % 10 letno preživetje

Chua, Sugarbaker et al. JCO, 2012

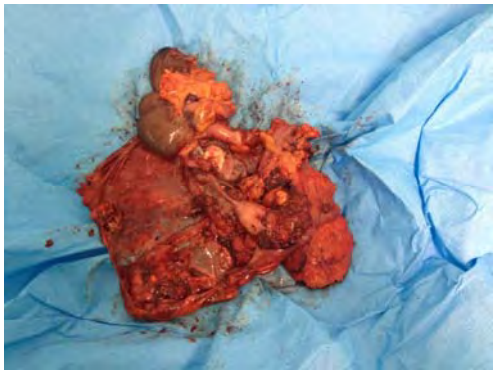
Klinični znaki PMP

	ženske	moški
Vnetje slepiča	20%	34%
Zvečan obseg trebuha	19%	27%
Ovarijski tumor	39%	-
Kila	4%	25%
Ascites	4%	5%
Bolečina v trebuhu	3%	5%
Drugo	11%	4%

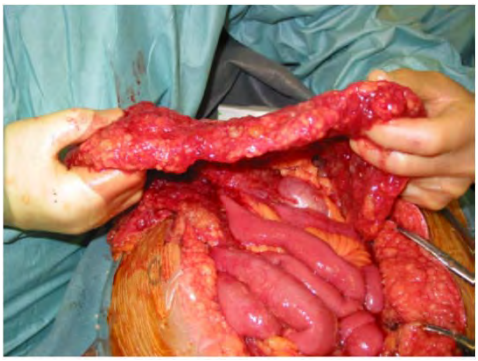
Sugarbaker, Cancer J, 2009



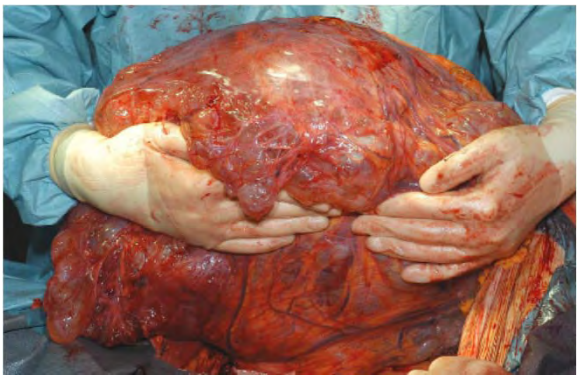
Mukokela slepiča



Mukokela slepiča

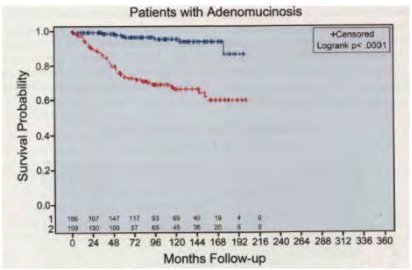


Omental cake



Mucinska cista

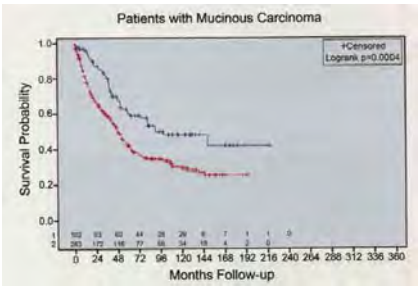
Preživetje glede na PCI



----- PCI 1-20
----- PCI 21-39

Sugarbaker, Cancer J, 2009

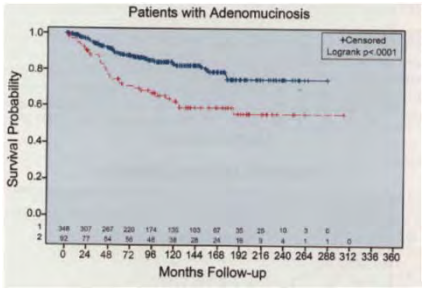
Preživetje glede na PCI



----- PCI 1-20
----- PCI 21-39

Sugarbaker, Cancer J, 2009

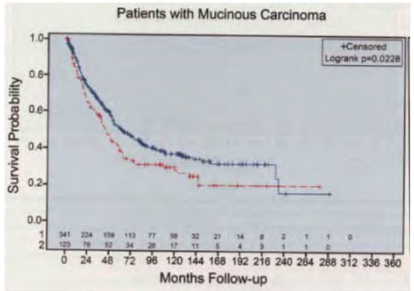
Preživetje glede na PSS



----- PSS 0-2
----- PSS 3

Sugarbaker, J Surg Oncol, 2007

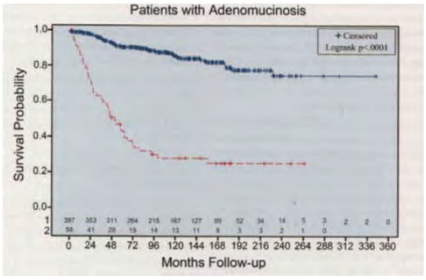
Preživetje glede na PSS



----- PSS 0-2
----- PSS 3

Sugarbaker, J Surg Oncol, 2007

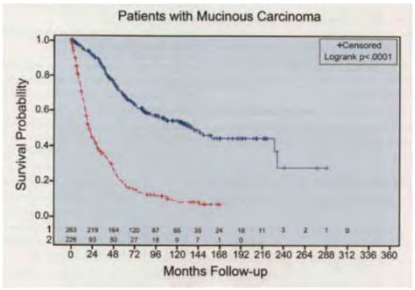
Preživetje glede na CCS



----- CCS 0-1
----- CCS 2-3

Sugarbaker, J Surg Oncol, 2007

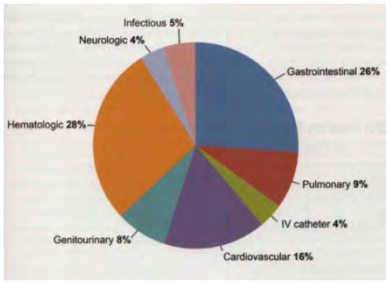
Preživetje glede na CCS



----- CCS 0-1
----- CCS 2-3

Sugarbaker, J Surg Oncol, 2007

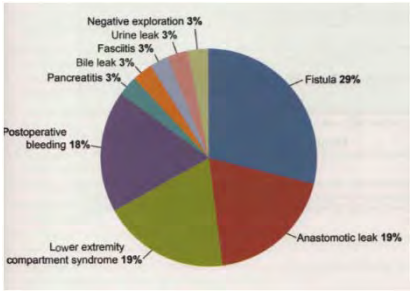
Zapleti



Zapleti 4.stopnje – 19%

Sugarbaker, Ann Surg Oncol, 2007

Reoperacije zaradi zapletov



~11,2%

Sugarbaker, Ann Surg Oncol, 2007

Indikacije

standardno zdravljenje:

- peritonealni psevdomiksom
- peritonealni mezoteliom
- kolorektalni rak z omejeno karcinozo

v fazi raziskovanja:

- ovarijski karcinom
- rak želodca

Elias et al. EJC, 2014

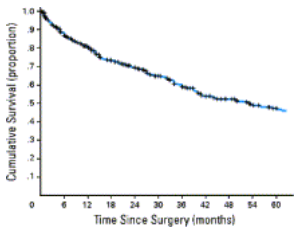
Peritonealni mezoteliom

- 0,3-3/1000000
- vloga azbesta(?)
- različni podtipi →
  - epiteloidni
  - tubulo-papilarni
  - sarkomatoidni
  - bifazični
  - nediferencirani
  - limfo-histiocitoidni
  - malocelični
  - deciduoidni

Yan, Deraco et al. JCO, 2009

Peritonealni mezoteliom

- KT: srednje preživetje 12 mesecev
- CCRS + HIPEC: srednje preživetje 53 mesecev, 5 letno preživetje 47 %
- PCI vpliva na prognozo (meja?)
- CCS 0-3



Yan, Deraco et al. JCO, 2009

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<u>v fazi raziskovanja:</u>

- ovarijski karcinom
- rak želodca

Elias et al. EJC, 2014

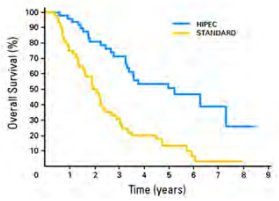
Kolorektalni rak

- karcinoza peritoneja 20 %
- 50 % brez oddaljenih zasevkov
- preživetje:
  * brez zdravljenja: srednje preživetje 6 mesecev
  * KT: srednje preživetje 12 mesecev
  * KT + tarčna zdravila: srednje preživetje 15 mesecev, 5 letno preživetje 4 %

Klaver et al. EJSO, 2012

Kolorektalni rak

- CRS + HIPEC: srednje preživetje 50-60 mesecev;
  1, 2 in 5 letno preživetje: 86, 70 in 51 %



Elias et al. JCO, 2009

Table 2 Characteristics of the major studies reporting outcomes of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal metastases from colorectal cancer
(N = number of patients; NR = not reported)

Complete cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

Reference	Institution/City	Year	Level of Evidence	N	Overall Survival (months)	One-year Survival (%)	Two-year Survival (%)	Three-year Survival (%)	Five-year Survival (%)
Elias (93)	Multicentre	2010	III	439	32	85	60	45	30
Chua (126)	St. George Hospital, Sydney	2009	III	54	33	87	70	44	NR
Elias (74)	Institut Gustave Roussy, Villejuif	2009	II	48	63	NR	81	NR	51
Shen (137)	Wake Forest University Winston-Salem	2008	III	30	41	NR	NR	NR	NR
Franko (138)	University of Pittsburgh Medical Center, Pittsburgh	2008	III	36	20	85	NR	45	NR
Bijelic (139)	Washington Cancer Institute Washington, DC	2008	III	49	33	NR	NR	50	20
Kianmanesh (101)	Louis-Mourier University Hospital, Paris	2007	III	30	38	NR	72	NR	44
Verwaal (140)	Netherlands Cancer Institute, Amsterdam	2005	III	59	43	94	NR	56	43
Glehen (141)	Multi-institutional	2004	III	377	32	90	NR	55	40
Verwaal (86)	Netherlands Cancer Institute, Amsterdam	2003	I	39	22	70	45	NR	NR
Total				1084					
Median					33	86	70	48	42
Range					20 to 63	70 to 94	45 to 81	44 to 56	20 to 51

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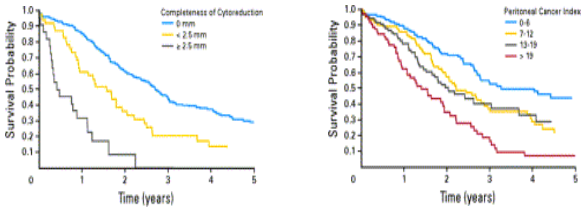
Range					20 to 63	70 to 94	45 to 81	44 to 56	20 to 51

Kolorektalni rak

- CCR in PCI vplivata na prognozo
- PCI > 20 kontraindikacija za operacijo



Elias et al. JCO, 2010

Kolorektalni rak

Karcinoza peritoneja in jetrni zasevki:

- operacija v selektivnih primerih
- PCI < 12
- < 3 jetrni zasevki → 3 letno preživetje 27%
  srednje preživetje 40 mesecev

Maggiori et al. Ann Surg, 2013

Kontraindikacije za CRS in HIPEC

- prizadetost več kot 2/3 tankega črevesa oziroma mezenterija TČ
- metastatska bolezen jeter (več kot 3 nekapsularni zasevki)
- metastatska bolezen plevre
- PCI >20

Naši rezultati

Naši rezultati

2009-2015(marec)

- 37 CCRS + HIPEC pri 36 bolnikih
- 10 M, 26 Ž
- starost 25-70 let, mean 51, median 52 let
- diagnoza:
  * 14 kolorektalni rak
  * 15 ovarijski karcinom
  * 6 psevdomiksom
  * 1 mezoteliom

Naši rezultati

- čas hospitalizacije 10 – 114 dni, mean 32, median 24 dni
- mortaliteta 0%
- morbiditeta 50 %
  * absces: 8 bolnikov
  * dehiscenca anastomoze: 4 bolniki
  * ARDS, ledvična odpoved, vnetje rane, krvavitev, pljučnica, PE, odpoved prebavil

Naši rezultati

- spremljanje 1-71 mesecev, mean 29, median 25 mesecev
- živih 64 %
- živih brez bolezni 42 %

Kolorektalni rak

- 14 bolnikov
- 9 M, 5 Ž
- starost 30-70 let, mean 52, median 52 let
- CCR-0 in 1 93 %
  CCR-2 in 3 7 %
- PCI 4-35, mean 13, median 10

Kolorektalni rak

- pri 71,5 % ponovitev bolezni
  * 28 % jetra
  * 28 % trebuh
  * 21 % pljuča
- 43 % živih
- 28,5 % živih brez bolezni
- srednje preživetje 41 mesecev
- 2 letno preživetje 78 %

Peritonealni psevdomiksom

- 7 operacij pri 6 bolnikih
- 1 M, 5 Ž
- starost 30-70 let, mean 54, median 57 let
- CCR-0 ali 1 pri 6 posegih (86 %)
  CCR-2 ali 3 pri 1 posegu (14 %)
- PCI 13-29, mean 21, median 19

Peritonealni psevdomiksom

- pri 1 bolniku (17%) ponovitev bolezni v trebuhu
- vsi živi
- 5 bolnikov (83%) živih brez bolezni

Povzetek

CRS in HIPEC

Sta metodi zdravljenja skrbno izbranih bolnikov zaradi peritonealne karcinomatoze s katero dosežemo izboljšanje preživetja teh bolnikov.

