



ONKOLOŠKI
INŠTITUT
LJUBLJANA

INSTITUTE
OF ONCOLOGY
LJUBLJANA



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 napreduvalih 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 Brecej, 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...

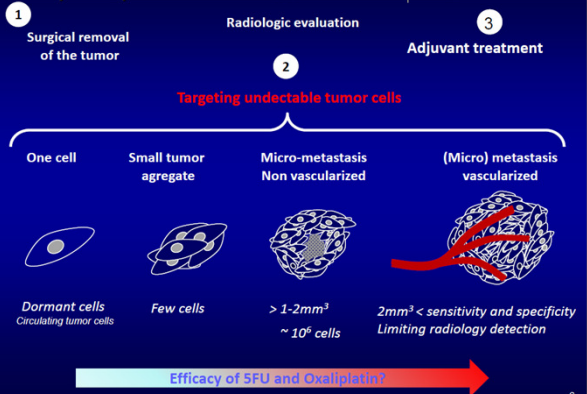
		5-letno preživetje
Dukes*A	Omejen na mukoza	61%-81%
Dukes B	Invazija skozi muskularis mukoze, brez zasevkov v regionalnih bezgavkah	25%-64%
Dukes C	Zasevki v regionalnih bezgavkah	6%-28%

...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

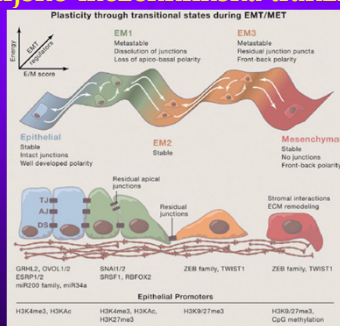
TUMOR

- ❖ 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 al. Cell 2016

Molekularni podtipi raka debelega črevesa

- Iskanje podtipov RČC, 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 DRCD

Consensus molecular subtype in CRC			
CMS1 MSI Immune 14%	CMS2 Canonical 37%	CMS3 Metabolic 13%	CMS4 Mesenchymal 23%
MSI, CIMP high, hypermutation	SCNA high	Mixed MSI status, SCNA low, CIMP low	SCNA high
BRAF mutations	WNT and MYC activation	KRAS mutations	Stromal infiltration, TGFβ activation, angiogenesis
Immune infiltration and activation		Metabolic deregulation	
Worse survival after relapse			Worse relapse-free and overall survival

Figure 3. Proposed taxonomy of colorectal cancer reflecting significant biological differences in the four consensus molecular subtypes. CIMP, CpG Island Methylator Phenotype; MSI, microsatellite instability; SCNA, somatic copy number alterations; TGFβ, transforming growth factor beta. Guinney et al. Nat Med 2015

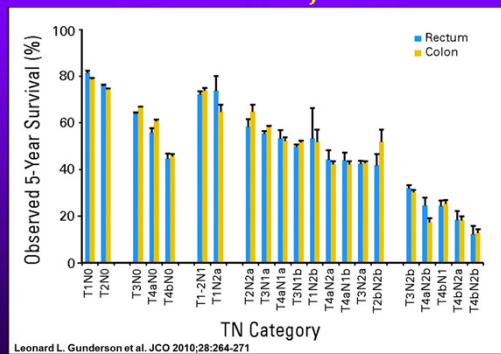
Še niso v klinični praksi!

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

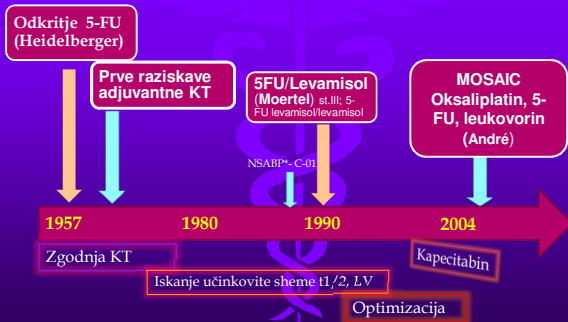
Opazovano 5-letno preživetje glede na TN stadij



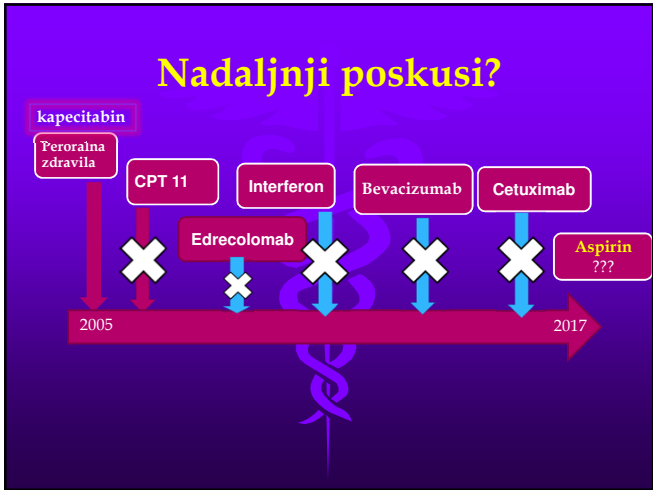
Leonard L. Gunderson et al. JCO 2010;28:264-271

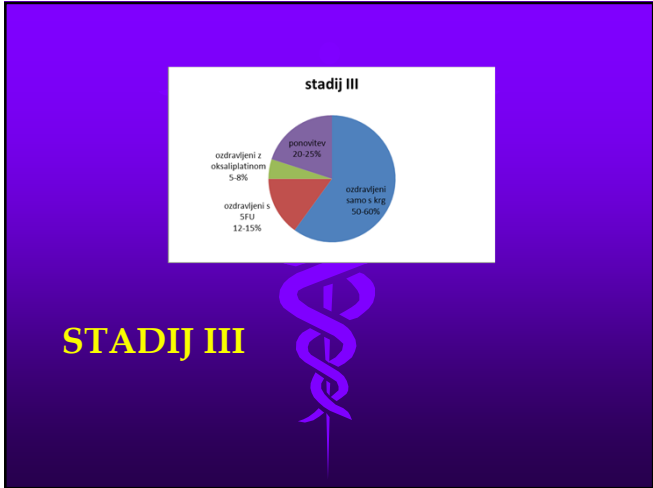
JOURNAL OF CLINICAL ONCOLOGY ASCO

Razvoj adjuvantne kemoterapije RDC



*NSABP: National Surgical Adjuvant Breast and Bowel Project





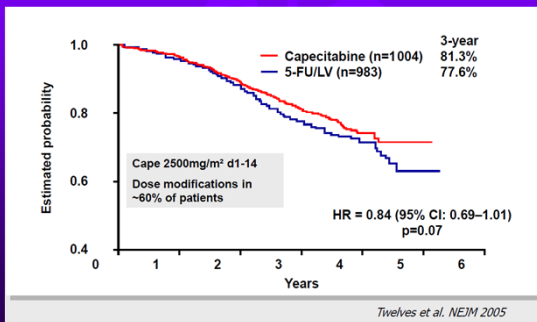
STADIJ III

Izboljšanje celokupnega preživetja: 5FU vs kontrola

Stadij III:

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

Stadij III: X-ACT celokupno preživetje



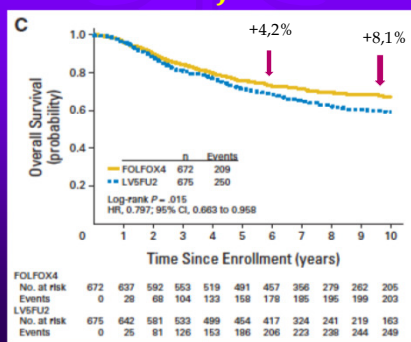
Oksaliplatin

MOSAIC¹ : 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

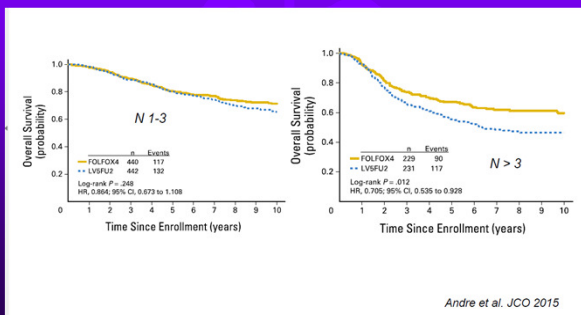
1. André T et al. N Engl J Med 2004

MOSAIC - 10-letno obdobje stadij III



André T et al. J Clin Oncol 2015

Adjuvantni FOLFOX st. III pT3-4 N+

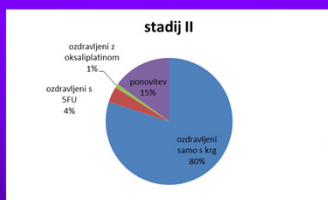


Standard za st. III: fluoropirimidini + oksaliplatin

	HR for DFS	P value	DFS Δ (%)	HR for OS	P value	Δ OS (%)
MOSAIC (FOLFOX₂) ¹	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% 73.3% vs 76.0% @ 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)

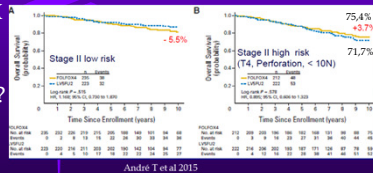
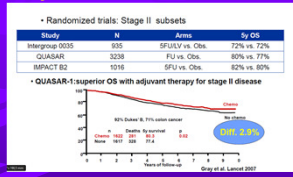
1. Andre T. J Clin Oncol 2009
2. Yothers G. J Clin Oncol 2011
3. Haller D. J Clin Oncol 2011

STADIJ II



Stadij II

- Majhna dobit s 5FU - le 3%
- Ni izboljšanja s FOLFOX
- Korist FOLFOX V podskupini z visokim tveganjem za ponovitev?



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)

Mismatch Repair Deficiency (MMR-D): Unique Biological Subgroup of Colon Cancer

IHC for MMR protein status

MLH1+ MSH2+
MLH1- MSH2+

BAT 25 bp

Thus, IHC for MMR proteins and PCR for MSI detect two manifestations of the same tumor biology:

- MMR-D is synonymous with MSI-H
- MMR-P is synonymous with MSI-L/MSS

Sitrali K, et al. Carcinogenesis. 2008;29:973-980.
Umetani N, et al. Ann Surg Oncol. 2000;7:279-280.
Rozen DC, et al. Med Pathol. 2006;39:1618-1630.

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

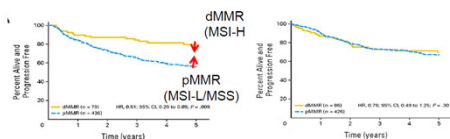
MSI kot prognostični dejavnik za stadij II in III

			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

Stage II and III MSI is prognostic and predictive

DFS by MMR status



Untreated

5Y DFS; p=0.009
dMMR 80%
pMMR 56%

dMMR: deficient MMR
pMMR: proficient MMR

Treated

5Y DFS; p=0.30
dMMR 70%
pMMR 67%

Sargent D J et al. JCO 2010;28:3219

MSI kot prediktivni dejavnik za učinkovitost fluoropirimidinopv pri stadiju II?

Nasprotujoči si podatki:

ni škodljivega učinka pri KT v stadiju II:

- Quasar¹
- CALBG 9581, CALBG 89803²

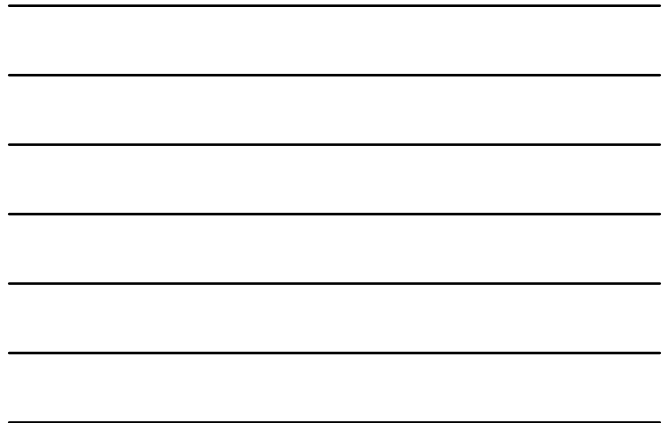
1. Hutchins G et al, 2011
2. Bertagnoli MM et al, 2011

NCCN smernice 2017

testiranje MSI za vse bolnike z RDČD:

- identifikacija bolnikov z Lynchvim 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!)



National Comprehensive Cancer Network
NCCN Guidelines Version 1.2017
Colon Cancer

PATHOLOGIC STAGE* ADJUVANT TREATMENT^{†,§,¶}

T1s, T1, N0, M0	Observation
T2, N0, M0	Observation
T3, N0, M0 ^{¶¶} (MSI-H or dMMR)	Observation
T3, N0, M0 ^{¶¶} (MSS) or MSS and no high-risk features	Clinical trial or Observation or Consider capecitabine [¶] or 5-Fluorouracil [¶]
T3, N0, M0 at high risk for systemic recurrence ^{¶¶¶} or T4, N0, M0	Capecitabine [¶] or 5-Fluorouracil [¶] or FOLFOX ^{¶¶¶} or CAPEOX ^{¶¶¶} or FLOX ^{¶¶¶} or Clinical trial
T any, N1-2, M0	Observation or FOLFOX ^{¶¶} or CAPEOX ^{¶¶} (both category 1 and preferred) Other options include: FLOX (category 1) ^{¶¶¶} or Capecitabine [¶] or 5-Fluorouracil [¶]

Note: See Discussion of Pathologic Stages (COL.1) - Pathologic stage testing for mismatch repair (MMR) proteins should be performed for all patients >70 years of age or with stage II disease. Stage II MSI-H patients may have a good prognosis and do not benefit from 5-FU adjuvant therapy. (Stage II, Murray S, Margolin S, et al. Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil-based adjuvant therapy in colon cancer: a pooled analysis of two randomised trials. Lancet Oncol. 2014;15(12):1049-1058.)

Note: See Discussion of Risk Assessment for Stage II Disease (COL.1) - High-risk factors for recurrence: poorly differentiated histology (relative to those cancers that are MSS), lymphovascular invasion, bowel obstruction, C3 lymph node extension, peritoneal implants, residual perforation or colic perforations, or positive findings in high-risk stage II patients, there are no data that correlate risk features and selection of chemotherapy. There are insufficient data to recommend the use of multi-gene assay panels to determine adjuvant therapy.

Note: See Discussion of Adjuvant Therapy (COL.1) - (Capecitabine, ethamsylol, panitumumab, irinotecan, 20-epifluor, ramuciclimab, regorafenil, telicicimab, larotrectinib, 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.

Note: See Discussion of Pathologic Stages (COL.1) - Microsatellite instability (MSI) or Mismatch Repair (MMR) testing for Lynch Syndrome.

Note: See Discussion of Adjuvant Therapy (COL.1) - A clinical benefit has not been demonstrated for the addition of capecitabine to 5-FU/leucovorin in stage II colon cancer. (Tevigand C, Andri T, Bonnetan F, et al. Adjuvant therapy with fluorouracil and leucovorin in stage II and early patients between ages 70 and 81 years) and colon cancer: subgroup analysis of the adjuvant randomized study of fluorouracil, leucovorin, and levamisole in the adjuvant treatment of colon cancer. J Clin Oncol. 2012; published online ahead of print August 25, 2012.)

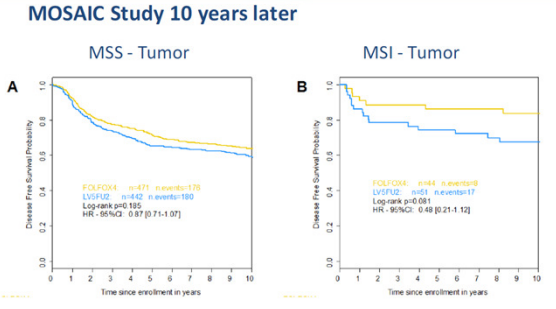
Note: See Discussion of Adjuvant Therapy (COL.1) - A benefit for the addition of oxaliplatin to 5-FU/leucovorin in patients age 70 and older has not been shown.

Note: See Discussion of Adjuvant Therapy (COL.1) - Oxaliplatin is considerably higher with FLOX than FOLFOX in cross-study comparison.

COL-3



Oksaliplatin in MSI/MSS status



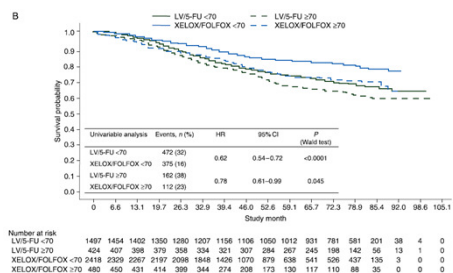
Prognostični in prediktivni dejavniki v raziskavah

- 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 ČREVEVA

Dopolnilna kemoterapija pri starejših?

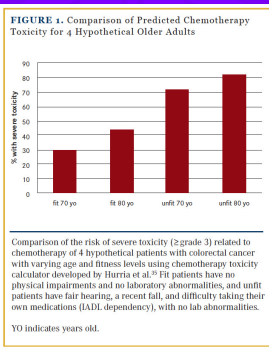
XELOXA, X-ACT, and AVANT) survival for age groups



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!

Reiffo LA. J Natl Cancer Inst. 2014



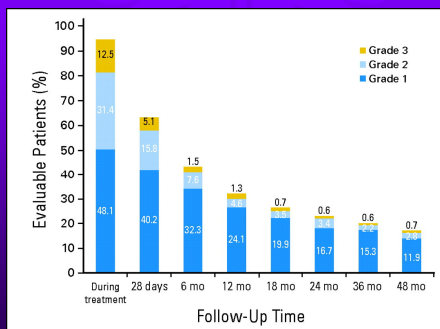
NEŽELENI UČINKI ZDRAVIL

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 - ralitrekseid (Tomudex®). Učinkovitost TOMOX = FOLFOX; ni rand raziskav faze III. Toksičnost ralitrekseida pri ledvični insuficienci! Druga možnost: tegafur-uracil.

1. Polk A. Cancer Treat Rev 2013

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



Andre et al, JCO 2009

Periferna polinevropatija

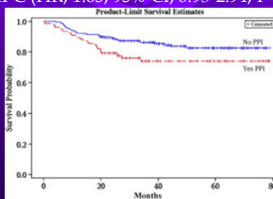
- Simptomi se lahko pokažejo 3 mesece po KT, pri večini izzvenijo 6-12 mesecev po KT
- preeksistentna nevropatija - samo fluoropirimidini

Neploidnost

- 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 • 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
- Metaanaliza¹ : 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-up¹

R. Labianca¹, B. Nordlinger², G. D. Barretta³, S. Mosconi¹, M. Mandà⁴, A. Cervantes⁵ & D. Arnold⁶ on behalf of the ESMO Guidelines Working Group

¹Division of Gastroenterology, Hepatology and Gastroenterology, Ospedale Civile, Pisa, Italy; ²Department of Hematology and Medical Oncology, IZMVA, University of Valencia, Valencia, Spain; ³Department of Medical Oncology, Tumor Biology Center, Freiburg, Germany

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

VOLUME 33 NUMBER 18 AUGUST 18, 2014

JOURNAL OF CLINICAL ONCOLOGY ASCO SPECIAL ARTICLE

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

With Recommendations on Adjuvant Chemotherapy for Stage II Colon Cancer
Parikh J, Flynn A, Khorram-Manesh A, et al. J Clin Oncol 32:3488-3497. 2014.

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 benefits 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 MMR⁴ or MSI⁵ 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.⁶

⁴IHC for MMR and PCR for MSI are different assays measuring the same biological effect.