Raziskave

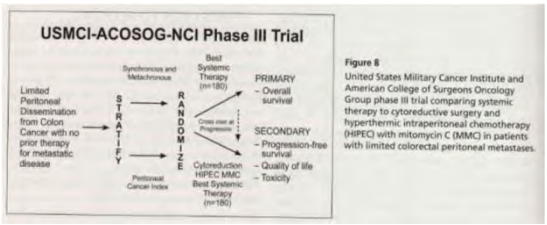


Figure 8
United States Military Cancer Institute and American College of Surgeons Oncology Group phase III trial comparing systemic therapy to cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) with mitomycin C (MMC) in patients with limited colorectal peritoneal metastases.

Raziskave

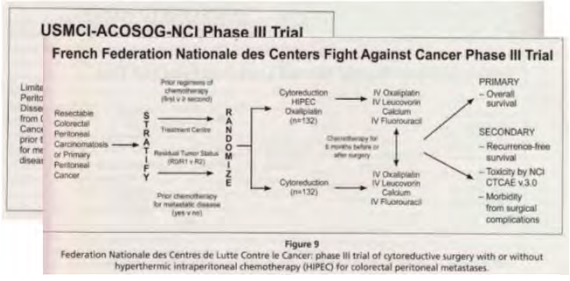


Figure 9
Federation Nationale des Centres de Lutte Contre le Cancer: phase III trial of cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy (HIPEC) for colorectal peritoneal metastases.

Raziskave

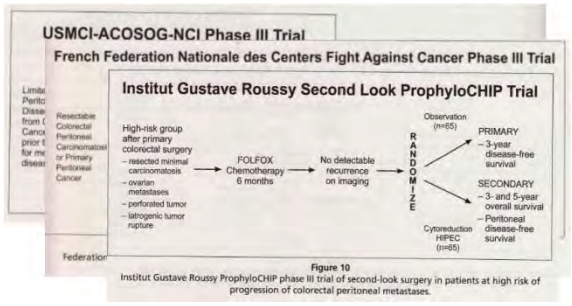


Figure 10
Institut Gustave Roussy ProphyloCHIP phase III trial of second-look surgery in patients at high risk of progression of colorectal peritoneal metastases.

Raziskave

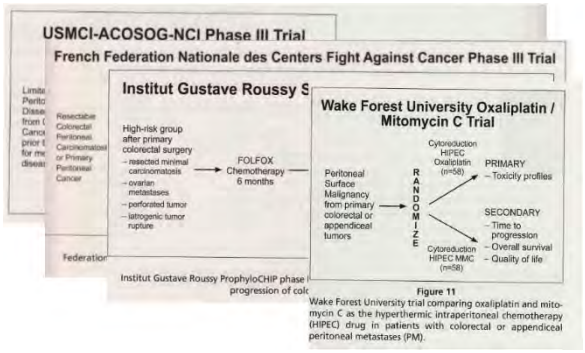


Figure 11
Wake Forest University trial comparing oxaliplatin and mitomycin C as the hyperthermic intraperitoneal chemotherapy (HIPEC) drug in patients with colorectal or appendiceal peritoneal metastases (PM).

Kolorektalni rak – bolniki s tveganjem za razvoj PC

- Perforiran primarni tumor
- Izoliran ovarijski zasevek
- Odstranjena lokalizirana karcinoza peritoneja

>40%

- T4 tumorji
- Pozitivna peritonealna citologija
- Okluzivni ali krvaveči tumorji

8-30%

HVALA

ONKOLOŠKI INŠTITUT LJUBLJANA
INSTITUTE OF ONCOLOGY LJUBLJANA

Elektrokemoterapija zasevkov v jetrih

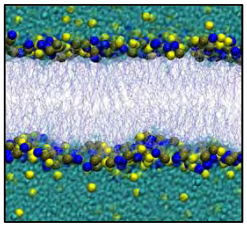
Ibrahim Edhemovic, Erik Brecelj
Institute of Oncology Ljubljana, Slovenia

What is electrochemoterapy?

It is a combination of reversibile electroporation and chemotherapy

Electroporation

- Electroporation is phenomenom which follows the application of high electric fields on a cell membrane which leads to the cell membrane permeabilization.



Courtesy of Dr. Mounir Tarek, Theory Modeling and Simulations group, Université de Lorraine, Nancy, France

Electroporation

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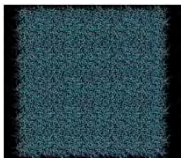
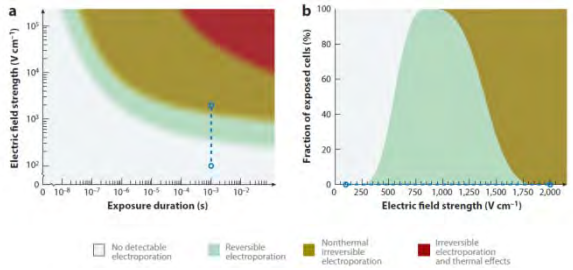


Reversibile

Ireversibile

Adapted from: Depertment of molecular dynamics studies. University of Buenos Aires

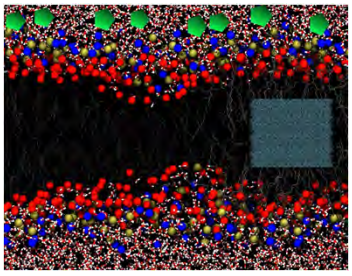
Reversibile, Irreversibile



Yarmush M, Golberg A, Sersa G, Kotnik T, Miklavcic D. Electroporation-Based Technologies for Medicine: Principles, Applications and Challenges. Annu. Rev. Biomed. Eng. 2014. 16:295–320

Reversibile electroporation

Cell membrane separates the cell from its surrounding environment and provides selective transport.

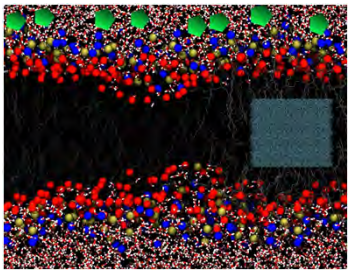


Adapted from: Depertment of molecular dynamics studies. University of Buenos Aires

Reversibile electroporation

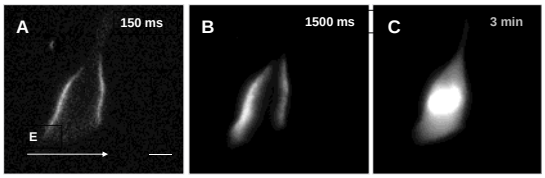
If a cell is exposed to an external electric field, cell membrane permeability is temporarily increased allowing molecules otherwise deprived of transport mechanisms to cross the cell membrane.

As electroporation is a transient phenomenon, after some time the cell membrane reseals and the transported molecules remain trapped inside the cell.



Adapted from: Depertment of molecular dynamics studies. University of Buenos Aires

Visualization of cell electropermeabilization

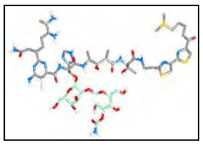


- **Fluorescence of the cell; A: 150 ms, B: 1500 ms, and C: 3 min after pulse delivery.**
- The images were corrected for background fluorescence and the brightness was automatically enhanced. The cell was exposed to a single 260 V (650 V/cm) rectangular pulse (750 µs). Propidium Iodide (100 µM) was added to suspension before the pulse was applied to visualize the permeabilized regions. Bar represents 10 µm.

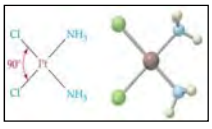
Sersa et al. EJSO 2007

Electrochemotherapy: Increased cytotoxicity of chemotherapeutic drugs

- Effective for hydrophilic drugs with hampered transport through the plasma membrane
- Drugs that have clinical applicability:
  - Bleomycin (BLM)
  - Cisplatin (CDDP)



BLM



CDDP

Cytotoxicity of drugs can be increased by electroporation

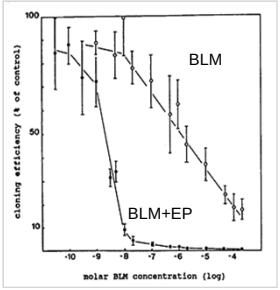
Drugs tested	Potentiation
Bleomycin	100-5000 -fold
Cisplatin	3-80 -fold
Carboplatin	10-13 -fold
Methotrexate	
Melphalan	
Mithramycin	
Actinomycin D	
Adriamycin	
Cyclophosphamide	
Mitomycin C	
Doxorubicin	
5-fluorouracil	
Vinblastine	
Vincristine	
Paclitaxel	
Taxotere	

Electroporation allows introduction of hydrophilic and nonpermeant molecules into the cytosol

- Drugs: electrochemotherapy
- Nucleic acids (DNA, siRNA…)
- Proteins
- Small molecules

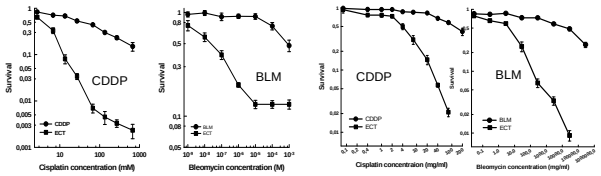
The first in vitro survival curve demonstration that cytotoxicity of BLM is increased by electroporation

- Cell suspension was mixed with drug solution and immediatelly exposed to electric pulses.
- Cytotoxicity was potentiated ~1000 fold.



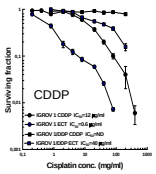
Orlowski et al. Biochem Pharmacol 1988

Electroporation increases cytotoxicity of chemotherapeutic drugs in different tumor cell lines



B16 melanoma

LPB fibrosarcoma

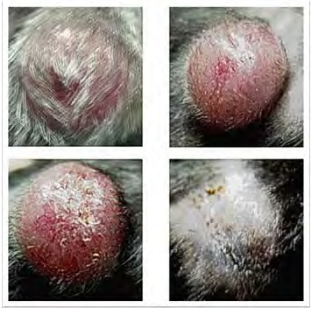


IGROV-1 and IGROV-1/DDP carcinoma

Sersa et al. Cancer Res 1995; Cemazar M et al. Jpn J Cancer Res 1998; Cemazar et al. Anticancer Res 1998

The effect of the ECT

Control



Only BLM 20 µg/mouse

Only EP: 8 pulses 1300 V/cm 1 Hz, 100 µs

ECT

Sersa G, Cemazar M, Miklavcic D, Rudolf Z. Elektrokemoterapija postaja standardno zdravljenje. Onkologija 2, 84-87. 29-11-2005

Electrochemotherapy

- Electrochemotherapy (ECT) is a new, non-thermal local treatment modality that combines the use of poorly or non-permeant chemotherapeutics, such as bleomycin (BLM) or cisplatin (CDDP) with electroporation which facilitates drug diffusion into the cells.
- This increases their cytotoxicity for >1000 times for BLM and >80 times for CDDP.