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.⁶
- Bevacizumab, cetuximab, panitumumab, irinotecan, ziv-aflibercept, ramucicromab, 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

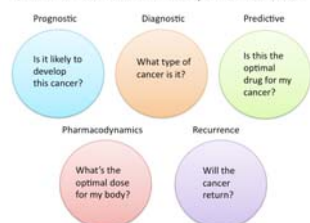
Asist.dr.Martina Reberšek, dr.med.

Definicija biomarkerja- NCI Dictionary of Cancer Terms (NATIONALCANCERINSTITUTE)

"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

Questions that can be answered by cancer biomarkers



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 22: 2479-2516, 2012)

Table 5. Established poor prognostic factors in advanced CRC

Group	Factor for poor prognosis
Patient related	Performance status ≥2 (biological) age ≥70 years CEA >50 µg/l
Neohistological	Absence of lymphovascular invasion Pitavoids >400 × 10 ³ Hemoglobin <11 g/dl White blood cell count <10 × 10 ⁹ /l High LDH
Molecular/genetic	Low tumor alkalinity KRAS mutation

CRC, colorectal cancer; CEA, carcinoembryonic antigen; LDH, lactate dehydrogenase

Table 6. Potential prognostic factors in advanced CRC

Group	Factor
Patient related	Presence of severe comorbidities High molecular weight albumin
Tumour related	High tumour alkalinity Metastatic sites • Liver & lung only versus multiple sites • Peritoneal involvement Previous adjuvant treatment with oxaliplatin Favorable sites of metastases • Liver & lung only Low volume/low symptoms Distance from standard clinical practice
Genetic related	High ESR KRAS mutation
Molecular/genetic	RAS mutation EGFR mutation
Treatment related	High tumor alkalinity High frequency microsatellite instability EGFR, epithelial growth factor receptor

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 22: 2479-2516, 2012)

Table 7. Predictive factors in advanced CRC

Group	Factor
Tumour related	Asymptomatic peritoneal carcinomatosis Multiple sites of metastases very extensive disease
Genetic related	Deviation from standard clinical practice
Biochemical	Efficacy after start of treatment • CEA rise and drop For toxicity of chemotherapy • CEA rise and drop • CEA rise and drop
Molecular/genetic	For treatment with EGFR-inhibitors • KRAS mutation For chemotherapy toxicity • UGT1A1*28 genotype for irinotecan • DPD deficiency for fluoropyrimidines

DPD, dihydropyrimidine dehydrogenase

Table 8. Potential predictive factors in advanced CRC

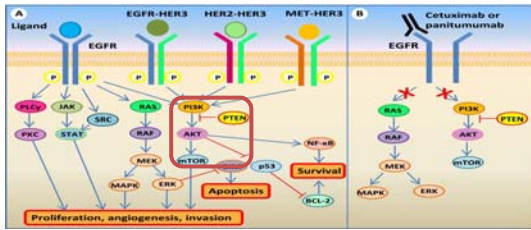
Group	Factor
Patient related	Performance status ≥2 Efficacy after start of treatment High tumor alkalinity for reoperation efficacy Hypertension for anti-VEGF-inhibitors efficacy For hypersensitivity-related toxicity • Calcium channel blocker-related thrombocytopenia • Calcium channel blocker-related thrombocytopenia
Molecular/genetic	Predictors for chemoresistance in localized rectal cancer High TS Low EGFR TS polymorphisms T>C or C>T show benefit from CRT, base T>C, C>T, or T>C For treatment with EGFR-inhibitors KRAS mutation EGFR mutation EGFR, epidermal growth factor receptor; TS, thymidylate synthase; EGFR, epidermal growth factor receptor
Tumour related	High TS Low EGFR TS polymorphisms T>C or C>T show benefit from CRT, base T>C, C>T, or T>C For treatment with EGFR-inhibitors KRAS mutation EGFR mutation EGFR, epidermal growth factor receptor; TS, thymidylate synthase; EGFR, epidermal growth factor receptor
Genetic related	High TS Low EGFR TS polymorphisms T>C or C>T show benefit from CRT, base T>C, C>T, or T>C For treatment with EGFR-inhibitors KRAS mutation EGFR mutation EGFR, epidermal growth factor receptor; TS, thymidylate synthase; EGFR, epidermal growth factor receptor
Molecular/genetic	High TS Low EGFR TS polymorphisms T>C or C>T show benefit from CRT, base T>C, C>T, or T>C For treatment with EGFR-inhibitors KRAS mutation EGFR mutation EGFR, epidermal growth factor receptor; TS, thymidylate synthase; EGFR, epidermal growth factor receptor
Treatment related	High TS Low EGFR TS polymorphisms T>C or C>T show benefit from CRT, base T>C, C>T, or T>C For treatment with EGFR-inhibitors KRAS mutation EGFR mutation EGFR, epidermal growth factor receptor; TS, thymidylate synthase; EGFR, epidermal growth factor receptor

VEGF, vascular endothelial growth factor; TS, thymidylate synthase; EGFR, epidermal growth factor receptor; CRT, chemotherapy

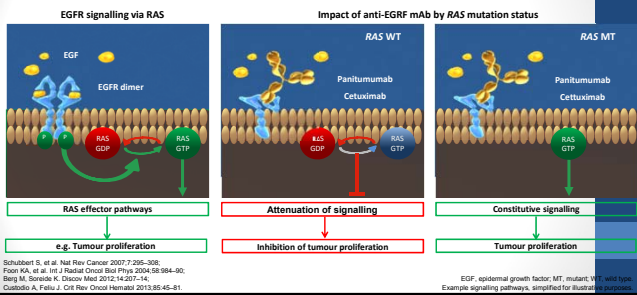
KRAS...RAS

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

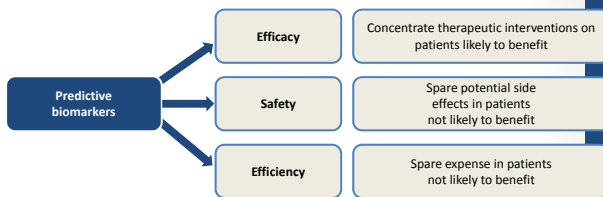
Mutacije vzdolž EGFR signalne poti pri mCRC



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



Biomarker-guided treatment has the potential to improve clinical outcomes



Conley BA, Taube SE. Dis Markers 2004;20:35-42.
Kellert S, Sigman CC. Eur J Cancer 2002;41:491-501.
President's Council of Advisors on Science and Technology (PCAST).
Priorities for Personalized Medicine. 2009 (accessed 13.01.16).
Helmreich 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 prevalenca 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%
- mtBRAF: 5-15%
- Rezultati- 5 klin.raziskav faze III in faze Ib/II, II z wtKRAS v eksonu 2: Vključenih 1860 bolnikov: Prevalenca drugih RAS mutacij- mtKRAS eksonih 3 in 4, mtNRAS v eksonih 2,3,4 19.1%

Peters 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.

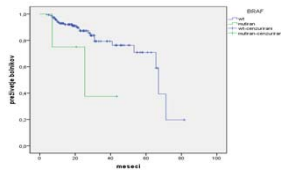
Prevalenca mtBRAF- 5 klin.raziskav

- Prevalenca mtBRAF 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%**

Petersen et al, Prevalence of RAS mutations among patients with metastatic colorectal cancer: a pooled analysis of randomized control trials. ASCO GI, 2013

mtBRAF 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 BOLNIKI Z RAZSEJANIM ADENOKARCINOMOM DEBELJEGA ČREVA IN DANKE OB SISTEMSKEM ZDRAVLJENJU, 2013.

Izkušnje OIL: SLOQUEST

A. Patient characteristics data

■ Total included: 315

■ Gender:

- 206 M (65.4%)

- 109 F (34.6%)

■ Performance status

- 0=103 (32.7%)

- 1=168 (53.3%)

- 2=32 (10.2%)

- 3=4 (1.3%)

- 4=0

- no data=8 (2.5%)

Gender



Performance status



C. Tumor characteristics

■ KRAS (315)

- Wild = 153 (48.6%)

- Mutated = 158 (50.2%)

- Genot. Not possible = 4 (1.3%)

■ NRAS (145)

- Wild = 129 (89%)

- Mutated = 13 (9%)

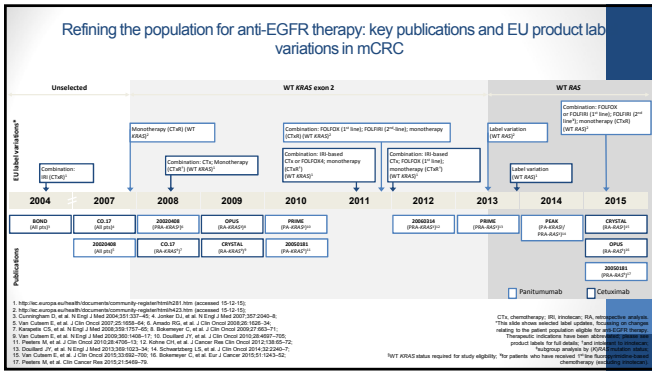
- Genot. Not possible = 3 (2%)

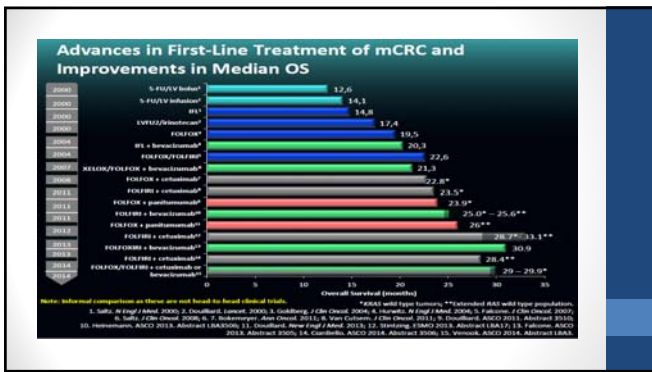
■ BRAF (151)

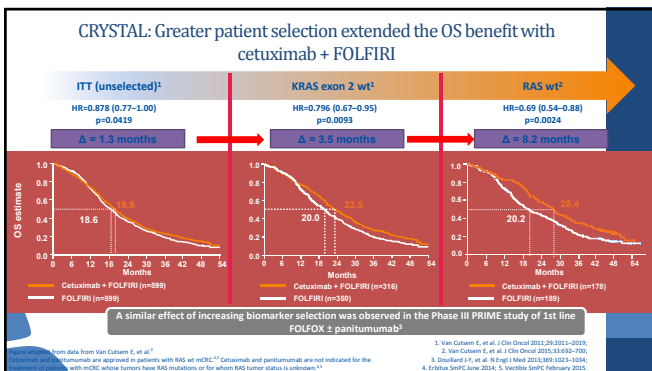
- Wild = 130 (86.1%)

- Mutated = 20 (13.2%)

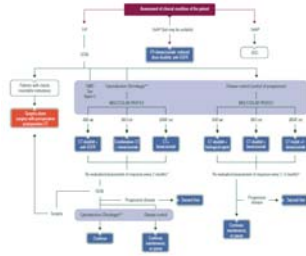
- Genot. Not possible = 1 (0.7%)







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

- Clinically validated 'gold standard'¹
- Source of analysed material known (i.e. primary tumour or metastasis)
- Provides tumour histology²



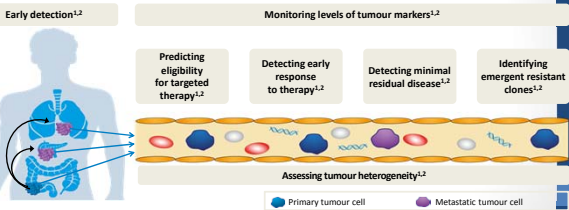
Liquid biopsy

- Minimally invasive¹
- Dynamic patient monitoring¹
- Source of fresh DNA¹
- Suitable for inaccessible tumours²
- May reflect tumour heterogeneity²

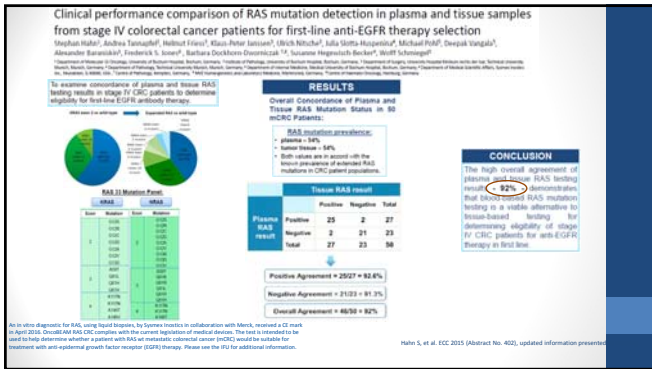
¹ Diaz LA, Bardelli A. J Clin Oncol 2014;32:279-86.
² Crowley E, et al. Nat Rev Clin Oncol 2013;10:472-84.

Potential clinical applications of liquid biopsy

Diagnosis Treatment Response Progression



¹ Diaz LA, Bardelli A. J Clin Oncol 2014;32:279-86.
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



HER 2 expression in gastric cancer

IMMUNOHISTOCHEMISTRY (IHC)

Study (first author, year)	n	Country	Overex-pression, %	Prog-
Yoshimura, 1991 [146]	260	Japan	14.9	yes
Wada, 1992 [17]	209	Japan	24.0	yes
Yoshimura, 1992 [148]	220	Japan	10.0	yes
Kochino, 1993 [150]	214	Japan	9.0	yes
Lee, 1996 [20]	223	Japan	37.8	yes
Gilman, 1997 [22]	112	Taiwan	36.5	yes
Choi, 1997 [23]	396	Japan	10.1	-
Idihkawa, 1997 [23]	275	Japan	10.8	-
Wada, 1997 [24]	163	Taiwan	26.8	yes
Allypov, 2000 [25]	189	Czechoslovakia	53.4	yes
Chigihara, 2000 [26]	116	Japan	16.0	-
Sanjo-Chiraga, 2000 [27]	143	Spain	34.0	yes
Wang, 2002 [28]	180	Taiwan	32.0	yes
Gilman, 2002 [29]	146	Taiwan	16.8	-
Takahashi, 2002 [30]	252	Japan	6.2	yes
Pinto-do-Souza, 2002 [31]	157	Portugal	15.3	yes
Lee, 2003 [32]	841	Japan	17.0	-
Yano, 2004 [33]	200	Japan	23.0	-
Fay, 2006 [34]	182	Japan	15.9	yes
Hofmann, 2008 [35]	168	China/Mexico/Mexico/Mexico	10.7	-
Baron-Hillel, 2009 [36]	463	Portugal	9.3	-
Mars, 2009 [37]	160	Germany	16.9	-
Vic, 2009 [38]	1343	China	28.0	-
Zhang, 2009 [39]	182	China	14.8	yes

Range: 8,2%-53,4%

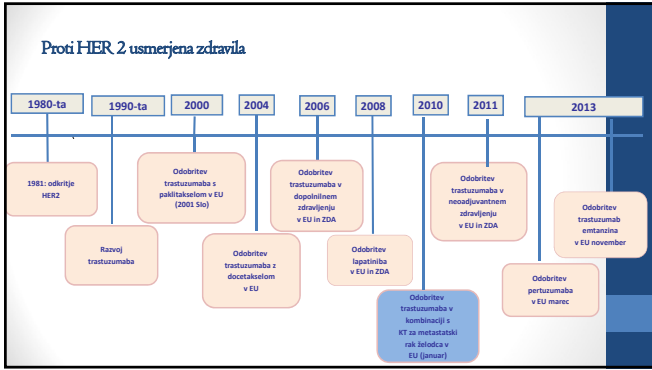
IN SITU HYBRIDISATION (ISH)

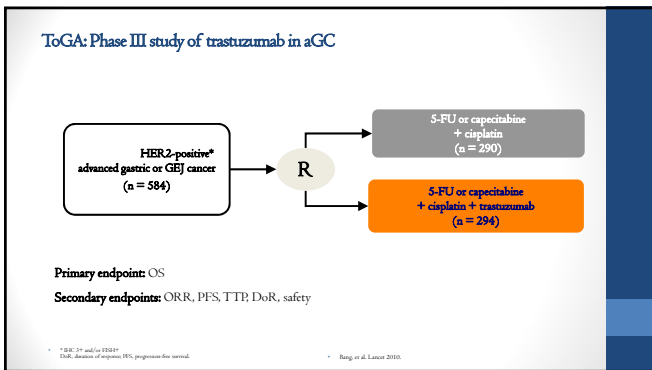
Study (first author, year)	Test	n	Country	Amplification, %	Prognostic
Idihkawa, 1997 [23]	FISH	105	Japan	18.1	-
Tanner, 2003 [40]	CISH	231	Finland	17.3	yes
Yano, 2006 [33]	FISH	199	Japan	27.1	-
Hofmann, 2008 [35]	FISH	168	China/Mexico/Germany	17.4	-
Mars, 2009 [37]	FISH	166	Germany	16.8	-

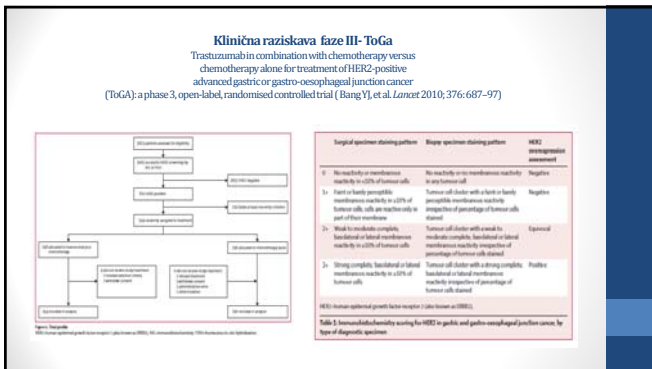
Range: 16%-27,1%

Jorgensen et al Oncology 2010; 78: 26

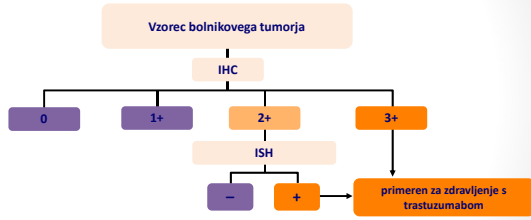






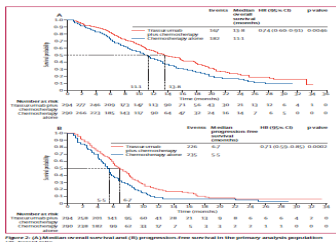


HER2 testiranje pri karcinomu želodca in GE prehoda (algotem)

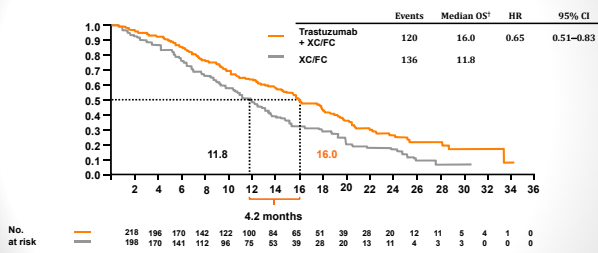


IHC - imunohistokemična metoda
ISH - in situ hibridizacijska metoda

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



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



* 1 MONTHS
† REC-3 OR REC-2-CONFIRMED BY INDEPENDENT READER
* RANZ, et al. Lancet 2010

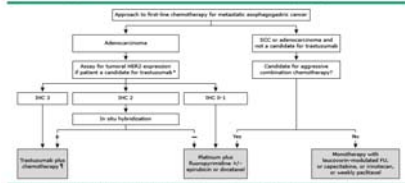
Testing of HER-2 positivity in adenocarcinoma of stomach and gastroesophageal junction (THEIA)

Kavalari 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:
 - Biopsijski 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

Algorithmic approach to first-line treatment of metastatic esophagogastric cancer



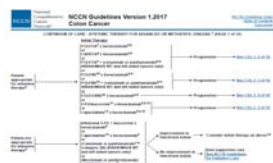
Flu: Fluorescence; IHC: immunohistochemical staining; HER2: human epidermal growth factor receptor 2; SCC: squamous cell cancer.