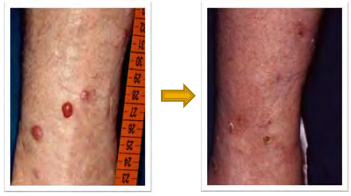
Mir LM, Orlowski S, Belehradek J, Jr., Paoletti C. Electrochemotherapy potentiation of antitumour effect of bleomycin by local electric pulses. Eur J Cancer 1991;27(1):68-72.

Sersa G, Cemazar M, Miklavcic D. Antitumor effectiveness of electrochemotherapy with cis-diamminedichloroplatinum(II) in mice. Cancer Res 1995 Aug 1;55(15):3450-5.

Tumor and electrodes

Electrochemotherapy today

- Approx. 80% objective of responses in treatment of primary and metastatic tumors in skin*:
  - Melanoma
  - Basal cell carcinoma
  - Kaposi sarcoma
  - Cervix leiomyosarcoma
  - Head and neck cancer
  - Hypernephroma
  - Squamous cell carcinoma of the skin
  - Breast cancer



*Marty M, Sersa G, Garbay JR, Gehl J, Collins CG, Snoj M, et al. Electrochemotherapy - An easy, highly effective and safe treatment of cutaneous and subcutaneous metastases: Results of ESOPE (European Standard Operating Procedures of Electrochemotherapy) study. European Journal of Cancer Supplements 2006 Nov;4(11):3-13.

* Sersa. The state-of-the-art of electrochemotherapy before the ESOPE study; advantages and clinical uses. European Journal of Cancer Supplements 2006 Nov;4(11):52-9.

Treatment

US guided insertion of the electrodes

Inserted electrodes

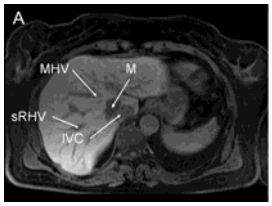
Electric pulse generator – Cliniporator Vitae

Two necessary conditions for successful treatment

- Sufficient coverage of the tumor with electric field
- Sufficient concentration of the cytotoxic drug in the tumor

Liver metastases - first case

- Single metastasis in Sg1, on the inferior caval vein, between the right hepatic vein and the common trunk treated with ChT and cetiximab – some downsizing achieved.
- Considering specific location RFA could not be effective because of cooling effect of the veins.
- Radical resection was potentially possible with right trisectionectomy (leaving only lateral part of the left liver – too small liver remnant – damage from ChT)



- Axial T1W **MRI image,** showing a hypointense lesion (M) in between inferior vena cava (IVC), superior right hepatic vein (sRHV) and middle hepatic vein (MHV), in late liver phase, 20 min post Gd-EOB-DTPA.

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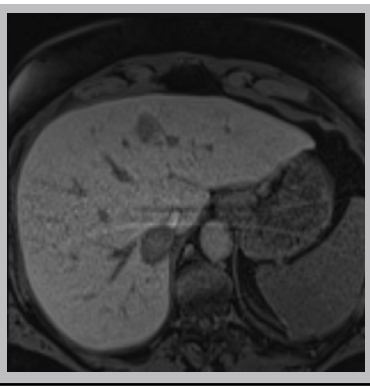
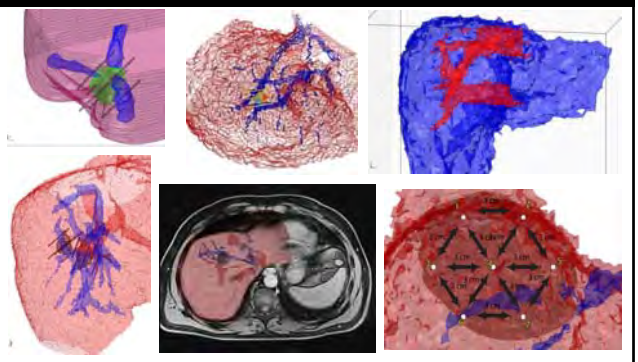
Treatment planing – Images importing and analysing

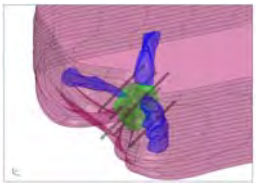


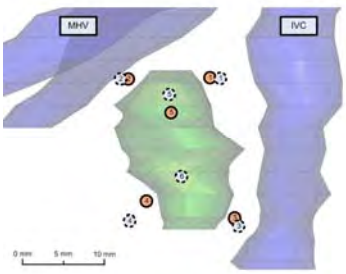
Segmentation



Numerical treatment planning

- 3-D model geometry was built based on segmented MRI images of the patient
- Positioning of the electrodes for optimal coverage of the tumor with electric field





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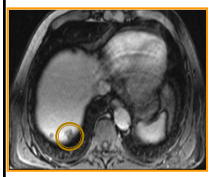
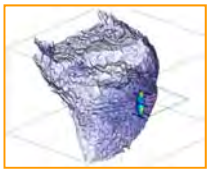
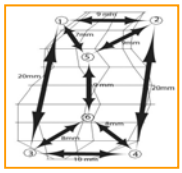
Treatment planing and executing

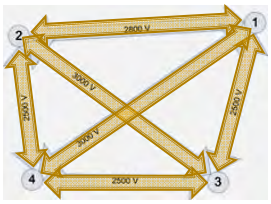






Electrode pair	Voltage according to plan [V]	No. of pulses according to plan	Predicted current [A]	Delivered voltage [V]	Delivered No. of pulses	Measured current [A]
1-5	2100	8	31	1300	20	32.3
1-6	2100	8	26	2100	8	45.2
2-5	2100	8	26	1700	21	44.7
2-6	2100	8	25	2100	8	48.3
3-5	2100	8	25	2100	8	48.9
3-6	2100	8	29	1900	8	48.8
4-5	2100	8	28	2100	8	47.5
4-6	2100	8	33	1700	16	41.1
5-6	1700	8	40	1700	8	48.9
Total		72			105	

Treatment planning



Voltage between electrode pairs

Tumor coverage

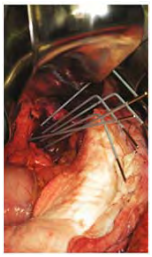
Miklavcic et al. Towards treatment planning and treatment of deep-seated solid tumors by Electrochemotherapy. BioMedical Engineering OnLine 2010, 9:10

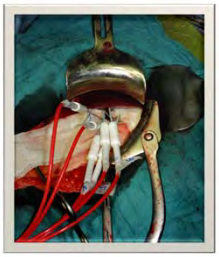
Online treatment planing

www.visifield.com

Identification of metastasis and preparatory procedures needed before delivery of electric pulses

- Verification of target lesion
- Ultrasound guided insertion of electrodes according to the treatment plan
- Connection of electrodes to Cliniporator Vitae
- Injection of Bleomycin intravenously (15 000 IU/m²)





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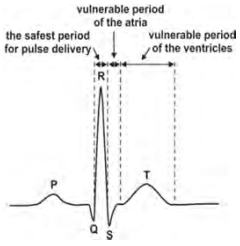
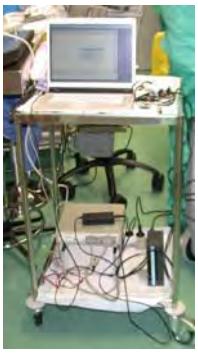
ECG syncronization





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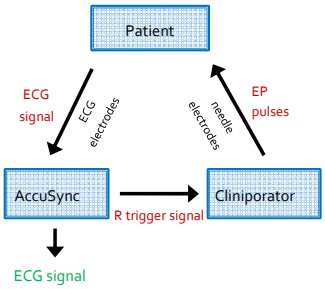
Delivery of electric pulses and ECG syncronization

- Delivery of pre-pulses is to verify the connections between the electrodes and Cliniporator *VITAE* outputs and also to predict (based on the current measured at low voltage) the current levels for the imminent electroporation pulses.
- Triggering of electric pulses was synchronized with ECG signals, through the ECG triggering device AccuSync to avoid delivery of pulses in vulnerable period of the heart



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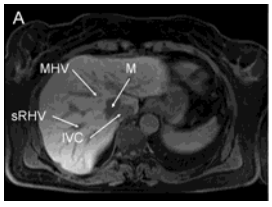
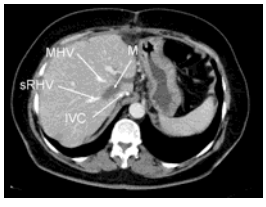
Post-treatment follow up





- Two months after electrochemotherapy CT was performed
- No change in size of the metastasis treated
- CT image showed that margins were blurred, which demonstrated that treatment had some effect
- Reoperation planned

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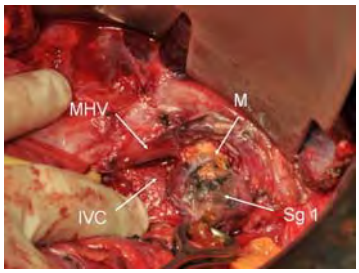
Surgical resection of the metastasis after electrochemotherapy

- The otherwise fragile and tender hepatic veins walls were firm and not vulnerable
- The whole tumor was resected
- Macroscopically the tumor was necrotic



Resection of Sg 1 with common trunk and MHV exposed: Necrotic metastasis (M) is visible in Sg 1, close to the MHV and IVC.

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ECT of liver metastases

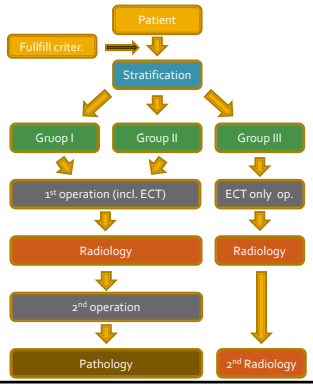
- The patient is 5 yrs. without reccurent disease

Professor Eldar M. Gadzijev

Electrochemotherapy – clinical trial

- Based on previous encouraging reports
- Phase I/II trial, approved by institutional and national ethical committee
- **The primary objective** of the study was evaluation of the feasibility and safety of intraoperative electrochemotherapy of colorectal liver metastases
- **The secondary objective** was to determine the efficacy of the treatment based on histological analysis of the treated metastases and radiological evaluation of the ECT treated metastases

Study design and patient groups - overview



Pulse generator end electrodes

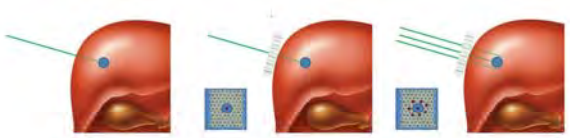
Cliniporator VITAE – IGEA S.p.A., Carpi Italy

Longe needle electrodes (left) with variable geometry and electrodes with fixed geometry (right)

Electrochemotherapy

- ***Agent:***
  - Bleomycin – BLM: Bleomycinum, Heinrich Mack Nachf. GmbH & Co. KG, Illertissen, Germany
  - Dosage: 15 mg/m^2
  - Administration: intravenous in bolus
  - Interval to application of electric pulses: 5-30 min
- ***Electroporation:***
  - Up to 6 singles electrodes, one (or two) inserted centrally into the tumor, the other around the tumor in normal tissue with 1.0 safety margin or electrodes with fixed geometry
  - Electrical parameters: electrical pulses with amplitude up to 3000 V, 100 µs duration, synchronized with hearth beat

Paralel position of electrodes

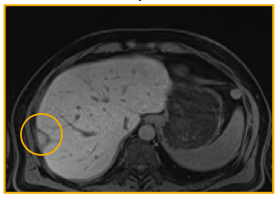


Results – Patients and Metastases

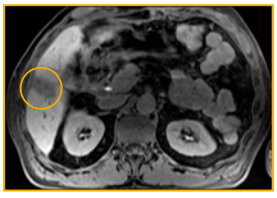
- 16 pts. (12 males, 4 females)
- Median age 60,3 (36,6 – 69,1)
- Response evaluable on 15 patients
- 27 evaluable metastases out of 29 treated
- 21 evaluable metastases treated with long needle electrodes and 6 with fixed geometry electrodes
- Median diameter of the metastases: 18 mm (6 – 29mm)
- 13 metastases (48%) were located near or in-between the major blood vessels of the liver
- The median duration of the patient's hospitalization was 13 days (range 7 – 42 days); excluding 3 patients that needed prolonged hospitalization due to the reoperation

How we measured - Radiology

- NC – no visible changes
- PR – mixed signs for vital and necrotic tumor tissue
- CR – complete respond – changes equal to changes induced by RFA

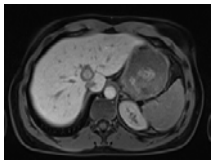


PR

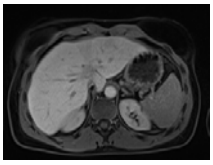


CR

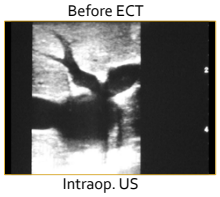
Successful ECT



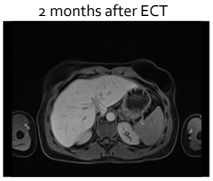
Before ECT



2 months after ECT



Intraop. US



6 months after ECT

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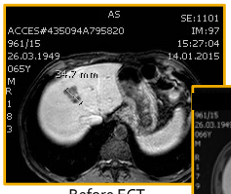
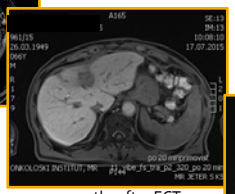
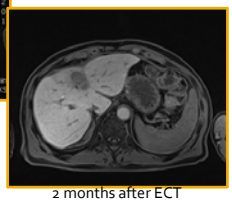
Unsuccessful ECT



Before ECT



1 months after ECT



2 months after ECT

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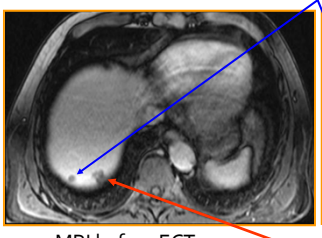
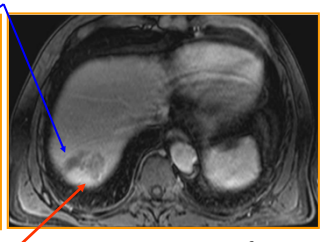
Radiology

ECT treated metastasis regressed,
visible are changes similiar than after RFA



MRI before ECT

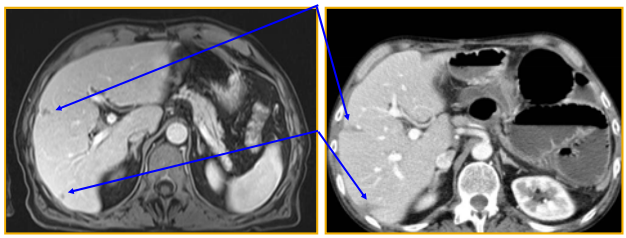


MRI after ECT

Non treated metastasis has grown

Radiology

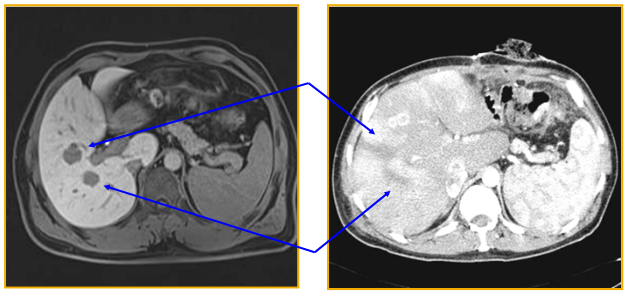
ECT treated metastases in Sg. V and VI regressed, changes are similiar to those after RFA



MRI before ECT

CT after ECT

Radiology



MRI before ECT

CT after ECT

Results – Patients and Metastases

	Closed trial	Extended trial (+ 8 new patients)
No. of patients	16 (12 m, 4 f)	24 (17 m, 7 f)
Median age	60,3 (36,6 – 69,1)	62,3 (32,4 – 76,6)
Response evaluable on	15 patients	23 patients
Response evaluable on	27/29 metastases	37/39 metastases
Electrode type	21 long, 6 fixed	23 long, 10 fixed (4 missing data)
Major vessels proximity	13 (48%)	17 (51%) (4 missing data)
Median diameter	18 mm (16 – 29)	20 mm (5 – 50)

Results - Radiology

23 evaluable pts, 37 metastases

Evaluation	Total evaluated	Complete response	Partial response	No Changes	Progress
All pts., 1st ev. evaluation	37	27 (73 %) 85 %*	7 (19 %) 15 %*	1 (3 %) -*	2 (5 %) -*
All pts., final evaluation	**37**	**26 (71 %)**	**5 (13 %)**	**1 (3 %)**	**5 (13 %)**

*results from our previous trial

Patients with 2 radiological evaluations – 11 pts, 19 metastases

Evaluation	Total evaluated	Complete response	Partial response	Progress
1st	19	15 (79 %)	4 (21 %)	0 (0 %)
2nd	19	14 (73 %)	0 (0%)	5 (26 %)

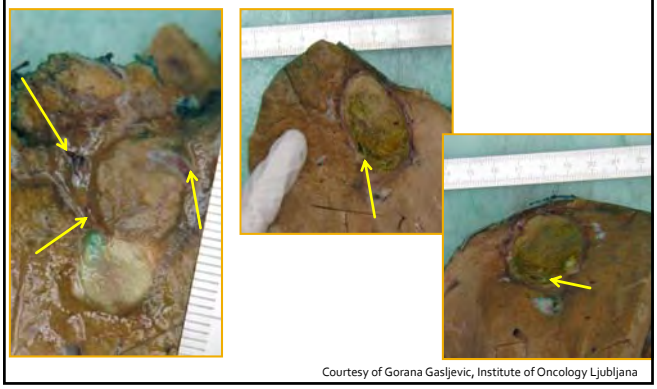
Results - Radiology

19 pts. 33 metastases, 4 pts. missing data

Location	Total evaluated	Complete response
Central (adjacent to the major vessels)	17	10 (59%)
Peripheral (away from major vessels)	16	15 (94%)

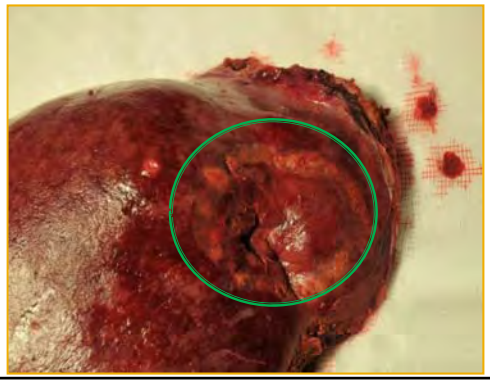
Chi-square test: $p = 1$

Preserved structures within electroprated field

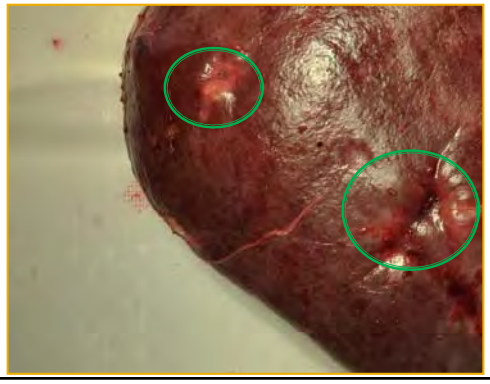


Courtesy of Gorana Gasljevic, Institute of Oncology Ljubljana

Macroscopic appearance

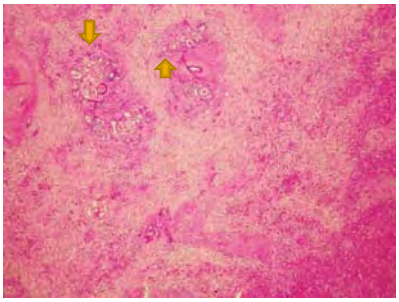


Macroscopic appearance



How we measured - Pathology

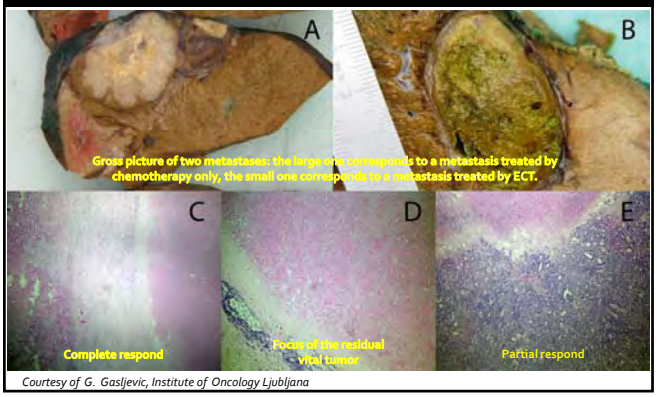
Percent of viable tumor tissue



Fibrotic involution of the metastasis with some smaller focuses of residual tumor tissue in the central part of the tumor (arrows).

Courtesy of G. Gasljevic, Institute of Oncology Ljubljana

Pathology



Courtesy of G. Gasljevic, Institute of Oncology Ljubljana

Results - Pathology

7 patients evaluable (all 6 from group I and 1 out of 2 from group II)

	Treated Metastases	Non Treated Metastases
Number of metastases	13	22
Viable tumor tissue	0 – 30%	0,25 – 70%
Average	9,2%	34,1%
Median	0,5%	35%

t-test: two-tailed P-value = 0,00116

Group	Pathologic response				
	Compl. (0-<1%)	Major(1-25%)	Medium(26-50%)	Minor (>51%)	All
Control	1 (4,5%)	9 (40,9%)	7 (31,9%)	5 (22,7%)	22
ECT	7 (54,0%)	3 (23,0%)	3 (23,0%)	0 (0,0%)	13
All	8	12	10	5	35

Chi-square test: $p = 0.006$

Edhemovic I, Brecelj et al. Electrochemotherapy of the liver metastases, *JSO*, 2104

Thermal vs. Non-Thermal

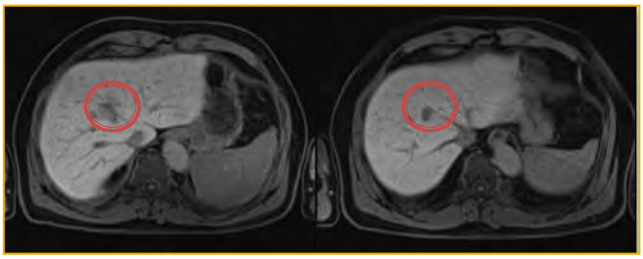
RFA

- Thermal injury of surrounding tissue
- Non – selective
- Takes longer
- Cooling effect
- Relasing of different tissue products

Electroporation

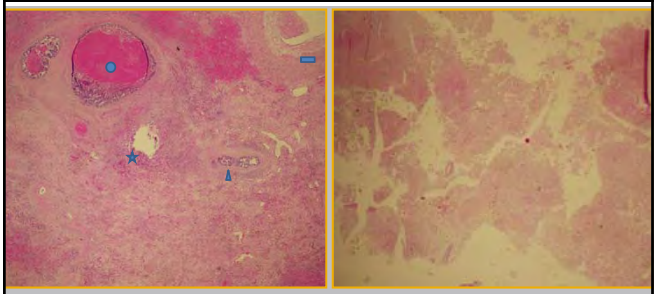
- No thermal injury
- Selective
- Takes less time
- No cooling effect