Bendall L, 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 monoklona 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

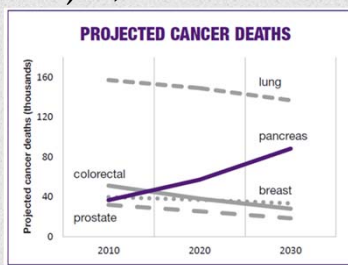


Novosti v sistemskem zdravljenju raka trebušne slinavke

Zvezdana Hlebanja

Zahrbtnen, pozno odkrit, hitro potekajoč, smrten

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



Matrisian, Cancer Res 2014

Zahrbtnen, 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 cancer	None needed		
Stage I	Tumor about 2 cm, found in pancreas only	Surgery, Surgery with chemo and radiation	7%	20%
Stage II	Spreads to nearby tissues and organs and possibly lymph nodes	Surgery, Surgery with chemo and radiation		
Stage III	Spreads to major blood vessels, main pancreas and possibly lymph nodes	Surgery with chemo and radiation, chemo with Gemzar, clinical trial therapies	26%	8.2%
Stage IV	Cancer of any size may have spread to distant organs	Chemo with Gemzar, treatments for pain, clinical trial therapies	52%	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	<1%

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

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

Adjuvantna kemoterapija

- o Po RO resekciji
- o Začetek 4 – 6 tednov po operaciji – skupno 6 mesecev
- o Pred uvedbo adjuvantne KT opravimo CT trebuha
- o Določimo nivo CA 19-9
- o 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%)

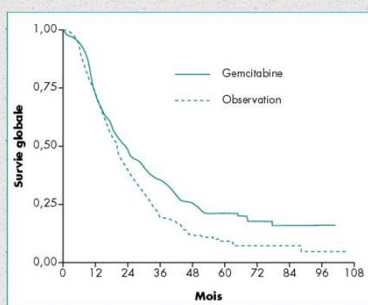
Adjuvantna kemoterapija

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

Gemcitabin adjuvantno vs BSC

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

CONKO - 001



Citostatiki v adjuvantnem zdravljenju

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

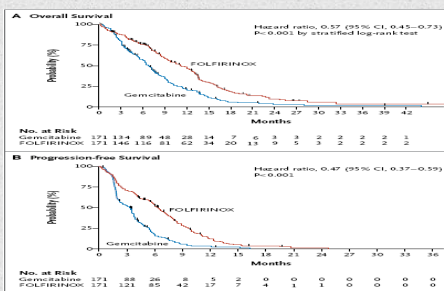
- NOBENA KT NE OZDRAVI METASTATKEGA RAKA TREBUŠNE SLINAVKE
- OLAJŠA SIMPTOME BOLEZNI
- UPOČASNI NAPREDOVANJE BOLEZNI
- PODALJŠA ŽIVLJENJE

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 dobit > 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

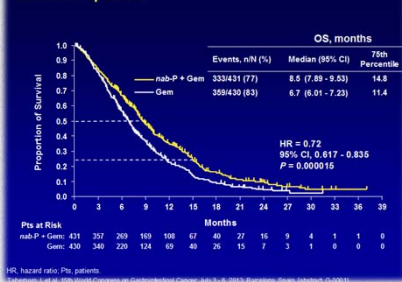
o Toksični profil

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

Event	FOLFIRINOX (N = 171) no. of patients/total no. (%)	Gemcitabine (N = 171) no. of patients/total no. (%)	P Value
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

OS in ITT Population

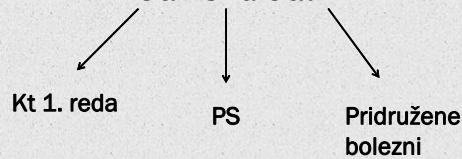


Sistemsko zdravljenje napredovalega raka trebušne slinavke – KT 1. reda

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

- o **PS = 2**
- o Zmerna komorbidnost
- o **Bilirubin < 1.5x zvišan** – mono Gemcitabin ali GEM CAP ali Kapecitabin ali S-1 mono
- o Zelo selekcionirani bolniki s PS = 2 in izredno visokim tumorskim bremenom GEM + Nab Pacli (boljši RR)
- o **Bilirubin > 1.5x zvišan** – Folfox
- o **PS >= 3** → izbira KT izrazito individualna **priporoča se BSC!**

Kemoterapija 2. reda je odvisna od:



Kemoterapija 2. reda

- o **PS (0-1)**
- o Za te bolnike ima kt 2. reda prednost pred BSC
- o Ni optimalnih kombinacij
- o 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

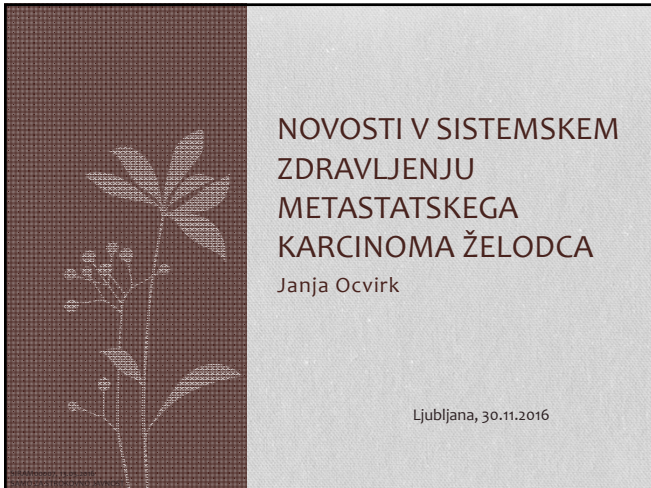
- o **PS (0-1)**
- o Če je kt 1. reda temeljila na derivatih 5-FU (Folfirinox), se za te bolnike v 2. redu priporočajo kombinacije Gemcitabina (+/- Nab Pacli)
- o Če je **PS = 2** – monoterapija Gemcitabin
- o Če je bila kt 1. reda Folfox (zaradi zvišanega Bilirubina) naj bo kt 2. reda Gemcitabin mono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

Povzetek in priporočila

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

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





NOVOSTI V SISTEMSKEM
ZDRAVLJENJU
METASTATSKEGA
KARCINOMA ŽELODCA
Janja Ocvirk

Ljubljana, 30.11.2016



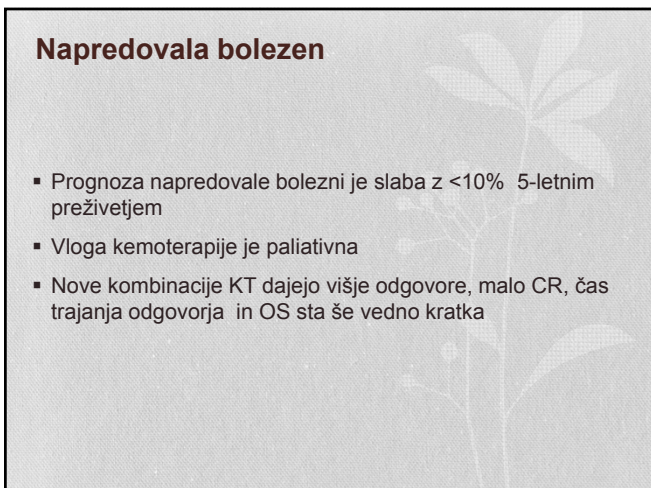
Razkritje

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

Predstavitvev 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

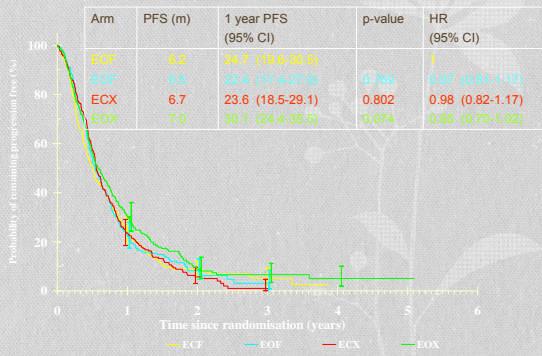
R
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- Epirubicin
■ Cisplatin
■ 5-FU
- Epirubicin
■ Cisplatin
■ Kapecitabin (X)
- Epirubicin
■ Ksaliplatin
■ 5-FU
- Epirubicin
■ Ksaliplatin
■ Kapecitabin (X)

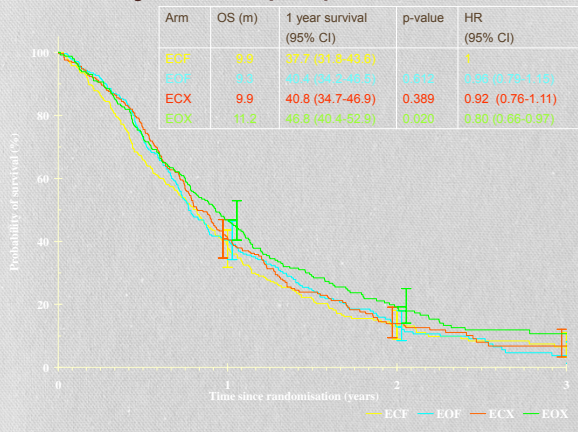
Načrt 2 X 2
n = 204 (interimna analiza)
n celokupno = 1002
Primarni cilj: OS (non-inferiority/superiority)

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

Čas do napredovanja bolezni



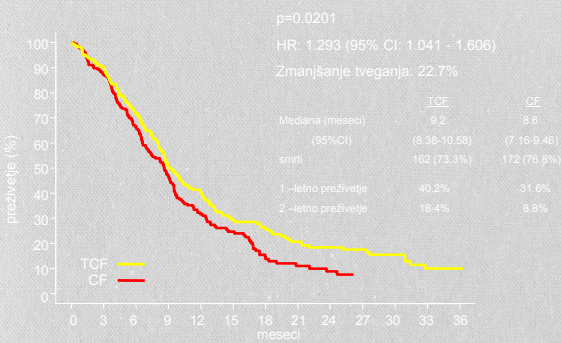
Preživetje m KŽ (ITT)



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



bolniki

TCF:	221	199	149	93	68	45	36	28	22	17	12	7	5
CF:	224	195	136	87	54	35	17	11	8				

ToGA

Zasnova raziskave¹

- Odrpta 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)

^a po presoji raziskovalca

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

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

Stratifikacija

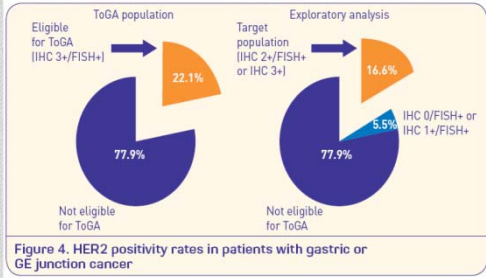
- napredovali vs. metastatski
- rak želodca vs. GEJ
- merljiva vs. nemerljiva bolezen
- ECOG PS 0-1 vs 2
- kapecitabin vs. 5-FU

Odmerki v shemah

- Xeloda 1000 mg/m² bid d1-14 q3w x 6
- 5-FU 800 mg/m²/dan v kontinuirani iv. infuziji d1-5 q3w x 6
- cisplatin 80 mg/m² q3w x 6
- Herceptin 8 mg/kg uvajalni, nato 6 mg/kg q3w do progressa

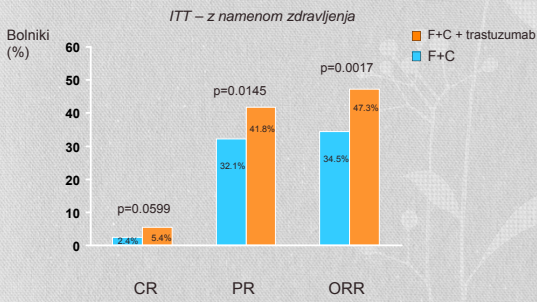
Izbor bolnikov

• Zožitev tarčne populacije z 22,1% na 16,6%¹



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

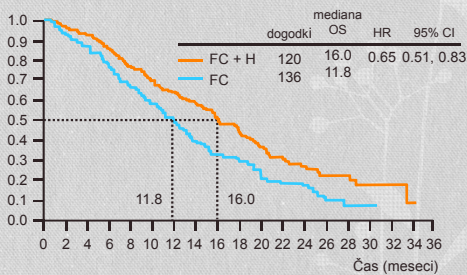
Celokupni odgovor¹ Sekundarni cilj



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



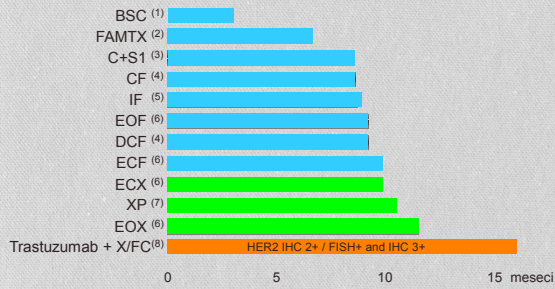
No. at risk

Time (months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36
FC + H	228	218	196	170	142	122	100	84	65	51	39	28	20	12	11	5	4	1	0
FC	218	198	170	141	112	96	75	53	39	28	20	13	11	4	3	3	0	0	0

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 | 5. Dank, 2008 |
| 2. Vanhoefler, 2000 | 6. Cunningham, NEIM 2008 |
| 3. Ajani, 2006 | 7. Kang, 2007 |
| 4. Van Cutsem, 2006 | 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 Pharmacol. 2013; 71: 481-88

ANTICANCER RESEARCH ON 2017-01-17 (part)

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

YASUHIRO KUDOHA*, SEIJI ITO*, YOSHINARI MACHIZUKI*, SHINICHI FUJITAKI*, KAZUHIKO KOBAYASHI*, YASUHIKO KAWAYAMA*, TAKASHI HAYASHI*, HIROSHI KOSHIMIZU*, TOSIYUKI TAKASHI*, NOBUHIRO OHGISHI*, MICHITAKA FUJWARA*, RINICHI SAKAMOTO* and AKIRAMA NAKAJI* for Chubei Clinical Cancer Group

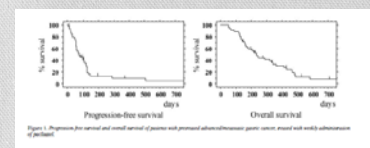


Figure 1. Progression-free survival and overall survival of patients with previously advanced/metastatic gastric cancer treated with weekly administration of paclitaxel

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 3. stopinji.

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

Xun Du Yoo · Jaehuk Hong · Jooe Park · Eun Kyung Cho · Jun-Hwan Lee · Young Ho Park · Chulsoo Kim · Min Young Kim · Hyoung-Min Kim · So Hyun Park · Dong Hwak Shim

Folfiri in irinotekan v monoterapiji sta enako učinkovita

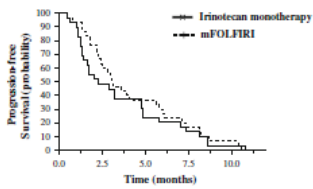


Fig. 1 Kaplan-Meier plot of progression-free survival

Biweekly irinotecan plus cisplatin versus irinotecan alone as second-line treatment for advanced gastric cancer: A randomised phase III trial (TCOG GI-080/BIRIP trial)

Katuhiko Higuchi^{1,2*}, Satoshi Tanabe³, Ken Shimada⁴, Hisashi Hosaka⁵, Etsuko Sasaki⁶, Noriaki Nakayama⁷, Yutai Takeda⁸, Toshiyuki Moriwaki⁹, Kenji Amagai¹⁰, Takashi Sekikawa¹¹, Toshikazu Nakayama¹², Tetsuo Kanda¹³, Tohru Sasaki¹⁴, Mutsunori Aruma¹⁵, Fumitsuki Takahashi¹⁶, Masahiro Takemchi¹⁷, Wasaburo Koizumi¹⁸, The Tokyo Cooperative Oncology Group, Tokyo, Japan

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

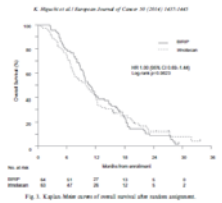
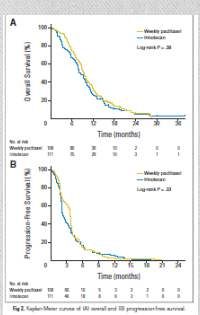


Fig. 1 Kaplan-Meier curves of overall survival after second treatment

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 med zdravljenjem z irinotekanom in paklitakselom v 2. liniji zdravljenja napredovelega karcinoma želodca

RAMUCIRUMAB (CYRAMZA)

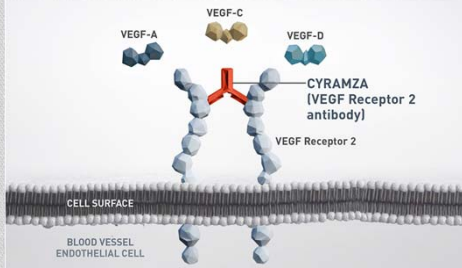
- Humano monoklonsko protitelo, usmerjeno proti receptorjem, je odobreno kot samostojno zdravilo ali v kombinaciji s paklitakselom za zdravljenje bolnikov z napredovalim rakom želodca ali adenokarcinomom OGJ po predhodni kemoterapiji.
- Specifično se veže na receptor VEGF 2 in zavira vezavo VEGF-A, VEGF-C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



OGJ = gastroezofagealni spoj; VEGF = vaskularni endoteljski rastni faktor
 Reference: 1. Clarke JM, Hurwitz H. Expert Opin Biol Ther. 2015;15(5):519-530. 2. Cyramza EU Summary of Product Characteristics, approved 24.9.2015. 3. Fuchs CS et al. Lancet. 2014;383(9911):31-39. 4. Wilke H et al. Lancet Oncol. 2014;15(1):1224-1235.

ZDRAVILO CYRAMZA JE ANTIANGIOGENO ZDRAVILO, KI SPECIFIČNO ZAVIRA AKTIVACIJO RECEPTORJA ZA VEGF 2¹

MEHANIZEM DELOVANJA: RAMUCIRUMAB – PREGLED



VEGF = vaskularni endoteljski rastni faktor
 Reference: 1. Cyramza EU Summary of Product Characteristics, approved 25.1.2016

CYRAMZA Ramucirumab – 2 raziskavi^{1,2}

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

NEOPERABILN, LOKALNO NAPREDOVALI ALI METASTATSKI RAK ŽELODCA/GE PREHODA	NEOPERABILN, LOKALNO NAPREDOVALI ALI METASTATSKI RAK ŽELODCA/GE PREHODA
<ul style="list-style-type: none"> • Napredovanje med ali v 4 mesecih po tL kemoterapije • ECOG PS 0-1 	<ul style="list-style-type: none"> • Napredovanje med ali po: - 4 mesecih tL kemoterapije ALI - 6 mesecih adjuvantne kemoterapije • ECOG PS 0-1

Randomizacija 1: 1*

Randomizacija 2: 1²

CYRAMZA + paklitaksel[†] (n = 330)	Placebo + paklitaksel [†] (n = 335)	CYRAMZA[‡] (n = 238)	Placebo [§] (n = 117)
8 mg/kg q2w (-60min infuzija) + 80 mg/m ² (-60min infuzija)	q2w + 80 mg/m ² (-60min infuzija)	8 mg/kg q2w (-60min infuzija) + BSC	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); q2w = dvotedenski interval; BSC = najboljša podpora zdravljenja; q2w = na 2 tedna
 * Stratifikacijski dejavniki: Geografsko območje, menijeva bolezen proti nemerljivi boleznini in čas do napredovanja bolezni po zdravljenju prve izbire (48 mesecev proti 2 8 mesecev).
 † Ciklus je trajal 63 dni.
 ‡ Stratifikacijski dejavniki: Geografsko območje, lokacija primarnega tumorja in izguba telesne mase v zadnjih 3 mesecih.
 § 1-10% proti <10%.
 † Ciklus je trajal 14 dni.

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

RAINBOW: ORR^{1,2}

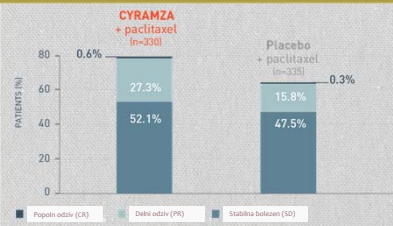
STOPNJA NADZORA BOLEZNI

Objektivna stopnja odziva (ORR)¹

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. 2019;19(11):1214-1224. 2. Data on file, Eli Lilly and Company, Lilly (E.16.1)B6 (MCLL CP2-0922).

RAINBOW: CYRAMZA JE V KOMBINACIJI S PAKLITAKSELOM V SPLOŠNEM DOSEGLA PROFIL TOKSIČNOSTI, KI SO GA BOLNIKI DOBRO PRENAŠALI¹

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

Neželene reakcije po organskem sistemu (MedDRA)	CYRAMZA + paklitaksel (n = 327)		PLACEBO + paklitaksel (n = 329)	
	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 ^a	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 ^b	25,1	14,7	5,8	2,7

Dodet: priskritiv 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
^a Vključuje analizo krvavitve, krvavitve ob drski, krvavitve v želodcu, gastrointestinalna krvavitve, hematemeseje, krvavitve iz hemoroidov, Malory-Weissov sindrom, melena, krvavitve požirnika, krvavitve zadnjica in krvavitve iz zgornjih prebavil.
^b Vključuje hipertenzijo kardiomorgano.

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

RAINBOW: NAJPOGOSTEJŠI NEŽELENI UČINKI¹

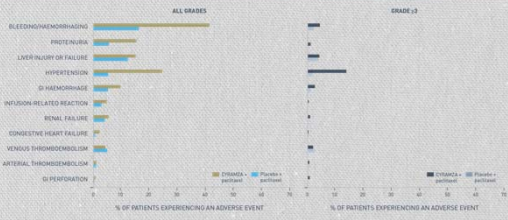


GI = gastrointestinalni

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

RAINBOW: izbrani neželeni učinki¹

» IZBRANI NEŽELENI UČINKI¹ SO UČINKI, POTENCIALNO POVEZANI Z ANTIANGIOGENIM UČINKOM ALI TERAPEVTSKIMI PROTITELESI. *

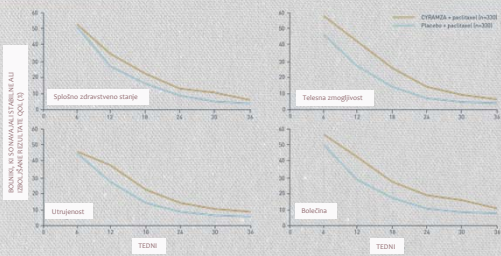


¹ Z zdravljem povezan nižersi učinek, ne glede na vzročnost, vključeni so znatni vzroci za redene učinke

Reference: v. Witte H et al. *Lancet Oncol*. 2016;17(1):124-135.

RAINBOW: IZBOLJŠANA QOL¹

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



QOL = kakovost življenja

Reference: v. Al-Batran S-E et al. *J Clin Oncol*. 2016;34(32):3895-3902. Abstract 4058.

REGARD¹

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 (vzročna skupina za sodobneje v onkologiji); PS = stopnja zmogljivosti; BSC = najboljša podpora zdravilne zdravila; q2w = na 2 tedna

[†] Stratiški kazalo: Geografsko območje, lokacija primarnega tumorja in splošna telesna masa v zadnjih 3 mesecih (n 10 % proti < 10 %).

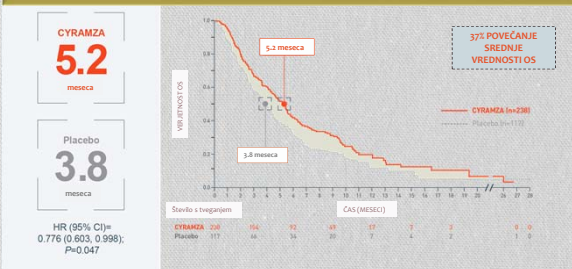
¹ Cilus je trajal 14 dni.

v. Fuchs CS et al. *Lancet*. 2016;388(9993):31-39.

REGARD: CELOKUPNO PREŽIVETJE¹

SREDNJA VREDNOST OS: MESECI

PRIMARNI OPAZOVANI DOGODEK

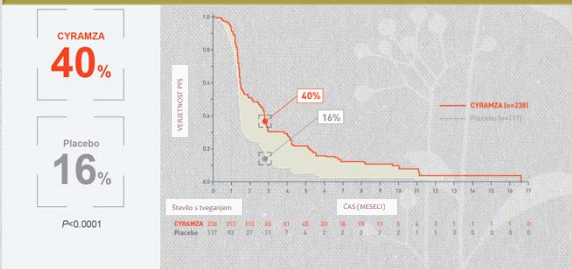


HR = razmerje tveganja; CI = interval zaupanja; OS = celokupno preživetje
 Reference: 1, Fuchs CS et al. Lancet. 2014;383(9911):31-39.

REGARD: PFS¹

STOPNJA PFS PO 12 TEDNIH

SEKUNDARNI OPAZOVANI DOGODEK (vnaprej določen)



PFS = preživetje brez napredovanja
 Reference: 1, Fuchs CS et al. Lancet. 2014;383(9911):31-39.

REGARD: SEKUNDARNI OPAZOVANI DOGODEK

QOL

GLOBALNI QOL 6 TEDNOV PO ZAČETKU ZDRAVLJENJA PO BOLNIKOVIM SAMONAVEDBI¹

IZHODIŠČE	CYRAMZA n = 238	n = 110	Placebo n = 117	n = 26
6 TEDNOV Improved	9.7%		Improved	4.3%
Stable	24.4%		Stable	9.4%
Worsened	12.2%		Worsened	8.5%

Zdravilo CYRAMZA proti placebu (izboljšeno 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 % prekinitve zdravljenja.²

QOL = kakovost življenja
 Reference: 1, Fuchs CS et al. Lancet. 2014;383(9911):31-39. 2, Chou J et al. Poster presented at: European Cancer Congress 2013; 27

SMERNICE NCCN IN ESMO 2016

NCCN Clinical Practice Guidelines in Oncology: Gastric Cancer: Version 1.2016

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-8])
- 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 (fluorouracil¹ or capecitabine) and cisplatin¹⁸⁻¹⁹ (category 1)
 - Fluoropyrimidine (fluorouracil¹ or capecitabine) and oxaliplatin^{18, 20}
- Other Regimens:
 - Paclitaxel with cisplatin or carboplatin²¹⁻²³
 - Docetaxel with cisplatin^{24, 25}
 - Fluoropyrimidine^{17, 26, 27} (fluorouracil¹ or capecitabine)
 - Docetaxel^{28, 29}
 - Paclitaxel^{30, 31}
 - Fluorouracil¹ and irinotecan (category 1)³²
- DCF modifications
 - Docetaxel, cisplatin, and fluorouracil³³
 - Docetaxel, oxaliplatin, and fluorouracil³⁴
 - Docetaxel, carboplatin, and fluorouracil (category 2B)³⁵
- ECF (epirubicin, cisplatin, and fluorouracil) (category 1)³⁶
- ECF modifications (category 1)^{3, 12}
 - 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:
 - Ramucicromab and paclitaxel (category 1)³⁷
 - Docetaxel (category 1)^{38, 39}
 - Paclitaxel (category 1)^{20, 31, 38}
 - Irinotecan (category 1)³⁸⁻⁴¹
 - Ramucicromab (category 1)⁴²
- Other Regimens:
 - Irinotecan and cisplatin^{18, 43}
 - Irinotecan and fluoropyrimidine (fluorouracil¹ or capecitabine)⁴⁴ (category 2B)
 - Docetaxel and irinotecan⁴⁵ (category 2B)

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

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
 - "Ramucicromab and paclitaxel for EGJ adenocarcinoma" changed to "Ramucicromab 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.
 - "Ramucicromab for EGJ adenocarcinoma" changed to "Ramucicromab 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 ramucicromab was removed: "Ramucicromab produced better results when combined with paclitaxel (RAINBOW trial) than it did as a single agent (REGARD trial); therefore, ramucicromab in combination with paclitaxel is preferred. The results of the RAINBOW trial have been presented only in abstract form and await full publication."

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)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:
 - DCF (docetaxel, cisplatin, and fluorouracil) (category 1)¹⁷
- DCF modifications
 - Docetaxel, cisplatin, and fluorouracil¹⁸
 - Docetaxel, oxaliplatin, and fluorouracil¹⁹
 - Docetaxel, carboplatin, and fluorouracil (category 2B)²⁰
- ECF (epirubicin, cisplatin, and fluorouracil) (category 1)²¹
- ECF modifications (category 1)²²
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 - Epirubicin, cisplatin, and capecitabine
 - Epirubicin, oxaliplatin, and capecitabine
- Fluorouracil and irinotecan (category 1)²³
- Fluoropyrimidine (fluorouracil or capecitabine) and cisplatin²⁴⁻²⁷ (category 1)
- Fluoropyrimidine (fluorouracil or capecitabine) and oxaliplatin^{28,29}
- Other Regimens:
 - Paclitaxel with cisplatin or carboplatin³⁰⁻³²
 - Docetaxel with cisplatin³⁴
 - Docetaxel and irinotecan³⁵ (category 2B)
 - Fluoropyrimidine^{24,36,37} (fluorouracil or capecitabine)
 - Docetaxel^{38,39}
 - Paclitaxel^{40,41}

Second-Line Therapy

- Dependent on prior therapy and PS:
- Preferred Regimens:
 - Ramucicromab and paclitaxel for adenocarcinoma (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma)⁴²
 - Docetaxel (category 1)^{38,39}
 - Paclitaxel (category 1)^{40,41,43}
 - Irinotecan (category 1)⁴²⁻⁴⁶
 - Ramucicromab for adenocarcinoma (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma)⁴⁷
 - Other Regimens:
 - Irinotecan and cisplatin^{48,49}
 - Irinotecan and fluoropyrimidine (fluorouracil or capecitabine)^{21,49} (category 2B)
 - Docetaxel and irinotecan³⁵ (category 2B)

Alternative Regimens for Consideration (category 2B)

- Mitomycin and irinotecan⁵⁰
- Mitomycin and fluorouracil⁵¹

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 - Epirubicin, oxaliplatin, and fluorouracil
 - Epirubicin, cisplatin, and capecitabine
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Alternative Regimens for Consideration (category 2B)

- Mitomycin and irinotecan⁵⁰
- Mitomycin and fluorouracil⁵¹

ESMO priporočila 2016

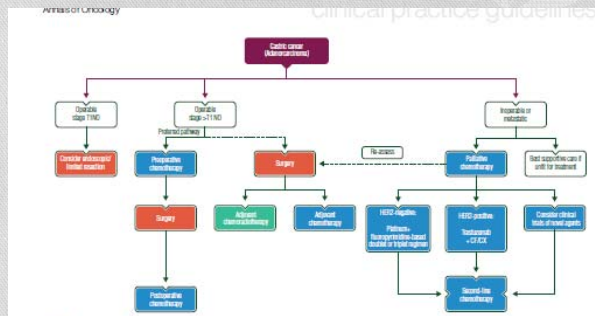


Figure 1. Gastric cancer treatment algorithm. HER2, human epidermal growth factor receptor 2; FOLFOX, oxaliplatin and 5-fluorouracil; FOLFIRI, oxaliplatin and capecitabine.

Zaključki

- kemoterapija na osnovi 5FU in platine
- kapecitabin in oksaliplatin sta uporabni alternativni 5FU in cisplatina
- docetaksel +5FU – večja učinkovitost v primerjavi 5FU/cisplatin
- vloga antraciklinov pri adenokarcinomu
- Trastuzumab je prvo tarčno zdravilo, ki ima dober učinek 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 kombinaciji 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 Farmaceutvska 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 jetih 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

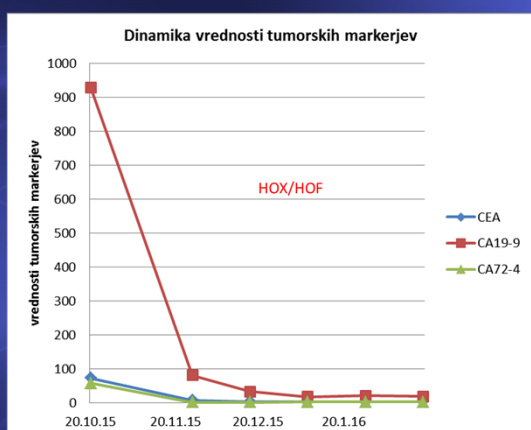
- MDT 30.9.2015: sistemsko specifično zdravljenje

I. red zdravljenja

- FISH:– gen za Her-2 pomnožen
- 20.10.2015 – HOX; po 10 dneh kapecitabina enterokolitis III. stopnje
- 2.-6. cikel 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

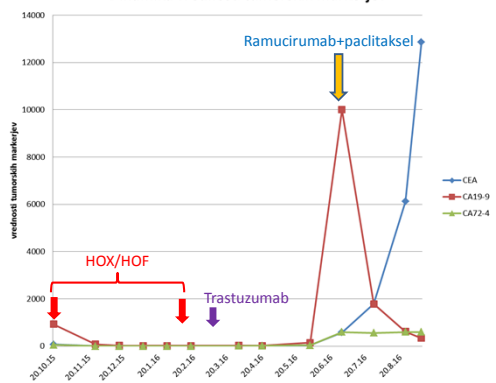
II. red systemskega zdravljenja

- **30.6.2016** uvedena Cynamza (**ramucirumab**) v kombinaciji s **paclitakselom** (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, prehodni 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 trunкус celiakus so večje in številnejše, 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.

Dinamika vrednosti tumorskih markerjev



Paliativna oskrba

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

Rainbow

	Ramucicromab plus paclitaxel (N=335)	Placebo plus paclitaxel (N=335)
Best overall response		
Complete response	2 (1%)	1 (1%)
Partial response	50 (15%)	13 (4%)
Stable disease	177 (53%)	153 (46%)
Progressive disease	43 (13%)	53 (16%)
Not evaluable or not assessed	23 (7%)	39 (12%)

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

Table 2. Best overall response

	Ramucicromab plus paclitaxel	Placebo plus paclitaxel	Hazard ratio (95% CI)	Odds ratio (95% CI)
Median overall survival				
Region 1 (n=385) and 2 (n=41)	8.5 months (7.4-9.8)	5.9 months (5.2-7.3)	0.732 (0.59-0.907)	
Region 3 (n=423)	1.1 months (1.0-1.3)	10.6 months (7.8-14.1)	0.686 (0.72-1.327)	
Median progression-free survival				
Region 1 (n=385) and 2 (n=41)	4.2 months (3.9-4.9)	2.9 months (2.4-3.5)	0.439 (0.318-0.585)	
Region 3 (n=423)	5.5 months (4.7-5.7)	2.8 months (2.8-4.1)	0.618 (0.473-0.814)	
Proportion of patients achieving an objective response				
Region 1 (n=385) and 2 (n=41)	55 (16%)	13 (4%)	2.087 (0.278-14.095)	
Region 3 (n=423)	37 (9%)	23 (6%)	1.726 (0.127-23.444)	

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 region 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

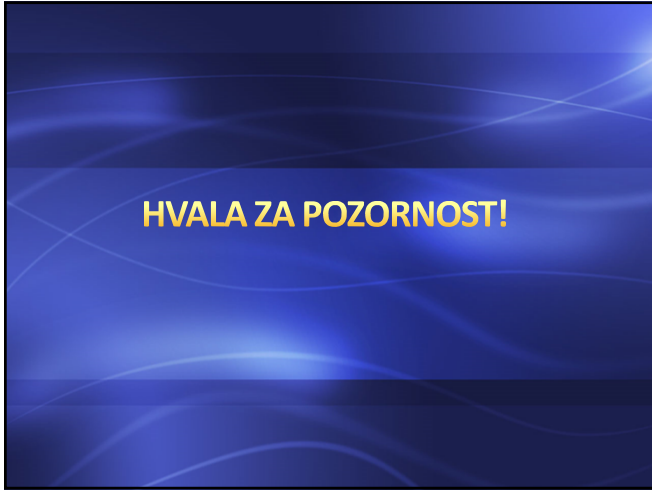
Rainbow

	Ramucicromab plus paclitaxel (n=335)				Placebo plus paclitaxel (n=335)			
	Grade 1-2	Grade 3	Grade 4	Grade 5	Grade 1-2	Grade 3	Grade 4	Grade 5
Any patients with a treatment-emergent adverse event	57 (17%)	58 (17%)	71 (21%)	31 (9%)	115 (34%)	138 (41%)	27 (8%)	31 (9%)
Non-haematological adverse events								
Fatigue*	147 (44%)	39 (12%)	0	0	134 (40%)	38 (11%)	0	0
Nausea*	121 (36%)	27 (8%)	0	0	184 (55%)	15 (4%)	0	0
Decreased appetite	111 (33%)	24 (7%)	0	0	91 (27%)	13 (4%)	0	0
Abnormal taste†	98 (29%)	20 (6%)	0	0	87 (26%)	10 (3%)	1 (0.3%)	0
Bleeding	109 (32%)	7 (2%)	1 (0.3%)	0	100 (30%)	8 (2%)	0	0
Allergies	107 (32%)	0	0	0	134 (40%)	1 (0.3%)	0	0
Dizziness	84 (25%)	11 (3%)	0	0	71 (21%)	4 (1%)	1 (0.3%)	0
Epistaxis	100 (30%)	0	0	0	13 (4%)	0	0	0
Vertigo	78 (23%)	9 (3%)	1 (0.3%)	0	56 (17%)	12 (4%)	0	0
Practical problems	77 (23%)	3 (1%)	0	0	43 (13%)	2 (1%)	0	0
Hypertension	32 (10%)	4 (1.2%)	0	0	8 (2%)	8 (2%)	0	0
Constipation	70 (21%)	1	0	0	59 (18%)	2 (1%)	0	0
Stomatitis	62 (19%)	2 (0.6%)	0	0	32 (10%)	2 (1%)	0	0
Pyrexia	56 (17%)	3 (1%)	0	0	36 (11%)	1 (0.3%)	0	0
Pruritus	50 (15%)	4 (1%)	0	0	30 (9%)	0	0	0
Malignant neoplasm progression	5 (2%)	18 (5%)	4 (1.2%)	27 (8%)	1 (0.3%)	24 (7%)	1 (0.3%)	34 (10%)
Weight decreased	39 (12%)	8 (2%)	0	0	45 (14%)	4 (1%)	0	0
Dyspnoea	24 (7%)	8 (2%)	0	0	29 (9%)	2 (1%)	0	0
Rash*	42 (13%)	0	0	0	31 (9%)	0	0	0
Cough	40 (12%)	0	0	0	35 (11%)	0	0	0
Back pain	35 (11%)	4 (1%)	0	0	35 (11%)	5 (2%)	0	0
Hypoaesthesia*	32 (10%)	4 (1%)	0	0	13 (4%)	2 (1%)	0	1 (0.3%)
Mutagen	24 (7%)	0	0	0	32 (10%)	1 (0.3%)	0	0
Asthenia	21 (6%)	11 (3%)	1 (0.3%)	0	14 (4%)	13 (4%)	0	0
Headache	21 (6%)	0	0	0	21 (6%)	1 (0.3%)	0	0
Haematological adverse events								
Neutropenia*	45 (14%)	71 (21%)	14 (4.2%)	0	40 (12%)	51 (15%)	11 (3%)	0
Anaemia*	84 (25%)	8 (2%)	0	0	82 (25%)	12 (4%)	1 (0.3%)	0
Leucopenia*	54 (16%)	5 (1.5%)	5 (1.5%)	0	47 (14%)	19 (6%)	3 (1%)	0
Thrombocytopenia*	38 (11%)	5 (1.5%)	0	0	14 (4%)	6 (2%)	0	0

Data are number (%) unless otherwise stated. *At least 1 adverse event category comprising ≥ 5 patients. †At least 1 patient.