Preserved major vessels



Courtesy of Maja Music, Institute of Oncology Ljubljana

ECT vs. RFA



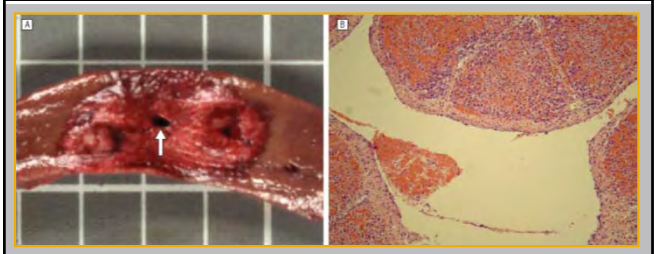
Star – fibroseus nodus (regresessicv changes) after ECT
Circle – residual, partialy necrotic tumor
Triangle – preserved biliar duct within fibroseous nodus
Rectangle – preserved, somehow edematoseus blood cessels within fibroseous nodus

Courtesy of Gorana Gasljevic, Institute of Oncology Ljubljana

RFA – the extent of destruction and heat sink effect

R. Czymek et al. Intrahepatic radiofrequency ablation versus electrochemical treatment in vivo/ Surgical Oncology 21 (2012)

No heat sink effect

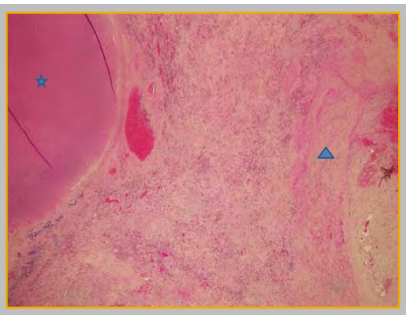


Irreversible Electroporation for the Ablation of Liver Tumors. Are We There Yet? Kevin P. Charpentier, MD. ARCH SURG/VOL 147 (NO. 11), NOV 2012

Preserved structures within electroprated field

Courtesy of Gorana Gasljevic, Institute of Oncology Ljubljana

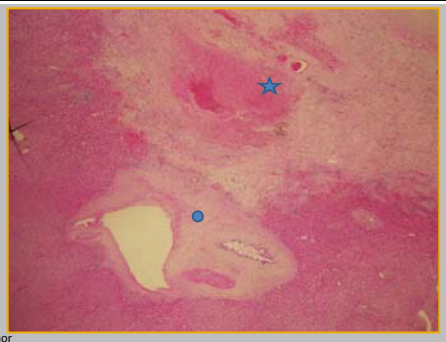
Preserved blood vessel close to the tumor



Star – necrotic tumor with some vital tumor tissue
Triangle – preserved blood vessel with recanalized thrombus

Courtesy of Gorana Gasljevic, Institute of Oncology Ljubljana

Preserved portal triad



Star – necrotic tumor
Circle – unchanged portal triad, surrounded with healthy liver tissue
Courtesy of Gorana Gasljevic, Institute of Oncology Ljubljana

Adverse effects – general remarks

- All patients included in the study were extensively pretreated with systemic therapy or had had previous abdominal operations
- All the post-operative adverse events that occurred can therefore be attributed to the general condition of the patients and the complexity of the surgery, so it is unlikely that any of these complications could be attributed to the ECT itself

ECT related postoperative complications

2 pts. with complications / 14 pts. with no complications

- Fever (CTC-AE grade 1) – 2 pts.

Non-ECT related postoperative complications within first 24 h

2 pts. with complications / 14 pts. with no complications

- Infection NOS (CTC-AE grade 1) – 1 pt.
- Pulmonary hypertension (CTC-AE grade 3) – 1 pt.

Non-ECT related postoperative complications after first 24 h (CTC-AE grade)

12 pts. with complications

4 pts. with no complications

SIRS (1)	**Small bowel obstr. (3)** Infection NOS (1)
Atrial fibrillation (2) **Colon perforation (3)**	Ascites (2) **Colon perforation (3)** Pleural effusion (2)
Infection NOS (1)	Abd. abscess (3)
Abd. abscess (3) Pneumonia (1) Wound infection (2)	Cholestatic icterus (2) Infection NOS (1) Biliary fistula (3) Transient liver failure (2) Transient renal failure (3) Pleural effusion (2)
Transient liver failure (2)	Infection NOS (1) Biliary fistula (3)
Ascites (2) Infection NOS (1)	Supravent. tachycard. (2)

Non-ECT related postoperative complications after first 24 h (CTC-AE grade)

Groups	ID	Complications
I (two stage)	01	SIRS (1)
	02	•
	03	Atrial fibrillation (2) **Colon perforation (3)**
	04	•
	05	•
	06	Infection NOS (1)
II (two operat.)	07	Abd. abscess (3) Pneumonia (1) Wound infection (2)
	08	Transient liver failure (2)

12 pts. with complications
4 pts. with no complications

Groups	ID	Complications
III (one operation)	09	Ascites (2) Infection NOS (1)
	10	Supravent. tachycard. (2)
	11	**Small bowel obstr. (3)** Infection NOS (1)
	12	Ascites (2) **Colon perforation (3)** Pleural effusion (2)
	13	Abd. abscess (3)
	14	•
	15	Cholestatic icterus (2) Infection NOS (1) Biliary fistula (3) Transient liver failure (2) Transient renal failure (3) Pleural effusion (2)
	16	Infection NOS (1) Biliary fistula (3)

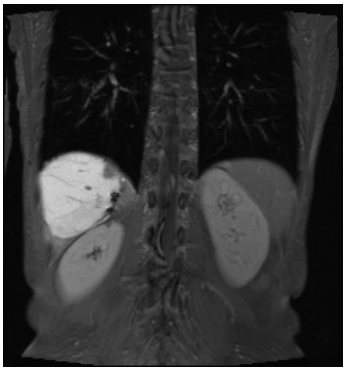
ECG analysis

- No significant heart rhythm disturbances or pathological morphological changes that would indicate the development of myocardial ischemia after ECT detected
- ECG analysis revealed some statistically significant but clinically irrelevant changes in the properties of the ECG during and after the surgical procedure
- The most obvious one was a mild increase in heart rate immediately after ECT (2 pts) and also during the first 24 hours after the procedure (3 pts)

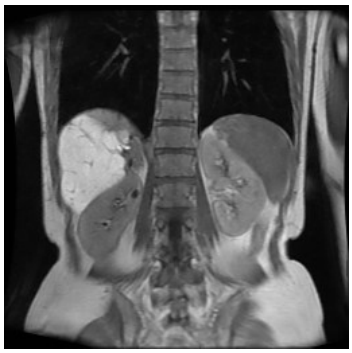
Electrode – related complications

- The treatment of 13 metastases (48%) that were located near or in-between the major blood vessels of the liver was safe
- Neither intraoperatively nor postoperatively was bleeding observed. In some cases, the retraction of the electrodes resulted in mild bleeding, which was immediately stopped by electrocoagulation.

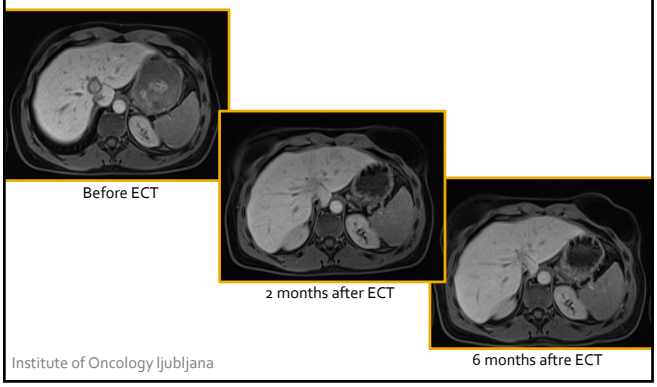
Before treatment



After treatment



Metastatic breast cancer



Institute of Oncology Ljubljana

Conclusions

- Electrochemotherapy is safe and efficient treatment modality
- It is widely accepted in national guidelines fom various skin tumors
- In liver, it was shown that ECT have a specific place in difficult to treat metastases, located in the vicinity of major hepatic vessels, not amenable to surgery or radiofrequency ablation
- Has the time come?

The team

- **Prof. dr. Eldar Gadžijev, surgeon, principal investigator**
- **Prof. dr. Gregor Serša, coordinator**
- Prof. dr. Maja Čemažar
- Dr. Erik Brecelj - surgeon
- Dr. Ibrahim Edhemović - surgeon
- Prof. dr. Marko Snoj – surgeon
- Dr. Janja Ocvirk – medical oncologist
- Dr. Maja Marolt Mušič - radiologist
- Dr. Gorana Gašljević - pathologist
- Tjaša Pečnik, research nurse

- **Prof. dr. Damijan Miklavčič**
- Dr. Anže Županič
- Dr. Bor Kos
- Prof. dr. Tomaž Jarm,
- Dr. Barbara Mali
- Dr. Denis Pavliha
- Dr. Marija Marčan

Disclosures

- The study was financially supported by the Slovenian Research Agency (P3-0003 and P2-0249)
- Research was conducted in the scope of the EBAM European Associated Laboratory (LEA)
- In collaboration with IGEA
- D.M. holds patents (US 7625729 B2; EP 1395333 B1; US 7306940 B2) of which some have been licensed to IGEA SpA

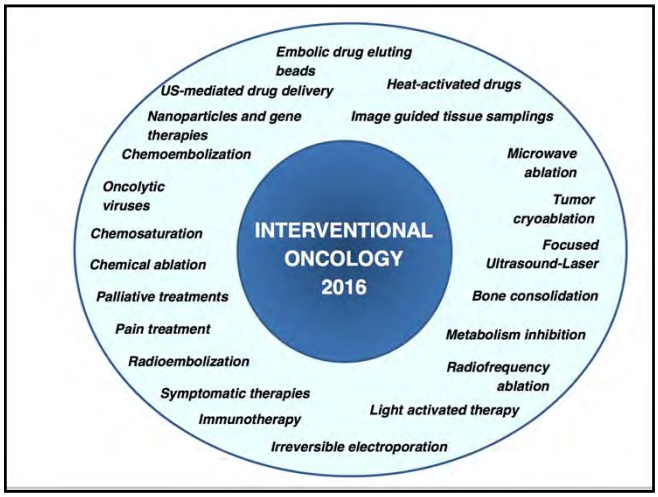
Thank you for you attention!

30.11.Ljubljana

Perkutano lokalno zdravljenje jetrnih lezij

Popovič Peter
Nina Boc

Klinični Inštitut za radiologijo, UKC Ljubljana
Oddelek za radiologijo, Onkološki Inštitit Ljubljana
Medicinska Fakulteta, Univerza v Ljubljani,



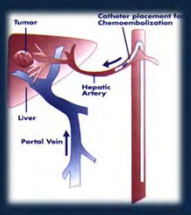
Intraarterijska lokoregionalna terapija

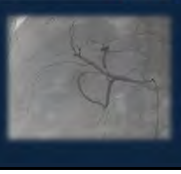
- **Transarterijska kemoembolizacija –**

  "conventional" *cTACE (*lipiodol)

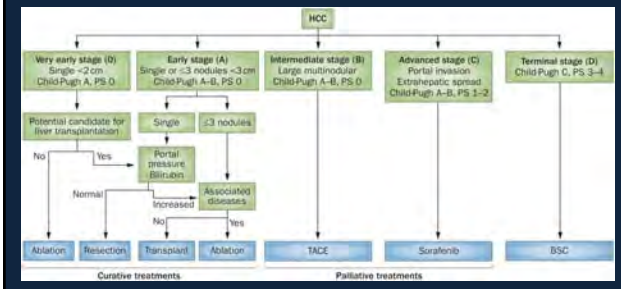
  "Drug-eluting Microspheres" TACE
  Doxorubicin - DEBDOX
  Irinotekan - DEBIRI

- **Radioembolizacija (SIRT)**:Ytrium 90 radioaktivni mikrodelci (<30 mikronov)





BCLC klasifikacija



Forner, A. *et al.* (2014) Treatment of intermediate-stage hepatocellular carcinoma. *Nat. Rev. Clin. Oncol.*