Table 3. Treatment-emergent adverse events occurring in at least 5% of patients on ramucicromab plus paclitaxel, irrespective of causality

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

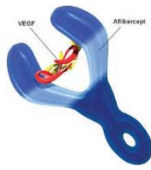
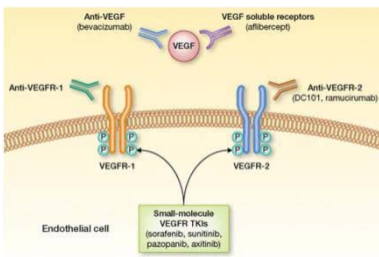


Novosti v sistemskem zdravljenju CRC

Dr.Tanja Mesti, dr.med

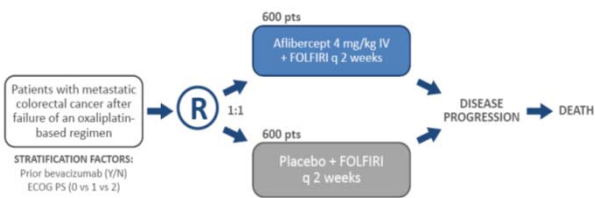
AFLIBERCEPT – VEGF zaviralec

Bevacizumab (humanizirano protitelo)



Aflibercept (himerno protitelo)

VELOUR: Aflibercept pri predhodno zdravljenih bolnikih z mRDČD



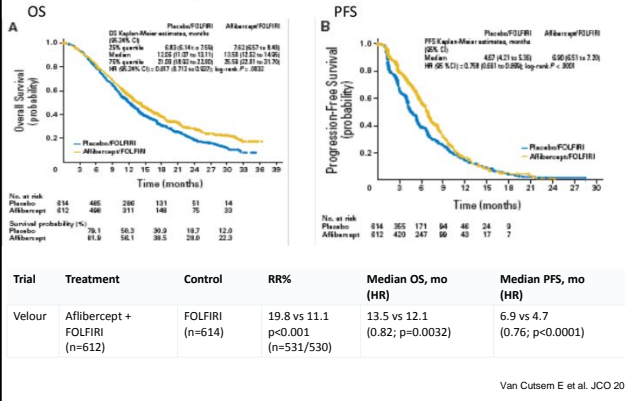
STRATIFICATION FACTORS:
Prior bevacizumab (Y/N)
ECOG PS (0 vs 1 vs 2)

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



VELOUR: Aflibercept pri predhodno zdravljenih bolnikih z mRDČD

Table 3. Summary of the Most Frequent Adverse Events (Incidence ≥ 10% in a 10% higher in aflibercept arm), Other Adverse Events, and Most Frequent Stage-Related Safety Events

Adverse Event	FOLFIRI (n = 614)		Aflibercept/FOLFIRI (n = 611)	
	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)
Diarrhea	87.5	17.4	86.2	21.4
Stomach pain	86.5	7.5	89.2	8.9
Abdominal conditions (incl. flatulence and ulceration)	86.2	6.2	86.4	8.8
Nausea	84.9	—	84.8	—
Nausea (PT)	54	—	53.4	—
Infections and infestations (SOC)	32.7	—	46.2	1.3
Hypertension	32.7	—	41.4	0.2
Neutropenia	19	—	37.8	0.2
Eggs	14	—	27.7	0.2
GI and abdominal pain (HLT)	20.1	3.1	34	0.3
Vomiting (PT)	39.4	3.5	32.9	2.6
Decreased appetite (PT)	29.4	1.7	29.9	3.4
Weight decreased	14.4	0.8	31.9	2.6
Abdominal PT	30.1	—	26.8	—
Dysphagia (PT)	3.3	—	25.4	0.5
Constipation (PT)	24.8	1.0	22.4	0.6
Nausea (PT)	6.8	0.3	22.3	1.6
Female genital atrophy/dyspareunia syndrome	4.3	0.6	11.0	2.6
Other anti-EGFR-associated events				
Arterial thromboembolic event	1.5	0.5	2.6	0.8
Venous thromboembolic event	7.3	2.6	8.7	3.1
Stroke from GI origin	0.2	0.2	1.1	0.3
Stroke from other than GI origin	0.2	—	0.3	—
GI perforation	0.5	0.2	0.3	0.2
Stage-related events				
Hematology				
Anemia	91.1	3.8	82.5	0.5
Neutropenia	86.3	18.1	87.8	23.1
Neutropenic complications	3.9	1.7	4.5	4.4
Thrombocytopenia	33.8	0.8	47.4	1.7
Nonhematology				
Proteinuria	40.7	1.2	42.2	0.3
ALT increased	37.1	—	47.3	2.5

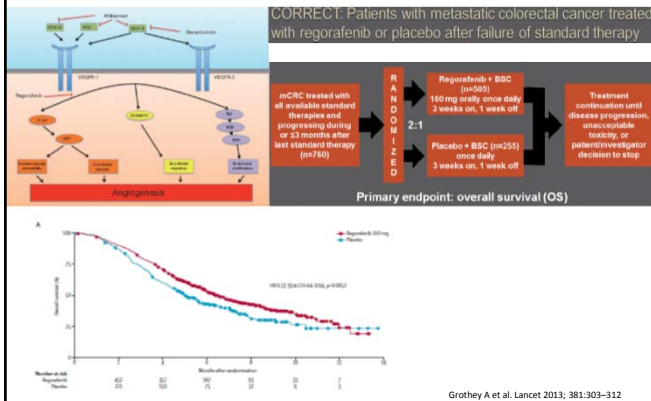
Abbreviations: FOLFIRI, infusional fluorouracil, leucovorin, and irinotecan; HLT, high-level term; PT, preferred term; SOC, system organ class; VEGF, vascular endothelial growth factor.
 *Grade was determined according to National Cancer Institute Common Terminology Criteria of Adverse Events, version 3.0.

Van Cutsem E et al. JCO 2012

Aflibercept

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

REGORAFENIB – Multikinazni zaviralec



Regorafenib

Any event	Regorafenib (N=200)			Placebo (N=253)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Clinical adverse event	405 (100%)	252 (100%)	17 (100%)	154 (100%)	15 (100%)	4 (100%)
Fatigue	227 (44%)	46 (9%)	2 (1%)	71 (28%)	13 (5%)	1 (1%)
Hand-foot skin reaction	223 (44%)	46 (9%)	0	59 (23%)	0	0
Diarrhoea	159 (31%)	0	1 (1%)	21 (8%)	0	0
Anorexia	152 (30%)	36 (7%)	0	39 (15%)	7 (3%)	0
Voice changes	147 (29%)	0	0	14 (5%)	0	0
Hypotension	139 (28%)	0	0	15 (6%)	0	0
Oral mucositis	136 (27%)	0	0	9 (4%)	0	0
Rash or dermatitis	120 (24%)	0	0	39 (15%)	0	0
Nausea	72 (14%)	0	0	28 (11%)	0	0
Weight loss	69 (14%)	0	0	6 (2%)	0	0
Fever	52 (10%)	0	0	7 (3%)	0	0
Constipation	43 (8%)	0	0	12 (5%)	0	0
Dry skin	39 (8%)	0	0	7 (3%)	0	0
Ataxia	36 (7%)	0	0	11 (4%)	0	0
Taste alteration	35 (7%)	0	0	5 (2%)	0	0
Vomiting	35 (7%)	0	0	13 (5%)	0	0
Serum amylase	34 (7%)	0	0	9 (4%)	0	0
Nose bleed	30 (6%)	0	0	5 (2%)	0	0
Dyspnoea	28 (6%)	0	0	4 (2%)	0	0
Muscle pain	28 (6%)	0	0	7 (3%)	1 (1%)	0
Headache	26 (5%)	0	0	8 (3%)	0	0
Pain, unknown	25 (5%)	0	0	30 (12%)	0	0
Laboratory abnormalities						
Thrombocytopenia	63 (12%)	13 (3%)	1 (1%)	5 (2%)	1 (1%)	0
Hypertension	45 (9%)	0	0	4 (2%)	0	0
Proteinuria	35 (7%)	7 (1%)	0	4 (2%)	1 (1%)	0
Alanine	33 (7%)	12 (2%)	2 (1%)	6 (2%)	0	0
Hypophosphataemia	25 (5%)	10 (2%)	0	11 (4%)	1 (1%)	0

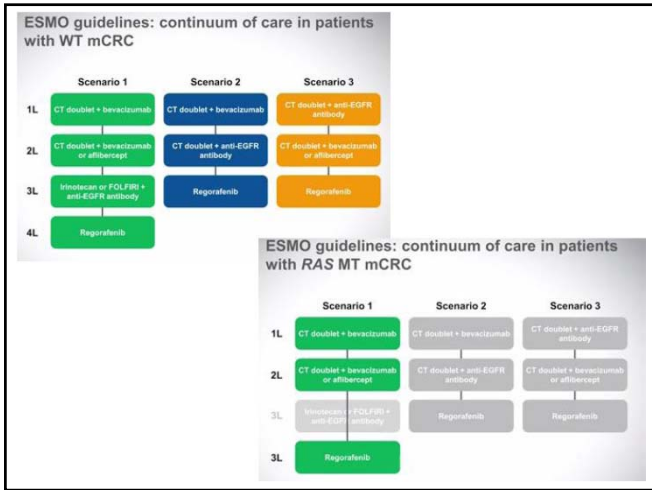
Data are n (%). *The appendix provides a detailed breakdown of all adverse events by National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0) category or term and worst grade.

Table 2. Treatment-related adverse events occurring in 10% of patients in either group from start of treatment to 30 days after end of treatment (safety population)

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

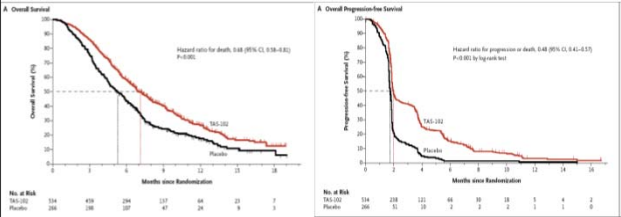
Regorafenib

- Zdravljenje RAS WT in RAS MT bolnikov
- 3L ali 4L zdravljenja
- Neželjeni 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 deaths 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 33.8% 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

Event	TAS-102 (N=513)		Placebo (N=265)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any event — no. (%)	528 (96)	179 (35)	247 (93)	137 (52)
Any serious event — no. (%)	174 (34)		81 (30)	
Most common events — no. (%)				
Nausea	278 (54)	39 (8)	63 (24)	3 (1)
Neutropenia	148 (29)	31 (6)	34 (13)	2 (1)
Decreased appetite	208 (41)	19 (4)	78 (30)	13 (5)
Fatigue	188 (37)	21 (4)	62 (23)	15 (6)
Diarrhea	179 (35)	18 (4)	33 (13)	2 (1)
Abdominal pain	113 (22)	31 (6)	49 (19)	30 (11)
Fever	89 (17)	7 (1)	17 (6)	1 (1)
Anemia	97 (19)	18 (4)	39 (15)	8 (3)
Events associated with fluoropyrimidine treatment — no. (%)				
Febrile neutropenia	29 (6)	0 (0)	0	0
Stomatitis	41 (8)	2 (1)	17 (6)	0
Hand-foot syndrome	22 (4)	0	6 (2)	0
Cardiac ischemia†	2 (1)	1 (1)	1 (1)	1 (1)
Laboratory abnormalities — no./total no. (%)				
Neutropenia	173/528 (33)	208/513 (41)	22/265 (8)	0
Leukopenia	407/528 (77)	113/513 (22)	22/265 (8)	0
Anemia	404/528 (77)	96/528 (18)	87/265 (33)	8/265 (3)
Thrombocytopenia	22/528 (4)	27/528 (5)	21/265 (8)	3/265 (1)
Increase in aspartate aminotransferase level	126/528 (24)	39/528 (8)	79/265 (30)	19/265 (7)
Increase in aspartate aminotransferase level	131/528 (25)	23/528 (4)	92/265 (35)	16/265 (6)
Increase in total bilirubin	189/528 (36)	45/528 (9)	69/265 (26)	12/265 (5)
Increase in alanine phosphatase level	205/528 (39)	42/528 (8)	126/265 (48)	26/265 (10)
Increase in creatinine level	71/527 (13)	5/527 (1)	32/263 (12)	2/263 (1)

* All adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.
 † Adverse events of any grade that are listed as most common occurred in 10% or more of patients in the TAS-102 group and 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.

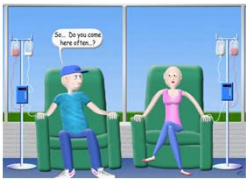
N Engl J Med 2015;372:1909-19. RJ Mayer, E Van Cutsem and al.

Povzetek

- Afibercept – 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

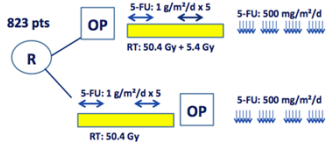


Kaj je standard?



Predop CRT je učinkovitejša kot poop CRT

CAO/ARO/AIO-04

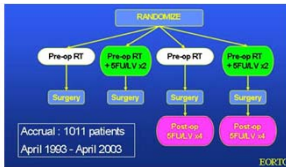
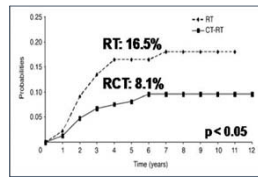


5 let (11 let)	Poop CRT	Preop CRT	p
Lok.ponovitev	13%	6%	0.006
Ohranitev sf	19%	39%	0.004
Akut.toks. G 3-4	40%	27%	0.001
Pozna toks. G 3-4	24%	14%	0.01
Odd.zasevki	38%	36%	0.84
OS	76%	74%	0.80

Sauer et al. N Eng J Med 2008

Predop CRT je učinkovitejša kot predop RT

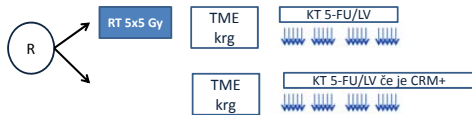
FFCD 9203



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		CI at 95%
	No.	Local Relapse Rate at 5 y	No.	Local Relapse Rate at 5 y	
SWEDISH (1977)	585	26%	583	9%	NR
DUTCH (2001)	504	11.4%	937	5.8%	2.85-5.71
MRC CR07 (2006)	676	17%	674	5%	1.61-3.79
TOTAL	2185	17.3%	2194	8.9%	

Kapiteijn E et al. N Eng J Med 2001
Sebag-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

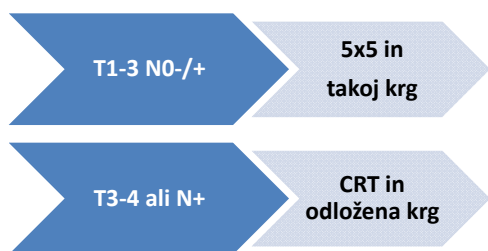
Sebaq-Montefiori D et al. Lancet 2009

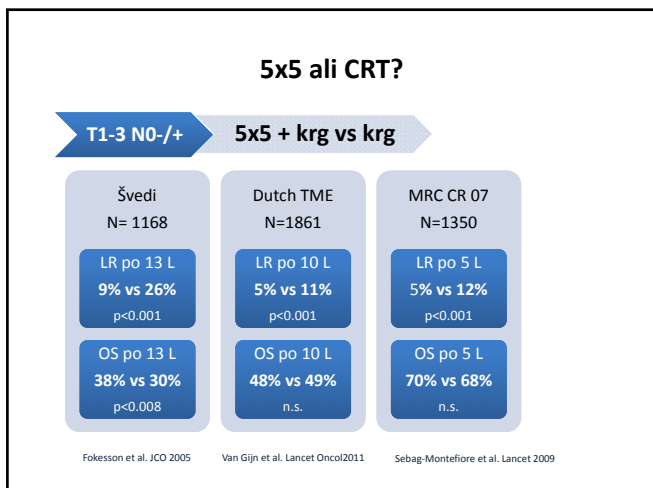
Kaj vemo?

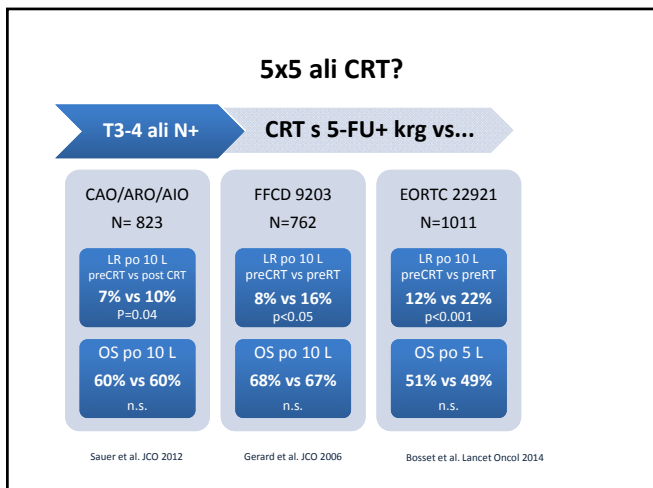


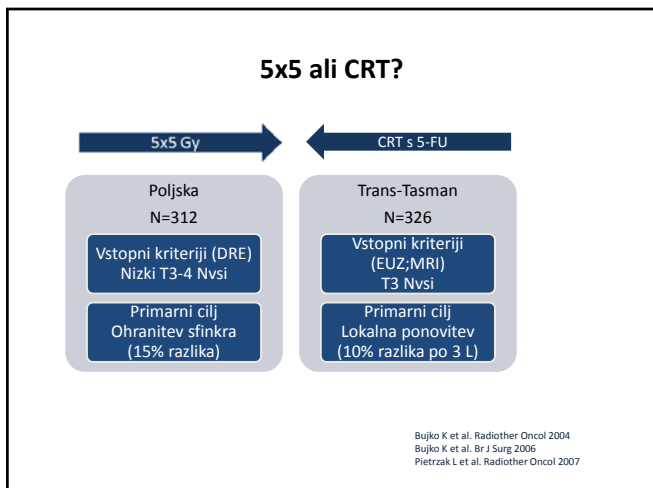
- Zaporedje RT, KT, krg je pomembno
(CAO/ARO/AIO-94)
- Sinergističen učinek RT- KT s 5-FU
(FFCD 9303, EORTC 22921)
- RT lahko dopolni le optimizirano operacijo
(Dutch TME, MRC CR 07)

5x5 ali CRT?









5x5 ali CRT?

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

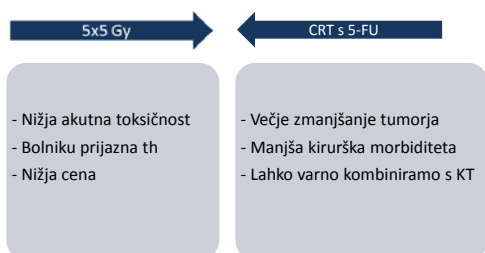
5x5 ali CRT?

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 et al. JCO 2012

5x5 ali CRT?

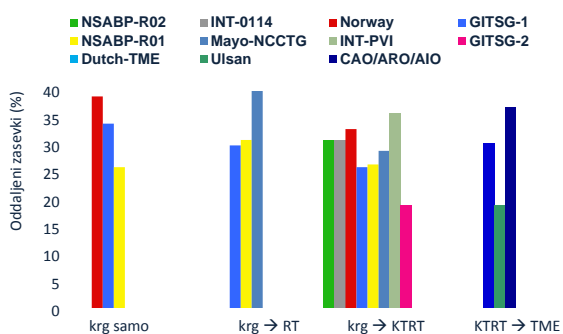


Kaj vemo?



- Standardna CRT zagotavlja:
 - boljše 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 Colino, Veronica Lonati, Sandro Barri



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 bolnikih z downstagingom in v retrospektivnih serijah
- 5y DFS je boljše v vseh raziskavah zaradi boljše LK

Adj. KT z oksaliplatinom je učinkovitejša

Systematic review

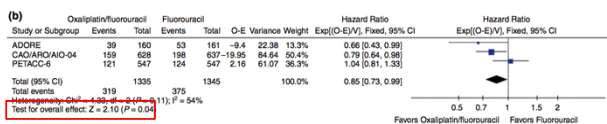
doi:10.1111/codi.13381

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, Ningling Hospital, Southern Medical University, Guangzhou, China and †Tongji 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 (e-mail: drsamartin@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

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3.3x večja verjetnost boljšega celokupnega preživetja
4.3 x večja verjetnost biti brez bolezni čez 5 let

Večina ne zaključi zdravljenja

- četrtnina 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.

Text Size: A A A

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

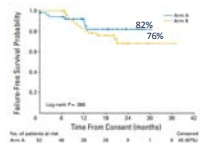
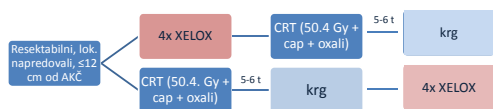
Kaj vemo?



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



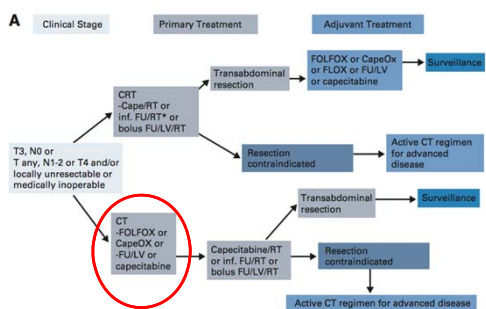
Celotno zdravljenje je neoadjuvantno



	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

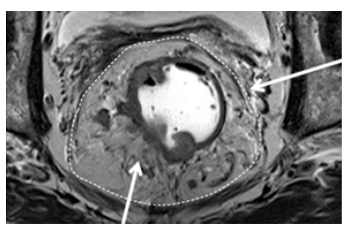


http://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf

Kaj je tudi pomembno danes?



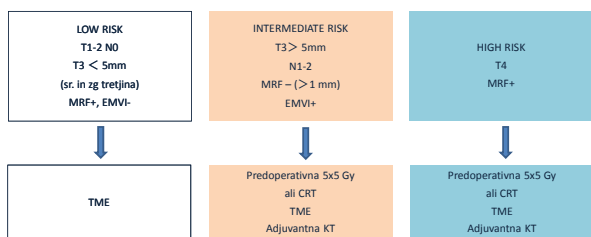
Skupine tveganja na osnovi MRI



Oddaljenost tumorja/lgi od MRF (v mm)

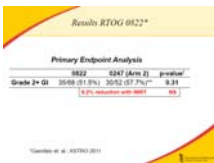
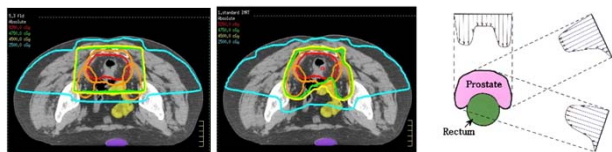
Prodor tumorja v mezorektalno maščevje v mm

Evropska/Skandinavska shema zdravljenja



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

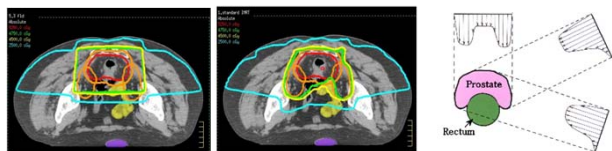
Intenzitetno Modulirano RT izpodriva 3D RT



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

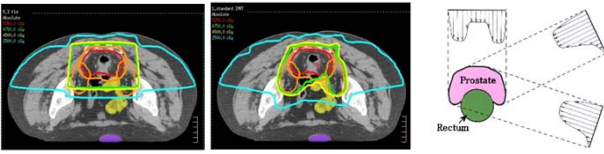
Rodel C et al. Curr Opin Oncol 2012

Intenzitetno Modulirano RT izpodriva 3D RT



Raziškava faza II	Št. pts	pCR	R1	LK	OS
Belgijska Engels 2014	108	8 %	8 %	97 % (5 I)	68 % (5 I)
Kitajska Jin-luan 2012	63	31 %	0 %	94 % (2 I)	96 % (2 I)
Španska Hernando 2014	72	30,6 %	3 %	95 % (3 I *)	86 % (3 I *)
Slovenska But 2016	51	25,5%	0%		

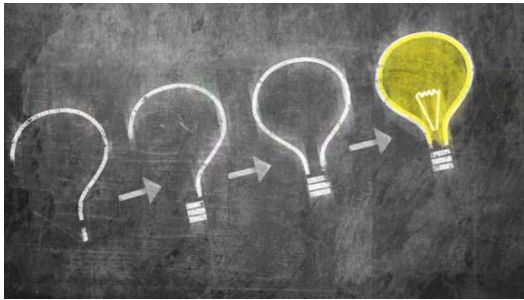
Intenzitetno Modulirano RT izpodriva 3D RT



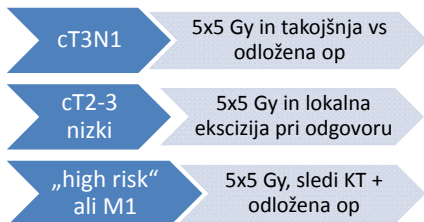
Raziskava faze II	Št. pts	pCR	Znižanje T	Znižanje N
But 2015	51	25.5 %	68 %	83 %
Velenik 2006	55	9 %	40 %	53 %

Velenik V et al. Cro Med J 2006
But J et al. UROBP 2016

Kako od tu dalje?



Raziskave s 5x5 Gy



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



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

Bujko C et al. Radiother Oncol 2013

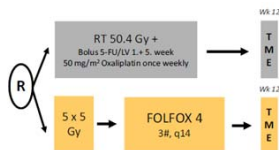


Nizozemska „M1“ (50 pts): pCR 26%, Ro resekcija vseh lokalizacij v 72%

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

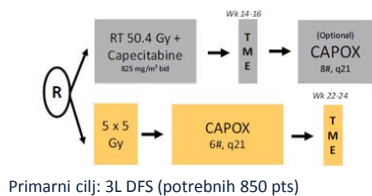
	50.4 Gy 5-FU/Ox	5x5 Gy FOLFOX	P-value
Number of pts	254	261	
R0 resection (%)	71	77	.07
pCR (%)	12	16	.21
Acute tox grade 1+2/ 3+4 / 5	60 / 21 / 3	60 / 23 / 1	.006
Postop complication	25	29	.18
Local Failure @3y (%)	21	22	.82
Disease-free Survival @ 3y (%)	62	63	.85
Overall Survival @ 3y (%)	65	73	.046

Srednji čas sledenja 35 mes

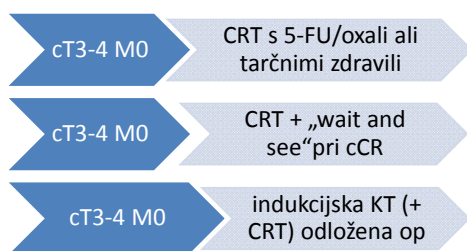
Bujko C et al. ASCO GI 2016

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+



Potekajoče raziskave s CRT



↑ 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

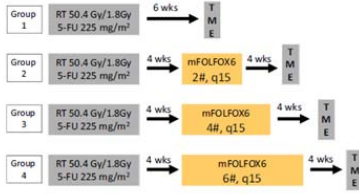
Annals of Surgery. 263(3):458-464, March 2016.

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

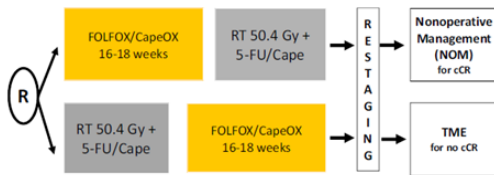
- TIMING raziskava

cT3/4 or N+	G 1	G 2	G 3	G 4	p
Number of pts	60	67	67	65	
ypTON0 (%)	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)
 - 2 MRI definirani T2-3N0 ali Tvs1 N1-2



Primarni cilj: 3L DFS

Zaključki (I): kaj smo se



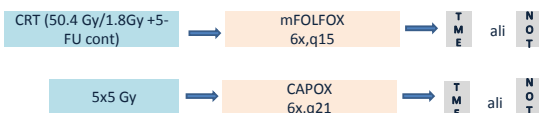
- Zaporedje RT, KT, krg je pomembno (CAO/ARO/AIO-94)
- Sinergističen učinek RT- KT s 5-FU (FFCD 9303, EORTC 22921)
- RT lahko dopolni le optimalno operacijo (Dutch TME, MRC CR 07)
- Pomemben je interval od RT do op (Timing, Stockholm III)
- Več bolnikov dokonča predoperativno kot pooperativno zdravljenje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

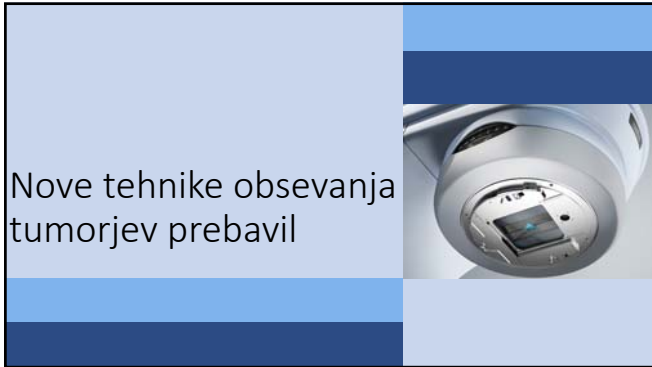
- Totalna Neoadjuvantna Terapija – Op odložena ali brez

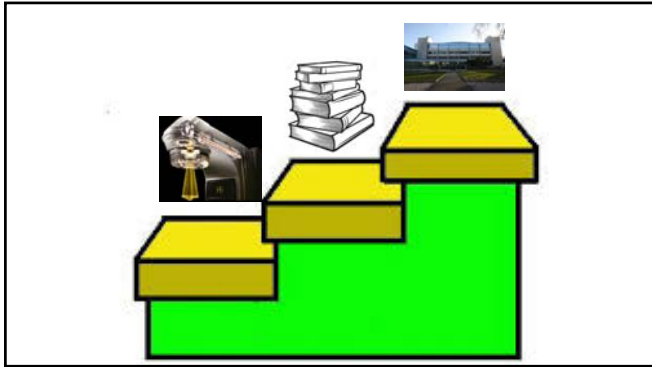


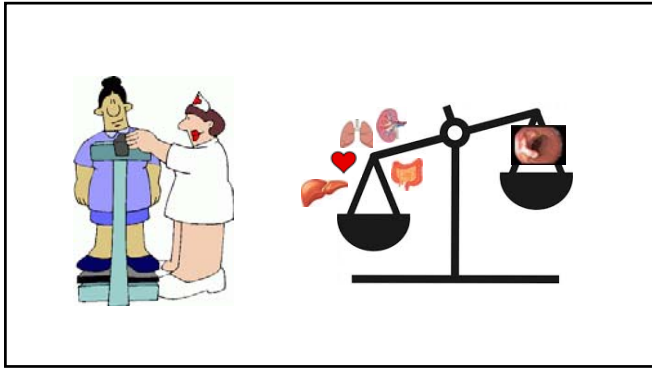
- Selekcija in monitoring z modernimi slikovnimi metodami!

Hvala za pozornost.









Pogled v preteklost...



IMRT (Intensity Modulated RadioTherapy)

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



IMRT

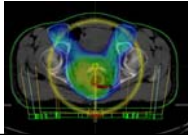
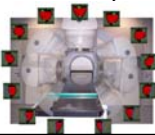


- ✓ bolj konformna in homogena porazdelitev doze
- ✓ strm dozni gradient na robu tarče
- ✓ ščitenje kritičnih organov
- ✓ simultani integrirani boost
- ✓ eskalacija doze

- 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 boleznj srca

pri IMRT kot pri 3D

Frellich 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

doprinosa v kliničnih rezultatih
?

- **Minn et al 2010:** - ni razlik v 2yr OS in LC
- ni razlik v GI toksičnosti $G \geq 2$, 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 $G \geq 2$, 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 + SIB , s TD 46Gy v 23 frakcijah s SIB 55,2Gy
Akutna GI toksičnost G2-3: 9%
Vse kasne toksičnosti G2-3: 13%
5 yr LC: 97%
5 yr PFS: 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!

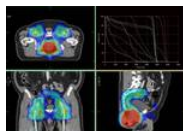


TABLE 5. Retrospective Studies Comparing 3 Dimensional Conformal Radiotherapy Versus Intensity Modulated Radiotherapy for Anal Cancer

STUDY	TREATMENT	NO.	MEDIAN DOSE (range), Gy	MEDIAN V10 (% of V10)	MEDIAN P10 (% of P10)	LR, %	LR, %	LR, %	LR, %	LR, %	LR, %
Lustgarten 2008 ¹⁷	3D CRT	39	56	37	58	82.3	58	58	12	12	12
	IMRT	20	58	19	58	85	58	58	11	16	16
		P				1.4			0.04	0.01	
Barnes 2001 ¹⁸	3D CRT	13	54 (41-62.4)	35	57	3	52	58	12	19	47
	IMRT	29	54 (45-59.4)	32	40	3	52	51	10	11	21
		P				<.0001			<.01	0.03	0.03
Deane 2012 ¹⁹	3D CRT	27	55.4 (38.8-66.8)	40	58	2	56.5	57.1	8.1	17.7	13.3
	IMRT	24	55.4 (38.8-66.8)	23	47	2	63	60.3	4.2	17.5	17.5
		P				0.003			1.2	58	17.6
Desjardins 2013 ¹⁴	3D CRT	176	45 (45-50.4)	23.2	39	2	62	51	56	58	58
	IMRT	40	54 (50-56)	27.6	40	2	47	47	13	58	58
		P				<.01			2	1	37
Chang 2013 ¹⁶	3D CRT	37	55.4 (45.6-6)	52	40	3	52	56	10*	10*	10
	IMRT	52	56 (50-62.5)	20	39	3	61	51.3	8*	14*	11.5
		P				<.0001			1.2	1.1	0.001

3D CRT, 3-dimensional conformal radiotherapy; LR, likelihood ratio; V10, volume at 10% isodose; P10, percentage of P10; IMRT, intensity modulated radiotherapy. *The rate of adverse GI or GU toxicity for 3D CRT versus IMRT was 24.3% versus 1.4%, respectively (P<.0001).

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 bezgavne lože: TD: 42-45 Gy
boost na tumor in prizadete bezgavne: 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

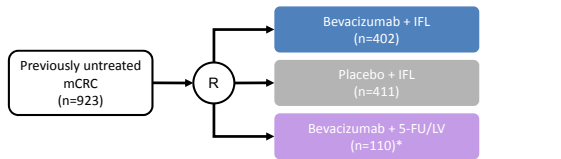
Vloga bioloških zdravil v zdravljenju mCRC

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

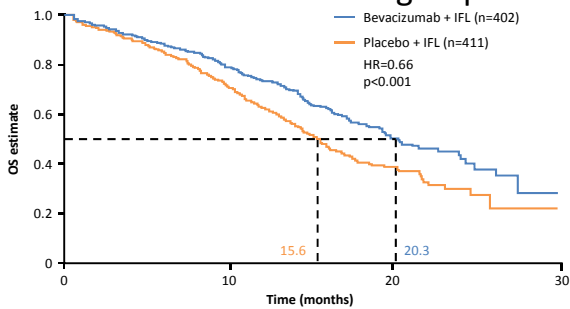
Secondary endpoints: PFS, ORR, duration of response, QoL

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

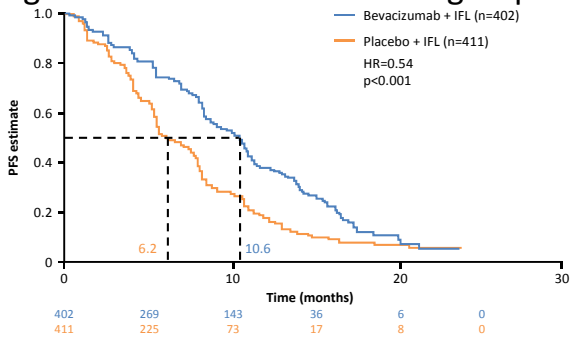
Hurwitz, et al. N Engl J Med 2004

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



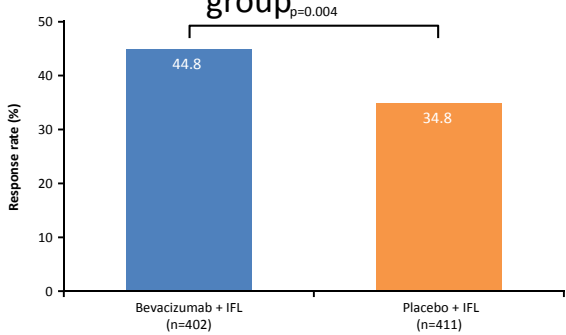
Hurwitz, et al. N Engl J Med 2004

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



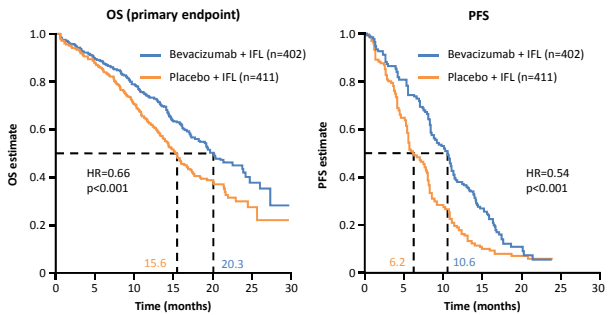
Hurwitz, et al. N Engl J Med 2004

AVF2107g: ORR was significantly increased in the bevacizumab + IFL group



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

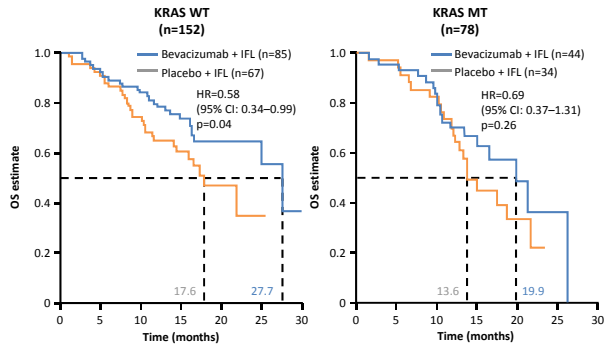
AVF2107g: survival benefit was independent of BRAF and KRAS mutation status¹