UKC Ljubljana

- Register raka 2009

133 HCC/leto*.

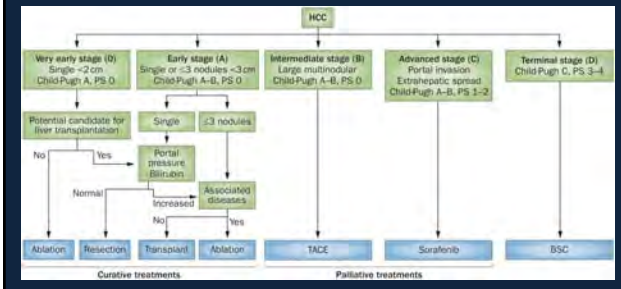
- Januar 2011- december 2012 (144 bol)
  - *kirurgija* *20 bol*
  - *TX jeter* *3 bol.* *(18,8%)*
  - *RFA* *4 bol*

  - *DEBDOX* *70 bol*
  - *Radioembolizacija* *5 bol* *(59,7%)*
  - *DEBDOX+sorafenib* *11 bol*

  - *sorafenib* *31 bol* *(21,5%)*

*www.onko-i.si/rss

BCLC klasifikacija



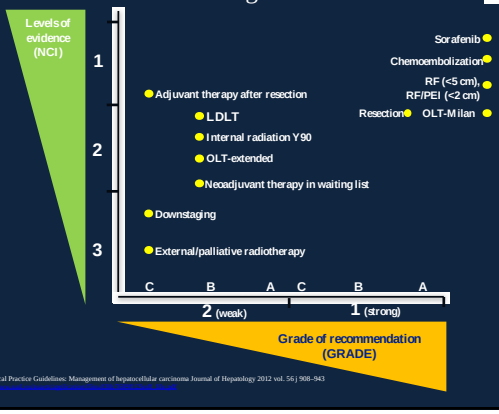
Forner, A. *et al.* (2014) Treatment of intermediate-stage hepatocellular carcinoma. *Nat. Rev. Clin. Oncol.*

Srednji štadij HCC: Prognoza - EASL, EORTC

- srednje preživetje 11- 16 mesecev
- multidisciplinarni pristop

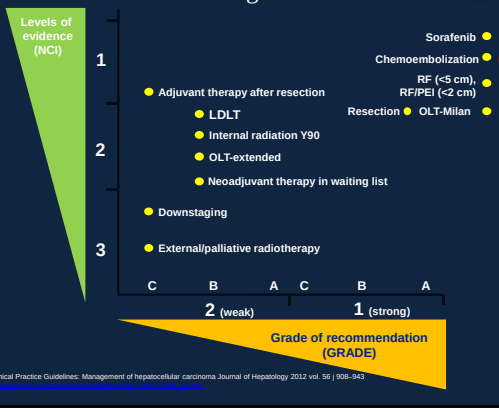
EASL–EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma Journal of Hepatology 2012 vol. 56 j 908–943

Intermediate stage HCC: Levels of evidence and grade of recommendati



EASL–EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma Journal of Hepatology 2012 vol. 56 j 908–943
Available on:

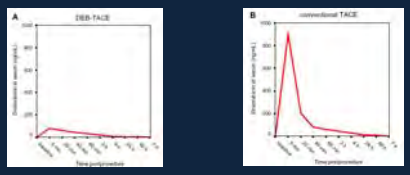
Intermediate stage HCC: Levels of evidence and grade of recommendation



EASL–EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma Journal of Hepatology 2012 vol. 56 j 908–943
Available on:

Chemoembolization of hepatocellular carcinoma with drug eluting beads: Efficacy and doxorubicin pharmacokinetics☆☆

María Varela[1], María Isabel Real[2], Marta Burrel[2], Alejandro Forner[1], Margarita Sala[1], Mercé Brunet[3], Carmen Ayuso[2], Lluis Castells[4], Xavier Montaná[2], Josep M. Llovet[1,5], Jordi Bruix[1,*]



Serum doxorubicin pic value (5 min)

Conventional TACE : 890ng/ml

Precision TACE : 90ng/ml

J Hepatology, 2007

Clinical Management and Research in HCC: Building Multidisciplinary Consensus

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Antitumour treatment

Evolving strategies for the management of intermediate-stage hepatocellular carcinoma: Available evidence and expert opinion on the use of transarterial chemoembolization

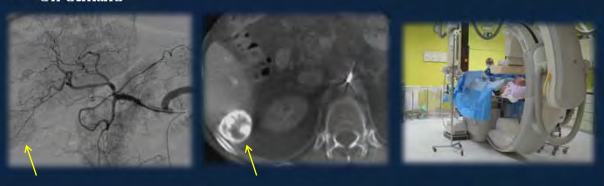
J.-L. Raoul[a,*], B. Sangro[b,c], A. Forner[d], V. Mazzaferro[e], F. Piscaglia[f], L. Bolondi[f], R. Lencioni[g]

"Compared with conventional TACE, drug eluting bead has a standardized methodology, is more reproducible, and offers improved response and a significantly better safety profile".

Cancer Treat Rev 2010

DEBDOX TACE-standardizirana metoda

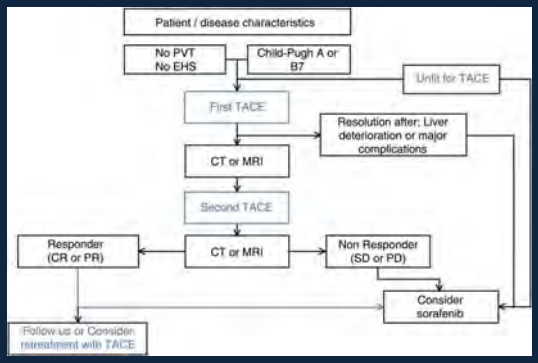
- 75 -100 μ ,100-150 mgDoxorubicin
- Superselektivni pristop (mikrokateter) pod kontrolo CBCT
- mRECIST
- "On demand"



 # Iwazawa, J., et al. Eur. J. rad., 2012

**Popovič P et al. Radiology and Oncology 2016*

Algoritem za vodenje bolnikov v srednjem štadiju HCC ("on demand")



Dufour J et al. Ann Oncol 2013

Odgovor na zdravljenje

- CT & MRI na 3 mesece
- **odgovor na zdravljenje**

  Response Evaluation Criteria in Solid Tumors (mRECIST).

Table 2. Overall response for all possible combinations of tumor response for target and nontarget lesions with or without the apperance of a new lesions*

Target lesion	Nontarget lesion	New lesion	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

*CR=complete response, PR=partial response, SD=stable disease, PD=progressive disease

Llovet JM, et al. J Natl Cancer Inst. 2008

Rezultati-preživetje

mOS 11-16 mesecev

	Malagari et al. CVIR 2012 DEB-TACE	Burrel M et al. J of Hepatol 2012 DEB-TACE	Popovic et al. Radiology and oncology 2016 DEB-TACE	Llovet et al Lancet 2002 Lo et al. Hepatology 2002 cTACE
mOS	43.8 mo	48.6 mo.	33.9 mo.	20-24 mo.
3-y OS	A/B 62/51%	A/B 68/64%		26-29%
5 - y OS	A/B 29/13%	A/B 34/39%		

mOS 25-37 mesecev

Radioembolizacija (SIRT)

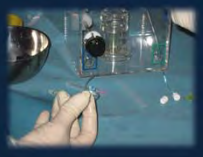
(selektivna notranja radioterapija, hepatična brahiterapija)

selektivna intraarterijska aplikacija zelo visoke doze sevanja v tumorje v jetrih, ob prejeti majhni dozi sevanja normalnega jetrnega tkiva

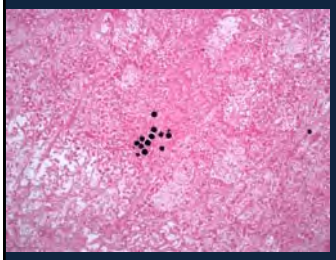
Mikrodelci (20-40 um) Y-90

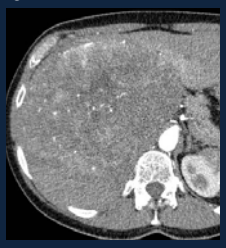
Y-90: Beta sevanje
povprečna razdalja: 2,5 mm
največja razdalja: 11 mm
doza do 3 GBg
120 Gy

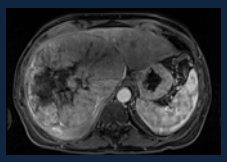
raspolovni čas: 64 h



51 let, Ž, HCC 18 cm, brez ciroze



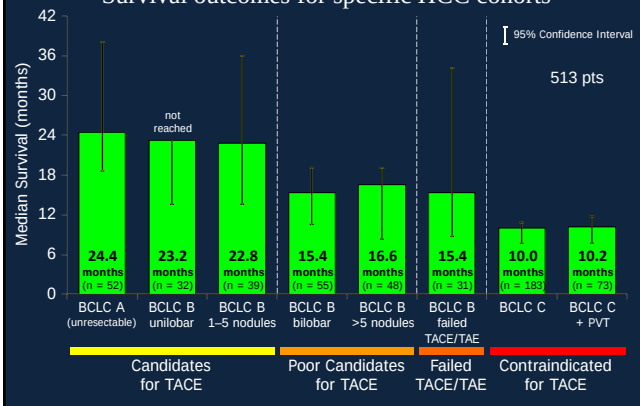




nekroza

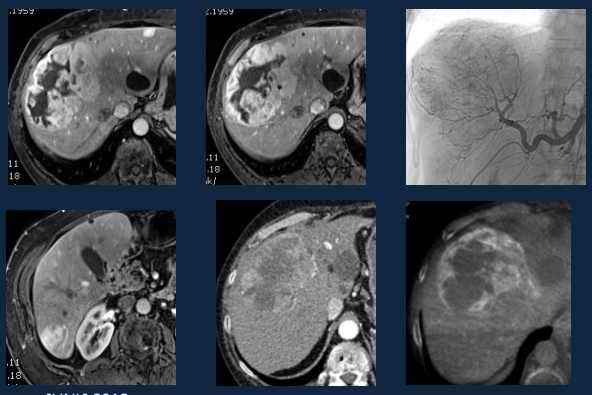
hcc

ENRY Study of SIR-Spheres microspheres in HCC: Survival outcomes for specific HCC cohorts



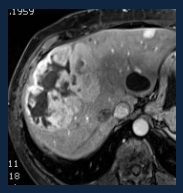
Sangro *et al. Hepatology* 2011; **54**: 868–878. Ettorre *et al. ASCO Annual Meeting, J Clin Oncol* 2011; **29** (Suppl): Abs. 4099.