Biomarker	Placebo + IFL		Bevacizumab + IFL		HR	(95% CI)	HR	
	N	n	Median (months)	n				Median (months)
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-2²

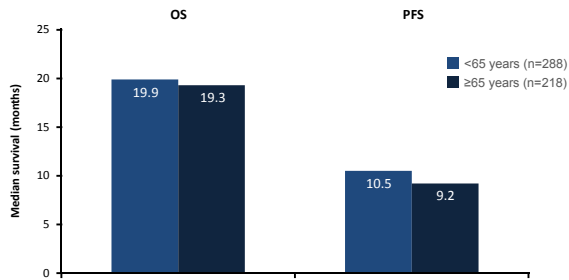
1. Ince, et al. J Natl Cancer Inst 2005; 2. Jubb, et al. J Clin Oncol 2006

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

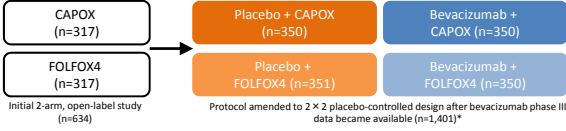
NO16966: study design and endpoints

Trial started 2003

[NCT00069095](https://clinicaltrials.gov/ct2/show/study/NCT00069095)

Recruitment
June 2003–May 2004

Recruitment
February 2004–February 2005



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

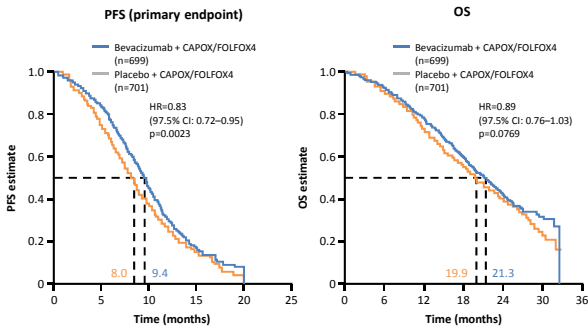
Secondary endpoints: on-treatment PFS (for events that occurred >28 days after the last intake of study medication, the patient was censored back to the date of last known nonprogression), OS, ORR, duration of response, time to treatment failure

Primary endpoint was met

Bevacizumab = 7.5mg/kg q14d with CAPOX; 5mg/kg q14d with FOLFOX4
CAPOX = capecitabine, 1200mg/m² qd, continuous; FOLFOX4 = folfox4
FOLFOX4 = oxaliplatin, 85mg/m² qd, ox, 200mg/m² qd, 5-fluorouracil 400mg/m² continuous infusion over 22h, qd and qd, qd

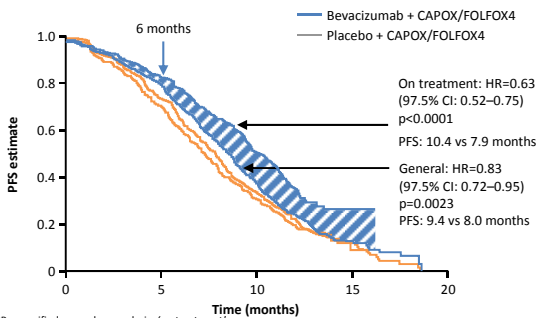
Saltz, et al. ASCO 2007
Saltz, et al. J Clin Oncol 2008

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



Saltz, et al. J Clin Oncol 2008

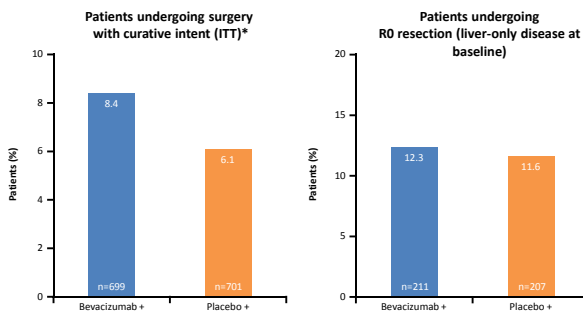
NO16966: clinical benefit in patients 'on treatment'*



*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

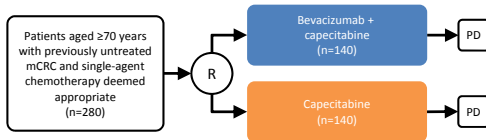
	FOLFOX4/ placebo + FOLFOX4 (n=668)	CAPOX/ placebo + CAPOX (n=667)	Bevacizumab + FOLFOX4 (n=349)	Bevacizumab + CAPOX (n=350)
No. of events	573	546	274	274
Median OS, months	18.9	19.0	21.0	21.6
HR (97.5% CI)		0.95 (0.83–1.09)		0.95 (0.78–1.15)

Cassidy, et al. Br J Cancer 2011

AVEX: study design and endpoints

Trial started 2007

[NCT00484939](#)



Primary endpoint: PFS

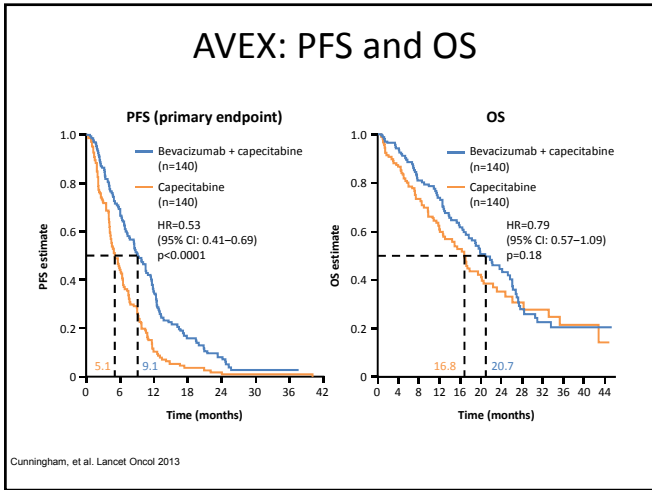
Secondary endpoints: OS, confirmed best overall response, ORR, DCR, duration of response, safety

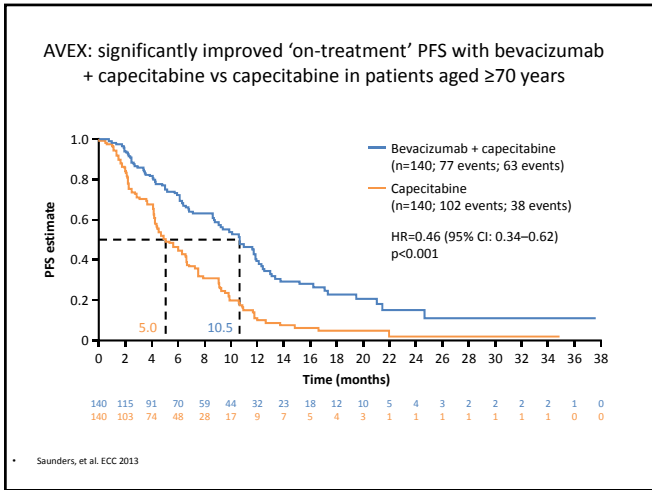
Patients had a median age of 76 (70–87) years

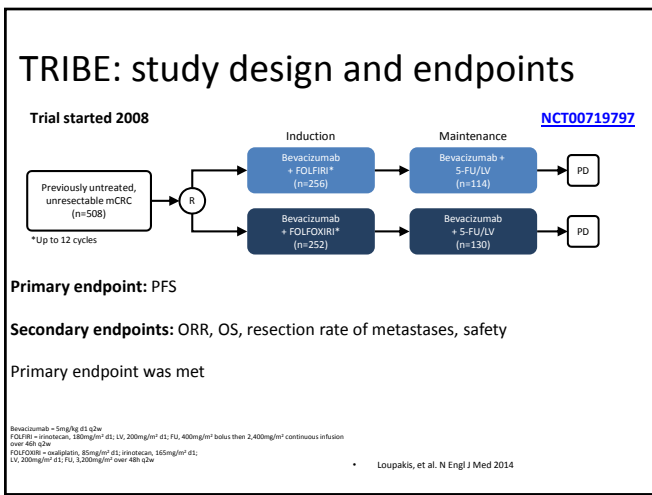
Primary endpoint was met

Bevacizumab = 7.5mg/kg d1 q3w
Capecitabine = 1,000mg/m² bid d1–14 q3w

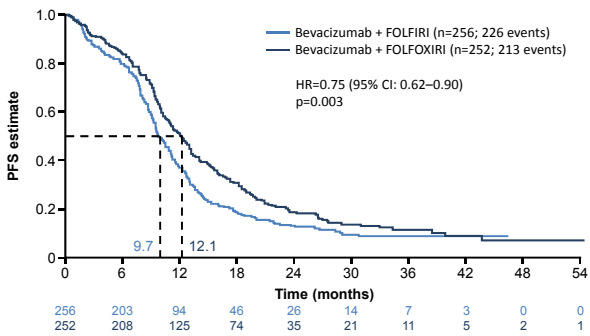
Cunningham, et al. Lancet Oncol 2013



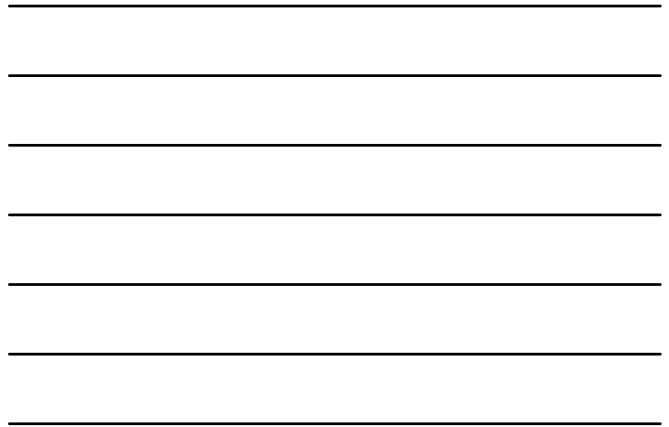




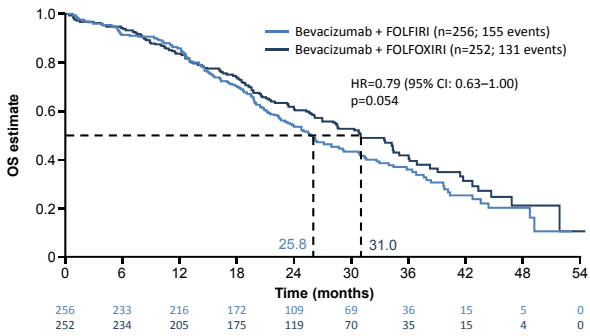
TRIBE: 1L bevacizumab + FOLFOXIRI produces superior PFS to bevacizumab + FOLFIRI



Loupakis, et al. N Engl J Med 2014



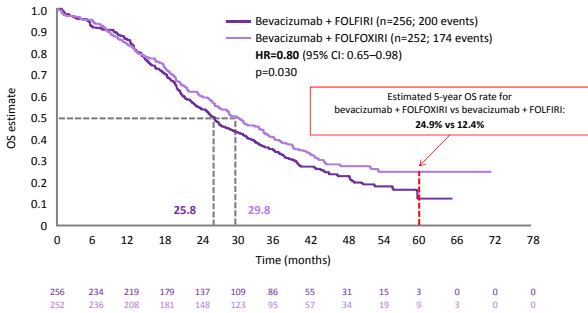
TRIBE: trend towards improved OS with bevacizumab + FOLFOXIRI (data immature)



* Median follow-up = 32.2 months
Loupakis, et al. N Engl J Med 2014



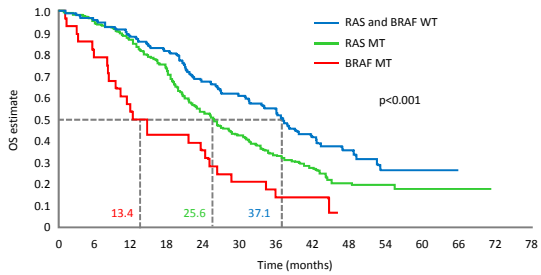
TRIBE: updated OS (follow-up of 48.1 months)



* Cremolini, et al. WCCG 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 ASCO 2015, PFS new data at WCGC 2015

	n	Median OS, months		HR	P value	Median PFS, months		HR	P value
		Bevacizumab + FOLFIRI	Bevacizumab + FOLFOXIRI			Bevacizumab + FOLFIRI	Bevacizumab + FOLFOXIRI		
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

ETS¹
 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

DpR¹
 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 patients³

n=443*	Bevacizumab + FOLFIRI		p value	n=494*	Bevacizumab + FOLFOXIRI		p value
	(n=222)	(n=221)			(n=245)	(n=239)	
Range, %	-100 to +56.9	-100 to +54.5		-100 to +56.9	-100 to +54.5		
Median, %	-21.4	-30.2	<0.0001	-33.8	-42.2	0.0009	
ETS >20%, n (%)	114 (51)	142 (64)		103 (42)	138 (58)		
ETS ≤20%, n (%)	108 (49)	79 (36)	0.006	142 (58)	101 (42)	0.0008	

*65 patients were not evaluable for ETS

**24 patients were not evaluable for DpR

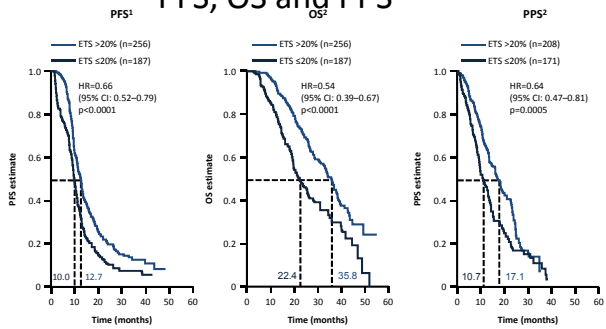
1. Cremonini, et al. ECC 2013
 2. Pliessevaux, et al. J Clin Oncol 2013
 3. Mansmann, et al. ASCO 2013

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	

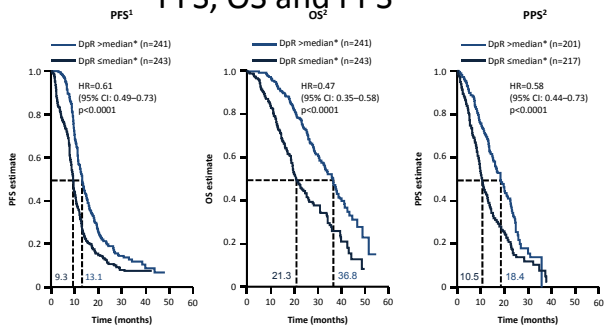
- *Median DpR = 38.9%
- Cremolini, et al. ASCO GI 2014

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

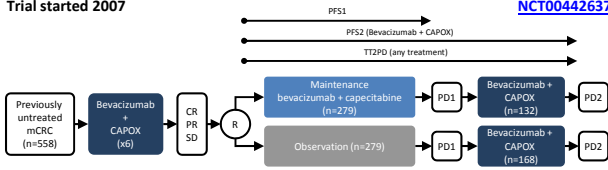


- 1. Cremolini, et al. ECC 2013
- 2. Cremolini, et al. ASCO GI 2014

CAIRO3: study design and endpoints

Trial started 2007

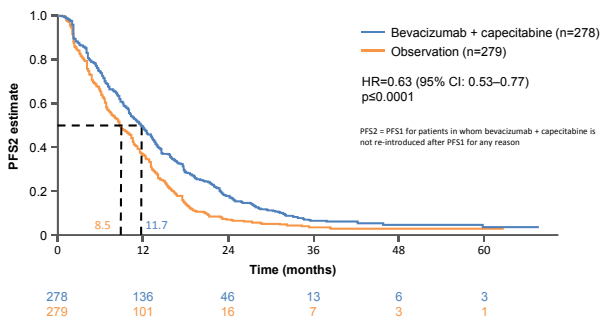
[NCT00442637](#)



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

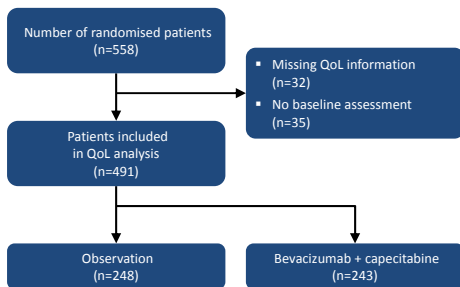
Bevacizumab = 7.5mg/kg d1 q3w
 Capecitabine = 625mg/m² bid
 CAPOX = oxaliplatin, 130mg/m² d1; capecitabine, 1,000mg/m² bid d1-d14 q3w
 Simkens, et al. Lancet 2015

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



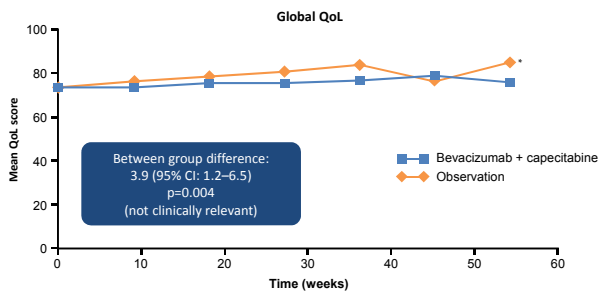
Simkens, et al. Lancet 2015

CAIRO3: QoL analysis



Punt, et al. ECC 2013

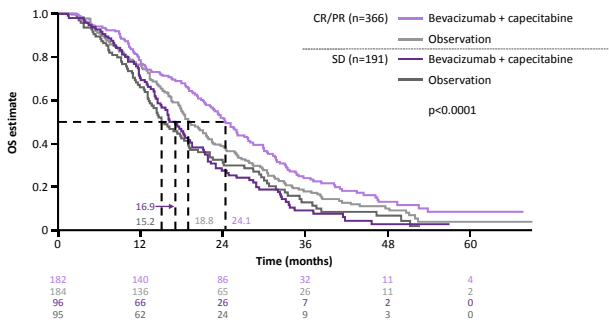
CAIRO3: QoL was higher in the observation group compared with maintenance bevacizumab + capecitabine



* 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



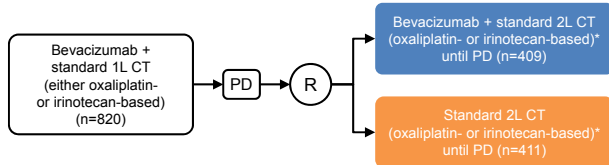
* Induction treatment of six cycles bevacizumab + CAPOX prior to randomisation not included (4-5 months)

* Koopman, et al. ASCO 2014

ML18147: study design and endpoints

Trial started 2006

NCT00700102



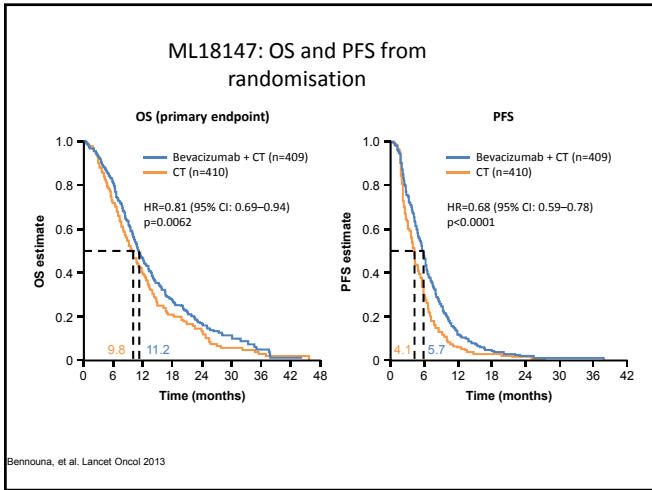
Primary endpoint: OS from randomisation

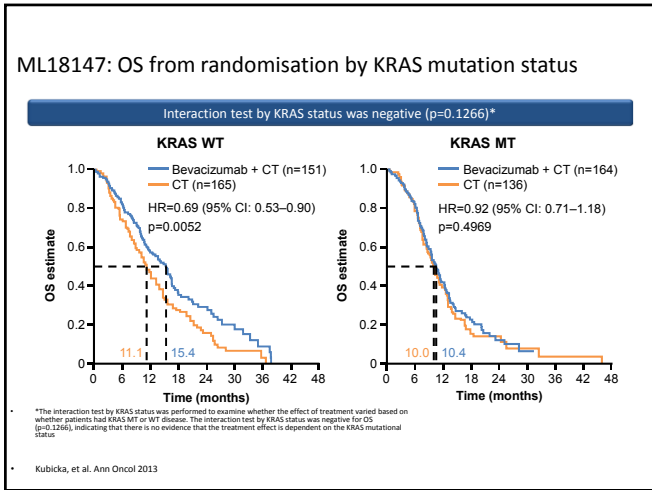
Secondary endpoints: PFS, best overall response, OS from start of 1L therapy, 'on treatment' PFS (i.e. disease progression occurred ≤28 days after the last confirmed dose of study treatment)

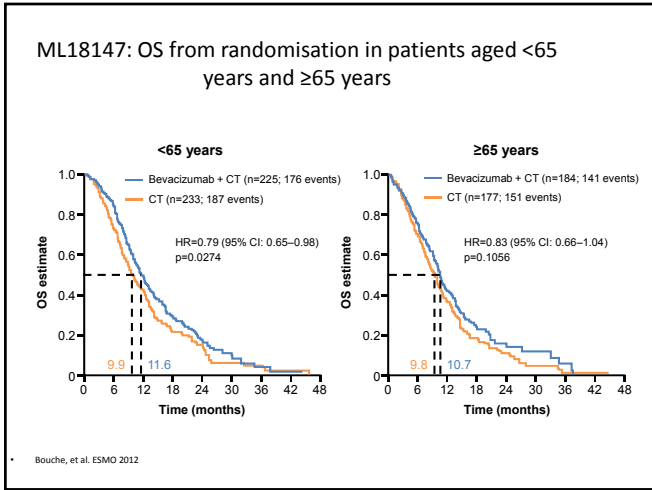
Primary endpoint was met

*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







BOND

NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

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

David Cunningham, M.D., Yun-Ho Hong, M.D., Ph.D., Shivon Soma, M.D., David Khayat, M.D., Ph.D., Henry Blotock, M.D., Ph.D., Armando Santoni, M.D., Doreen Sire, M.D., Matthew Blomens, M.D., Andrew Harrison, M.D., Chouh-Wei Cheng, M.D., Ph.D., Ian Chau, M.B., B.S., and Eric Van Cutsem, M.D., Ph.D.