54 let, Ž, multifokalni HCC 12 cm, BCLC B, Child A

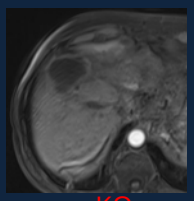


JUNIJ 2013

54 let, Ž, multifokalni HCC 12 cm, BCLC B, Child A



3 x SIRT
&
Nexavar



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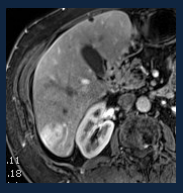
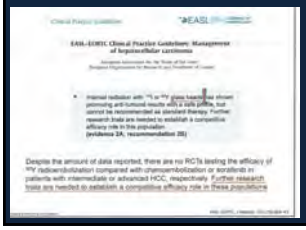
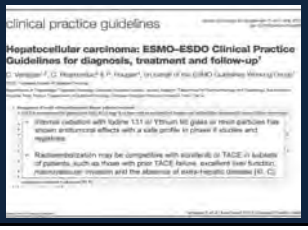


36 mesecev

Junij 2013

Oktober 2016





Klinične raziskave v teku SIRT pri bolnikih v srednjem in napredovalem štadiju HCC

	SARAH[1]	SORAMIC[2]	SIRveNIB[3]	YES-P[4]	STOP-HCC[5]
No. Patients	400 RC: Mar-15	665 RC: Feb-16	360 RC: Mar-16	328 Non-recruiting	400 EC: Oct-19
Control Arm	SOR	SOR	SOR	SOR	SOR
Exp. Arm	RE	RE + SOR	RE	RE	RE + SOR
Endpoint	OS	OS	OS	OS	OS
Area	France	EU	Asia-Pacific	US + EU	Global

SIRT- naše izkušnje

- junij 2012-februar 2016
- 13 bolnikov, povprečne starosti 62 let (razpon 50 – 85 let)
  - HCC 12 bol
  - *(slabi kandidati za TACE - bilobarna bolezen in/ali velik tumor >10 cm; neuspešen TACE, progres po TACE)*
  - jetrni zasevki karcinoma želodca 1 bol

SIRT naše izkušnje zapleti

3/20 posegov (15%)

Manjši zapleti		
zaplet	**število**	**zdravljenje**
bolečina	3	Ne opijatni analgetiki

SIRT naše izkušnje odgovor na zdravljenje

SIRT	Objektivni odgovor (CR+PR)	Stabilna bolezen (SD)	Progres NT
13 pts	10/13 pts.	1/13 pts.	2/13 pts.
	76.9%	7.7%	15.4%

mCRC-oligometastatska bolezen

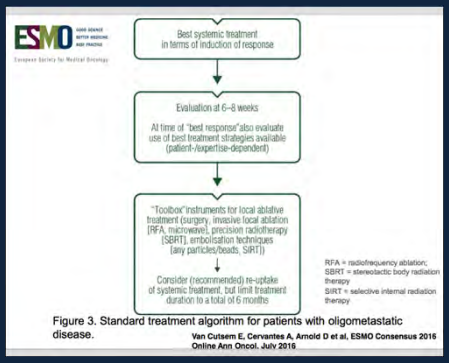
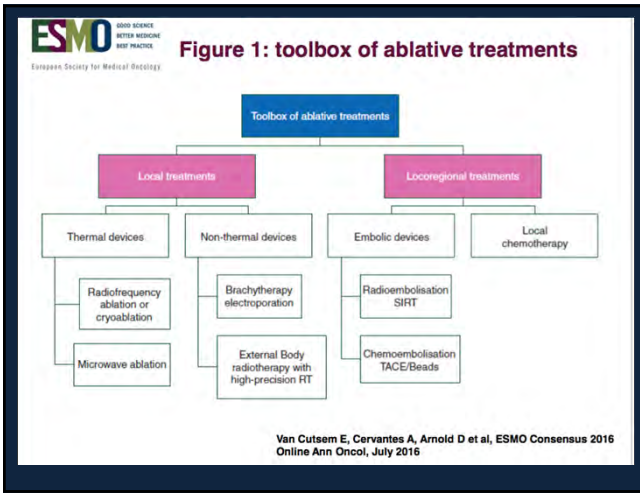


Figure 3. Standard treatment algorithm for patients with oligometastatic disease.

Van Cutsem E, Cervantes A, Arnold D et al, ESMO Consensus 2016 Online Ann Oncol, July 2016



Van Cutsem E, Cervantes A, Arnold D et al, ESMO Consensus 2016 Online Ann Oncol, July 2016

Annals of Oncology

Annals of Oncology Advance Access published July 7, 2016

Annals of Oncology 0: 1–38, 2016
doi:10.1093/annonc/mdw235

ESMO consensus guidelines for the management of patients with metastatic colorectal cancer

E. Van Cutsem[1*], A. Cervantes[2], R. Adam[3], A. Sobrero[4], J. H. Van Krieken[5], D. Aderka[6], E. Aranda Aguilar[7], A. Bardelli[8], A. Benson[9], G. Bodoky[10], F. Ciardiello[11], A. D'Hoore[12], E. Diaz-Rubio[13], J.-Y. Douillard[14], M. Ducreux[15], A. Falcone[16,17], A. Grothey[18], T. Gruenberger[19], K. Haustermans[20], V. Heinemann[21], P. Hoff[22], C.-H. Köhne[23], R. Labianca[24], P. Laurent-Puig[25], B. Ma[26], T. Maughan[27], K. Muro[28], N. Normanno[29], P. Österlund[30,31], W. J. G. Oyen[32], D. Papamichael[33], G. Pentheroudakis[34], P. Pfeiffer[35], T. J. Price[36], C. Punt[37], J. Ricke[38], A. Roth[39], R. Salazar[40], W. Scheithauer[41], H. J. Schmoll[42], J. Tabernero[43], J. Taieb[25], S. Tejpar[1], H. Wasan[44], T. Yoshino[45], A. Zaanan[25] & D. Arnold[46]

Recommendation 16: embolisation.

• For patients with liver-limited disease failing the available chemotherapeutic options

° Radioembolisation with yttrium-90 microspheres should be considered [II, B].

°Chemoembolisation may be also considered as a treatment option [IV, B].

• Radioembolisation (and chemoembolisation) of CLM in earlier treatment lines may be interesting as 'consolidation treatment' but should be limited to clinical trials.

mCRC - DEBIRI

Table II. *Key studies adopting DEBIRI in the treatment of not resectable LM from CRC.*

Author	Patients	Line of therapy	Drugs adopted	Embolic agent used	ORR %	PFS (months)	OS (months)
MARTIN (40)	55	STL	IRI	DC Bead	66 at 6 months 75 at 12 months	11	19
ALIBERTI (41)	82	STL	IRI	DC Bead	78	8	25
MARTIN (42)	10	FL	IRI (+ FOLFOX)	DC Bead	100	n.r	15.2
EICLHER (43)	11	TL	IRI	DC Bead	18	n.r	n.r.
FIORENTINI (44)	20	TL	IRI	DC Bead	65	6	14
FIORENTINI (45)	36	STL	IRI	DC Bead	68.6	7	22
	38		FOLFIRI		20	4	15

FL: first line; SL: second line; TL: third line; STL: second and third line; IRI: irinotecan; FOLOFOX: folinic acid, fluorouracil and oxaliplatin given intravenously; FOLFIRI: folinic acid, fluorouracil and irinotecan given intravenously; n.r.: not reported; ORR: overall response rate; PFS: period free survival; OS: overall survival.

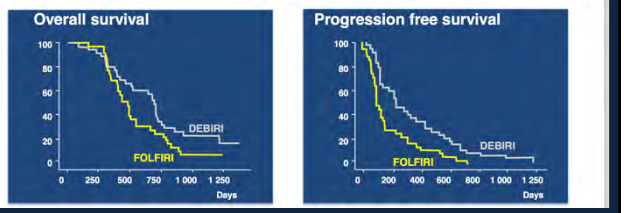
13,3-25 mesecev

Fiorentini et al., Anticancer Research 2014;34:575-84

RCT: DEBIRI&FOLFIRI

Intra-arterial Infusion of Irinotecan-loaded Drug-eluting Beads (DEBIRI) *versus* Intravenous Therapy (FOLFIRI) for Hepatic Metastases from Colorectal Cancer: Final Results of a Phase III Study

GIAMMARIA FIORENTINI[1], CAMILLO ALIBERTI[2], MASSIMO TILLI[3], LUCA MULAZZANI[4], FRANCESCO GRAZIANO[5], PAOLO GIORDANI[6], ANDREA MAMBRINI[7], FRANCESCO MONTAGNANI[8], PAOLO ALESSANDRONI[9], VINCENZO CATALANO[1], PAOLO COSCHIERA[9]



Median survival was 22 months, for DEBIRI and 15 months for FOLFIRI (p=0.031, log-rank).

AnticancerRes 2012

Randomized Controlled Trial of Irinotecan Drug-Eluting Beads With Simultaneous FOLFOX and Bevacizumab for Patients With Unresectable Colorectal Liver-Limited Metastasis

Robert C. G. Martin II, MD, PhD[1,2]; Charles R. Scoggins, MD, MBA[1,2]; Marshall Schreeder, MD[3]; William S. Rilling, MD[4]; Christopher J. Laing, MD[5]; Clifton M. Tatum, MD[6]; Lawrence R. Kelly, MD[6]; Ricardo D. Garcia-Monaco, MD[7]; Vivek R. Sharma, MD[2,8]; Todd S. Crocenzi, MD[9]; and Steven M. Strasberg, MD[10]

In 2015

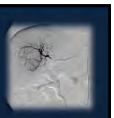
Cancer

- **70 patients : FOLFOX-DEBIRI *vs* FOLFOX/bevacizumab**

- Overall Response Rate
  - 2 months (78% vs 54%, p=.02)
  - 4 months (95% vs 70%, p=.03)
  - 6 months (76% vs 60%, p=.05)

- **Improved median progression-free survival was 15.3 vs 7.6 months and……**
- **downsizing to resection for FOLFOX-DEBIRI vs FOLFOX/bev (35% vs 16%, *P=.05*)**

TACE (DEBIRI) - indikacije



- stadij IV kolorektalni karcinom z neresektabilnimi zasevki v jetrih
- neodzivni na kemoterapijo (z/brez irinotekana)
- le jetrni zasevki ali minimalni ekstrahepatični zasevki
- zasevki zajemajo < 70% parenhima
- ustrezna jetrna in ledvična funkcija

Martin R.Journal of Oncology 2009

mCRC DEBIRI
Naše izkušnje

- Junij 2010 – juli 2016
- 21 bolnikov (63,9 let, razpon 34 -78 let)
- 63 DEBIRI (3,4 , razpon 2-4)
- Rektum 13 bol, kolon 8 bol
- Predhodna kemoterapija 11/21 bolnikov

Naše izkušnje - spremljanje

- ODGOVOR: Glede na mRECIST kriterije
- Popolni odgovor: ponovni CT vsake 3-4 mesece v 1. letu in vsake 6 mesecev v 2. letu
- Progres v jetrih: ponovna ocena lezij in obsega prizadetosti jeter ter načrtovanje ponovnega zdravljenja
- Progres zunaj jeter: načrtovanje nadaljnega zdravljenja v sodelovanju z onkologom (dodatna sistemska terapija ali nadaljevanje lokalnega zdravljenja)

Martin R.Journal of Oncology 2009

mCRC-naše izkušnje

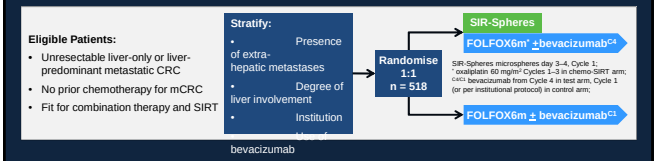
DEBIRI TACE	Spremljanje	Mrtvi	Srednje preživetje celokupno	Srednje preživetje po DEBIRI TACE
21 bol.	35,4 (1-68) mes.	17/21 bol.	43,4 mes. (22.2-64,6 m)	13,9 mes. (9,1-18,6m)

* Kaplan-Meier survival test.
Calculated with SPSS package version 19.

SIRFLOX raziskava

To assess the efficacy and safety of adding targeted radiation (SIR-Spheres® microspheres) to standard-of-care systemic chemotherapy (FOLFOX6m ± bevacizumab), compared to FOLFOX6m chemotherapy (± bevacizumab) alone as 1st-line therapy in patients with non-resectable colorectal liver metastases, with or without evidence of extra-hepatic metastases

Design: Prospective open-label, multi-centre, multi-national RCT



bevacizumab

Primary endpoint: Progression-free survival (PFS)

Sponsor: Sirtex

PIs: Prof. Peter Gibbs; Prof. Guy van Hazel

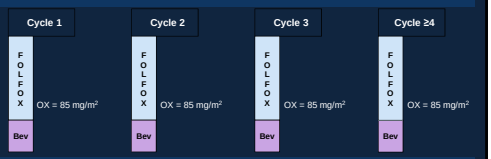
Status: Currently enrolling

Secondary endpoints: PFS in liver
Overall survival
Response rate
Quality of life
Recurrence rate
Toxicity
Resection rate

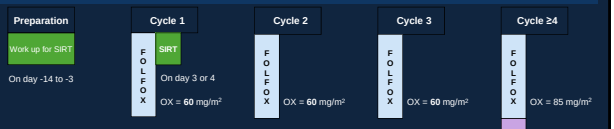
http://clinicaltrials.gov/ct2/show/NCT00724503; www.sirflox.com

SIRFLOX - protokol raziskave

Control arm: mFOLFOX6 (+ bevacizumab) [1]



Treatment arm: mFOLFOX6 (+ bevacizumab) [1] + SIRT [2]

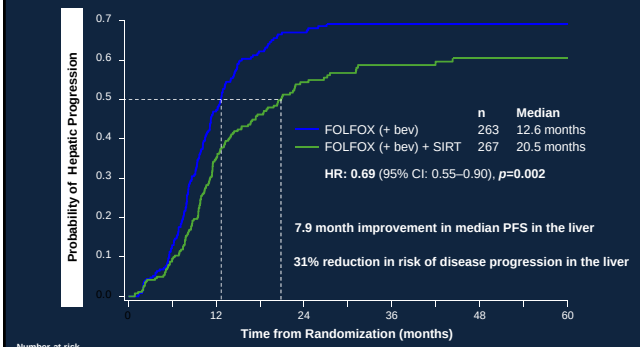


1. Bevacizumab allowed at investigator's discretion, per institutional practice.
2. Work-up procedure at Day (D) -14 to D-3 prior to SIRT; SIR-Spheres® Y-90 resin microspheres administered on either D3 or D4, of either Cycle 1 or Cycle 2.

Gibbs P *et al. Presented at 2015 ASCO Annual Meeting; J Clin Oncol* 2015; **33** (Suppl): Abs 3502.

Van Hazel G et al. J Clin Oncol 2016.

Progression-Free Survival in the Liver



Van Hazel G et al. J Clin Oncol 2016.

SIRT –rezultati preživetja 2017

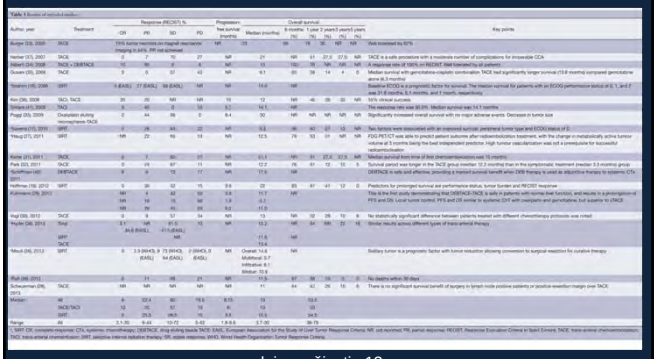
Study Name	Study Design	Geographic Region	Recruitment Completed	Patients Recruited	OS Data Expected
SIRFLOX	RCT	ANZ, EME, US	April 2013	530	2017
FOXFIRE	RCT	UK	November 2014	364	
FOXFIRE Global	RCT	ANZ, AP, EME, US	January 2015	209	
			Total accrual	1,103	

Holangiokarcinom - zdravljenje

- kirurgija (8-47% 5 let)
- 70% inoperabilni
- sistemska kemoterapija in radioterapija (srednje preživetje -11,7 mes)
- TACE/SIRT?

Khan S A et al., Lancet 2005
Valle JN et al., Engl J Med. 2010

Holangiokarcinom - TACE/DEBDOX/ SIRT

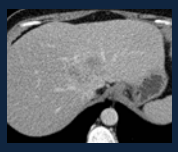


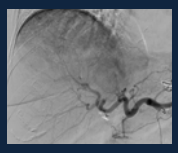
srednje preživetje 13 mesecev

Holangiokarcinom DEBDOX Naše izkušnje

- maj 2011 – februar 2016
- 8 bolnikov (62,8 let, razpon 50 -76 let)
- 21 DEBDOX (2,6 , razpon 1-6)
- Kemoterapija 6/8 (75%)

51 let. F, inoperabilni holangiokarcinom, januar 2013, DEBDOX TACE





TACE marec 2013

6 x DEBDOX TACE (4x 2013 in 2x 2015)

Sistemska KT

Preživetje 45,2 mes

Vir-arhiv KIR

Holangiokarcinom-naše izkušnje

DEBDOX TACE	Spremljanje	Mrtvi	Srednje preživetje	Srednje preživetje po TACE	prežievtje 1 let.	preživetje 2 let.
8 bol.	22,6 mes.	7/8 bol.	30,0 mes. (8.9-65 m)	22,6 mes. (2,5-54,4m)	75%	50 %

**Kaplan-Meier survival test.*
Calculated with SPSS package version 19.

clinical practice guidelines

Annals of Oncology 27 (Supplement 5): v28–v37, 2016
doi:10.1093/annonc/mdw324

Biliary cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

J. W. Valle[1], I. Borbath[2], S. A. Khan[3], F. Huguet[4], T. Gruenberger[5] & D. Arnold[6] On behalf of the ESMO Guidelines Committee*

- Radioembolisation may be considered in patients with inoperable iCCA, usually after first-line chemotherapy; patients should be encouraged to participate in clinical trials.

clinical practice guidelines

Annals of Oncology 23 (Supplement 7): vii124–vii130, 2012
doi:10.1093/annonc/mds295

Neuroendocrine gastro-entero-pancreatic tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

K. Öberg[1], U. Knigge[2], D. Kwekkeboom[3] & A. Perren[4] on behalf of the ESMO Guidelines Working Group*

[1]Department of Endocrine Oncology, University Hospital, Uppsala University, Uppsala, Sweden; [2]Department of Surgery, Rigshospitalet, Copenhagen, Denmark; [3]Department of Nuclear Medicine, Erasmus Medical Center, Rotterdam, The Netherlands; [4]Institute of Pathology, University of Bern, Bern, Switzerland

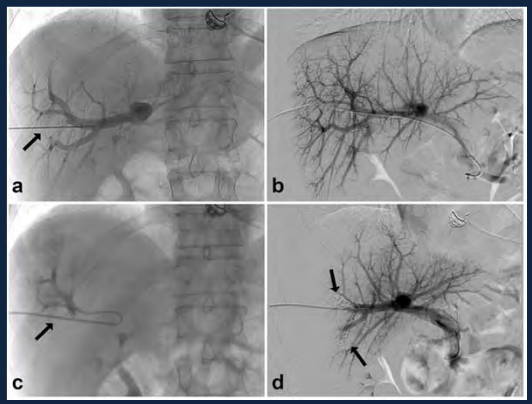
management of advanced/metastatic disease

The choice of the ablative or locoregional procedure such as radiofrequency ablation (RFA), laser-induced thermotherapy or selective hepatic transcatheter arterial embolization (TAE), chemoembolization (TACE) and selective internal radiotherapy (SIRT) depends on the local expertise, number and size of lesions and location of liver involvement

50 let, M, svetlo celični karcinom želodca, stanje po op želodca 2011, jetrni zasevki

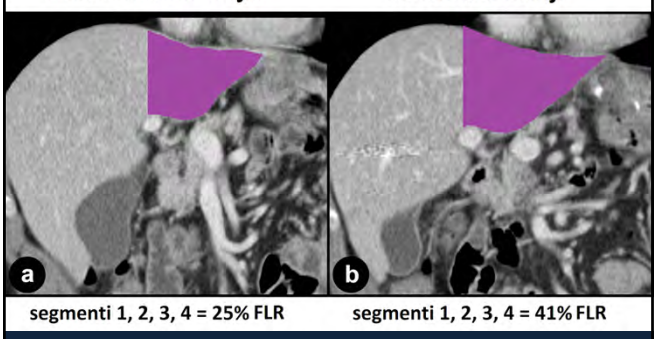
- Sistemska kemoterapija Oktober 2013 in 2014
- Junij 2014 progres (FRL 25%)
- TACE Julij & Avgust 2014 (pred op)
- PVE Avgust 2014 (pred op)

50 let, m, ca želodca, zasevki v jetrih, KT



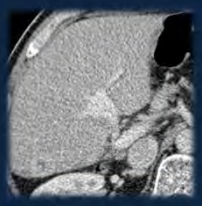
Embozene 250,500, 700, 900, 1300

50 let, m, ca želodca, zasevki v jetrih, KT



50 let, M, svetlo celični karcinom želodca, stanje po op želodca 2011, jetrni zasevki

- KT Oktober 2013
- KT 2014
- TACE Julij & Avgust 2014
- PVE Avgust 2014
- Desna hepatektomija oktober 2014
- *Zasevki v jetrih – progres maj 2015*



Histopathology

View issue TOC
Volume 65, Issue 1
July 2014
Pages 90–99

Original Article

Does clear cell carcinoma of stomach exist? Clinicopathological and prognostic significance of clear cell changes in gastric adenocarcinomas

Joo-Yeon Kim, Do Youn Park, Gwang Ha Kim, Tae-Yong Jeon, Gregory Y Lauwers

First published: 14 March 2014 Full publication history

Clear cell gastric adenocarcinoma is a unique subgroup of gastric cancer which, although heterogeneous, has a poor prognosis.

clinical practice guidelines

Annals of Oncology 27 (Supplement 5): v38–v49, 2016
doi:10.1093/annonc/mdw350

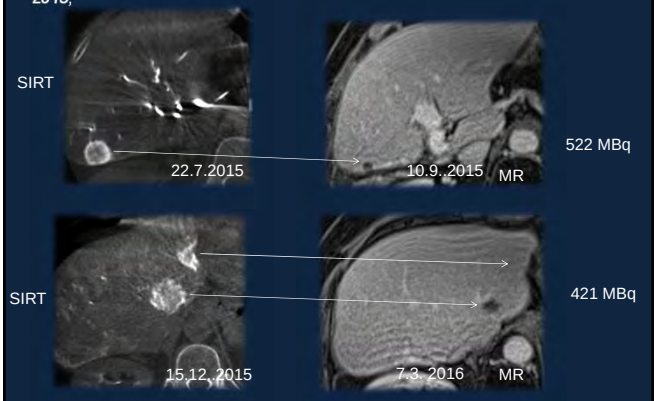
Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

E. C. Smyth[1], M. Verheij[2], W. Allum[3], D. Cunningham[4], A. Cervantes[5] & D. Arnold[6] on behalf of the ESMO Guidelines Committee*

[1]Department of Gastrointestinal Oncology, Royal Marsden Hospital, London and Surrey, UK; [2]Department of Radiation Oncology, The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands; [3]Department of Surgery, Royal Marsden Hospital, London and Surrey; [4]Department of Medicine, Royal Marsden Hospital, London and Surrey, UK; [5]Medical Oncology Department, INCLIVA University of Valencia, Valencia, Spain; [6]Instituto CUF de Oncologia (I.C.O.), Lisbon, Portugal.

- management of advanced/metastatic disease
  - first-line treatment: doublet or triplet platinum/fluoropyrimidine combinations are recommended for fit patients with advanced gastric cancer
  - second-line chemotherapy with a taxane (doc- etaxel, paclitaxel), or irinotecan, or ramucirumab as single agent or in combination with paclitaxel is recommended for patients who are of PS 0–1
- srednje preživetje 8 mesecev

*50 let, M, svetlo celični karcinom želodca, stanje po op želodca 2011, jetrni zasevki , KT, DEBDOX, PVE, desna hepatektomija, progres maj in nov., **2015**,*



50 let M

Svetlo celični karcinom želodca jetrni zasevki

- Delna gastrektomija 2011
- okctober 2013 ECX, ECF
- 2014 TOF
- 2014 TACE + PVE
- 2014 desna hepatektomija
- 2015 SIRT-julij 2015
- 2015 SIRT – december 2015
- october 2016 MR stabilna bolezen

36 months

THE CHANGING FACE OF CLINICAL TRIALS

Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D., John J.V. McMurray, M.D., James H. Ware, Ph.D., and Janet Woodcock, M.D., *Editors*

The NEW ENGLAND JOURNAL of MEDICINE

Pragmatic Trials

Ian Ford, Ph.D., and John Norrie, M.Sc.

In 2016

"Conventional randomized-controlled trials (RCTs) are the gold standard in terms of evidence generation, whenever possible. **In practice, however, there may be practical difficulties** in terms of blinding, risk of poor compliance for randomisation and treatment switches due to wide availability of the test treatment, strong preferences for one of the test treatments based and reluctance to challenge established practices.

Where appropriate, **alternative study designs should be considered**, including non-comparative, single-arm studies; under-powered RCTs, and **observational registry studies.**

realni svet

Zaključki

- Intervencijska onkologija - četrti steber v vodenju onkoloških bolnikov (kirurgija, kemoterapija, radioterapija)

- Multidisciplinarni pristop