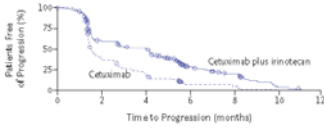


Table 2. Rates of Radiologic Response.[†]

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)	12 (10.8)	0.007
	[17.5–26.1]	[5.7–18.1]	
Disease control [§]	121 (55.5)	36 (32.4)	<0.001
	[48.6–62.2]	[23.9–42.0]	
Subgroup with progression during or within 4 wk after prestudy irinotecan			
No. of patients	115	71	
Response — no. (%)	34 (29.2)	10 (14.1)	0.07
	[18.1–33.4]	[7.0–24.4]	
Subgroup with prior oxaliplatin therapy			
No. of patients	115	71	
Response — no. (%)	30 (22.2)	6 (8.5)	0.01
	[15.5–30.2]	[3.2–17.5]	

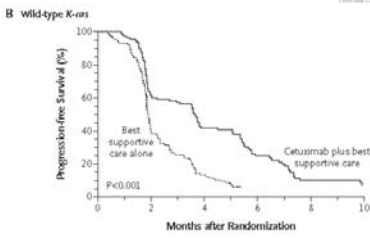
NCIC CTC Co 17

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED 1954 OCTOBER 23, 2008 VOL 359, NO 17

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

Christos S. Karapetis, M.D., Shun-Wen Hwu, M.D., Ph.D., David J. Jankin, M.D., Chao J. Ottaviano, Ph.D., Dingrong Yu, Ph.D., Hui C. Seltzer, Ph.D., & John Stein, M.D., Hui-Chieh M.D., Jeremy D. Shapiro, M.D., Soma Subramanian, M.D., Timothy J. Price, M.D., Eric Sargent, M.D., Ph.D., Hui-Chieh M.D., Christian Langer, M.D., Malcolm J. Moore, M.D., and John R. Zujewski, M.D., Ph.D.[†]

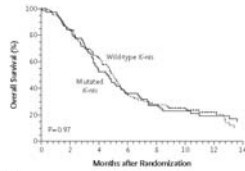
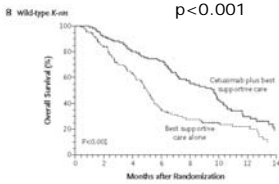


• PFS 3.7 vs 1.9
HR=0.40
p<0.001

NCIC CTC Co 17

• OS 9.5 vs 4.8
HR=0.55
p<0.001

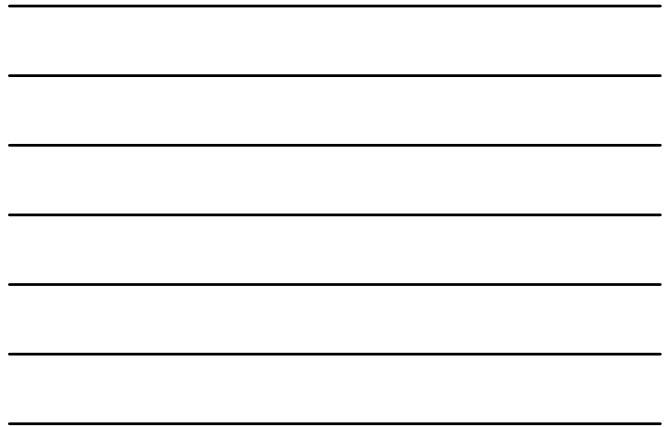
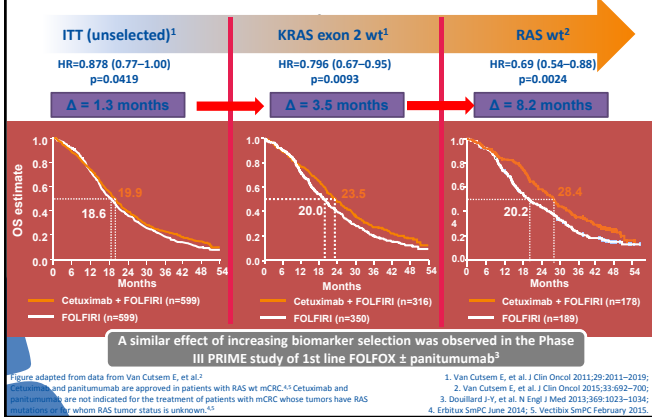
BSC
RR 13% vs 0



No. at Risk
Mutated K-ras: 76 64 39 26 19 12 10 7
Wild-type K-ras: 103 88 65 34 22 17 12 5

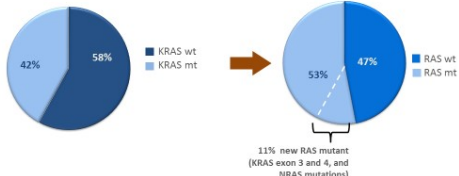
Figure 3. Kaplan-Meier Curves for Overall Survival According to K-ras Mutation Status among Patients Receiving Supportive Care Alone.

CRYSTAL: Greater patient selection extended the OS benefit with



Extended RAS mutation testing

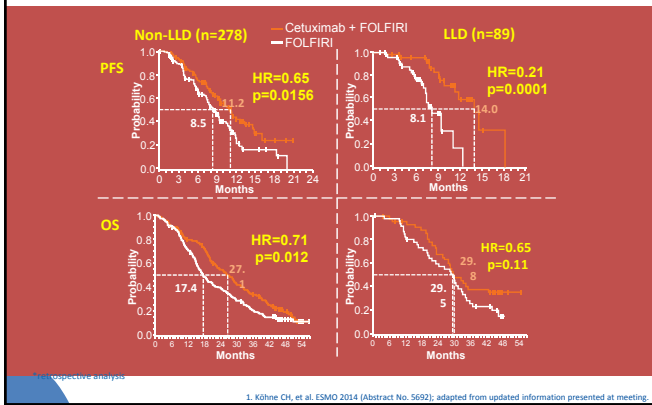
Meta-analysis of >5000 patients from randomized clinical trials¹



Cetuximab should not be used for the treatment of patients with mCRC whose tumors have RAS mutations in KRAS exon 3 and 4, or NRAS mutations.¹
 1. Sarin AP, et al. Ann Oncol 2012;23:13-21; 2. Eribix SmPC June 2014; 3. Vectibix SmPC February 2015.



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



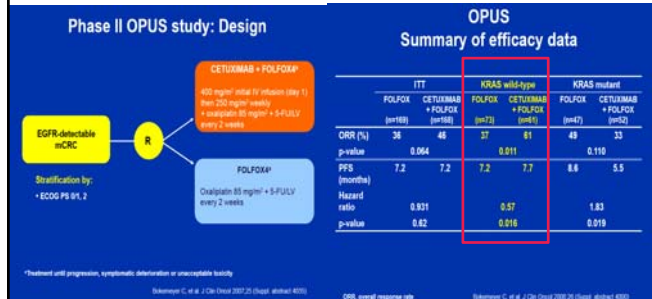
1. red zdravljenja: [faza II](#)

O original article

Annals of Oncology
doi:10.1016/j.annonc.2010.11.022

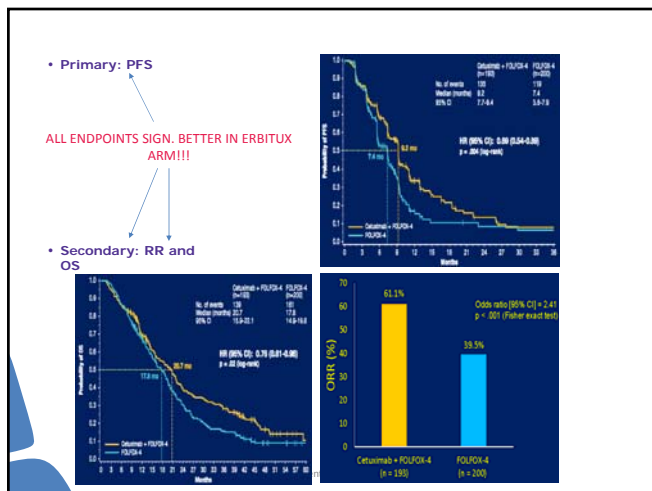
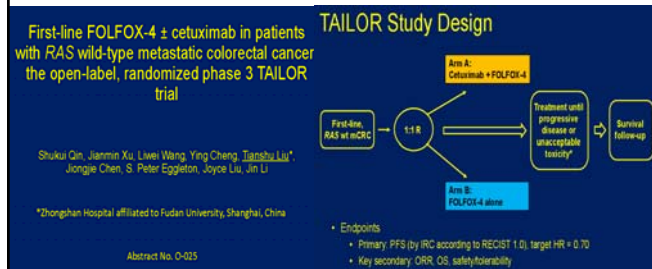
Efficacy according to biomarker status of cetuximab plus FOLFOX-4 as first-line treatment for metastatic colorectal cancer: the OPUS study

C. Bokemuehl¹, I. Bondaruk², J. T. Hartmann³, F. de Braud⁴, G. Schuch¹, A. Zuber⁵, I. Csik⁶, M. Schilling⁷ & P. Korabecnik⁸

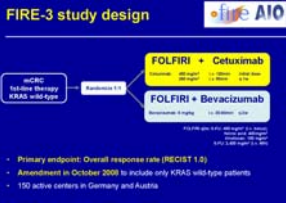


1. red zdravljenja: [faza III](#) (ERBITUX + FOLFOX vs FOLFOX)

TAYLOR (WCGIC Abstract No.O-025)



FIRE -3



Independent evaluation of response

CT evaluable population	FOLFIRI + Cetuximab	FOLFIRI + Bevacizumab	ORR %	95% CI	Odds ratio	p
KRAS exon 2 wt n=453	65.0	61.1 - 72.9	65.6	49.3 - 81.8	1.18	0.016
Final RAS wt n=338	72.9	64.3 - 79.8	66.1	48.5 - 83.8	2.05	0.005

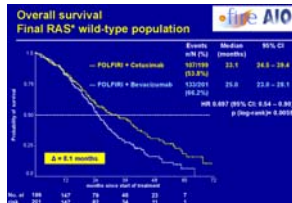
1. Stintzing S, et al. ESMO 2014 (Abstract No. LB411);
2. Heinemann V, et al. Lancet Oncol 2014;15:1065-1075.

FIRE - 3

Evaluation of Depth of Response (DpR*)

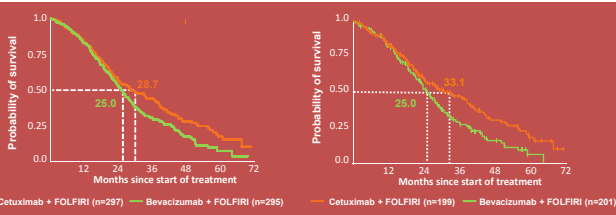
	FOLFIRI + Cetuximab	FOLFIRI + Bevacizumab	p
Median DpR			
KRAS exon 2 wt n=453	44.1 (±14.6%)	32.8 (±14.7%)	0.0003
Final RAS wt n=338	48.9 (±14.8%)	32.3 (±12.7%)	<0.0001

**DpR: percentage of maximal tumor shrinkage observed at the next response evaluation.*



1. Stintzing S, et al. ESMO 2014 (Abstract No. LB411);
2. Heinemann V, et al. Lancet Oncol 2014;15:1065-1075.

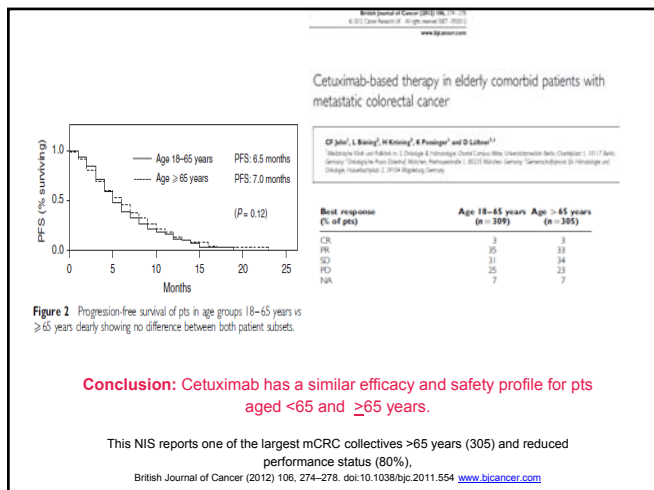
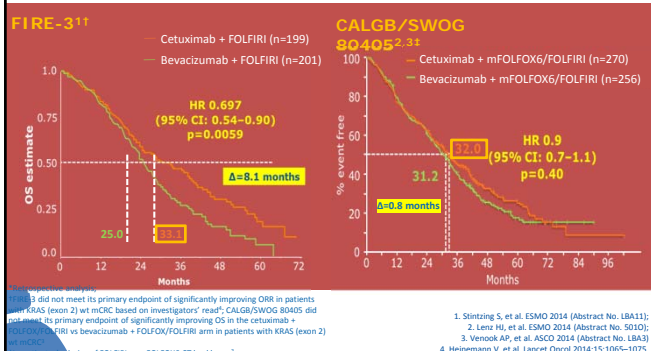
FIRE-3: Increased OS benefit with cetuximab in final RAS wt vs KRAS wt population^{1,2}



1. Heinemann V, et al. Lancet Oncol 2014;15:1065-1075;
2. Stintzing S, et al. ESMO 2014 (Abstract No. LB411), adapted from updated information presented at the meeting;
3. Eribix SmPC June 2014.

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

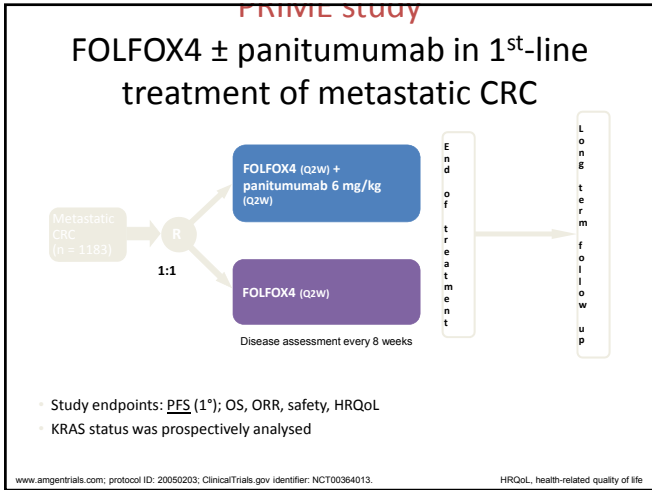
Randomized Phase III trials of cetuximab + CT vs bevacizumab + CT (RAS wt*)



Panitumumab in 1st-line mCRC

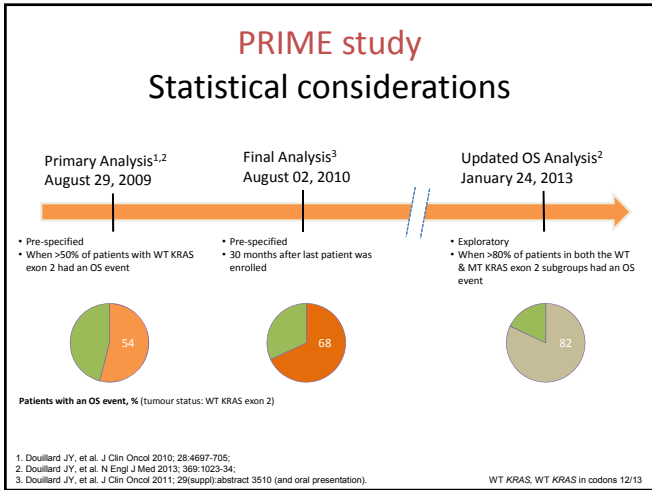
Randomised phase 3 study of panitumumab with FOLFOX4 vs. FOLFOX4 alone as 1st-line treatment in mCRC patients: the PRIME trial





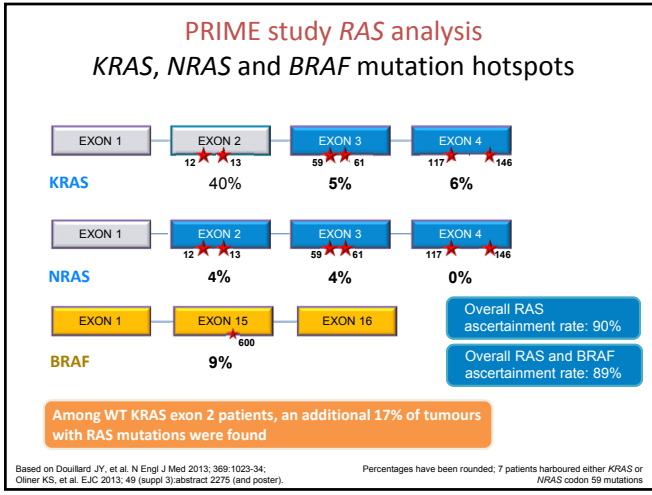
- PRIME study**
- ### Key eligibility criteria
- ≥18 years of age
 - Previously untreated metastatic adenocarcinoma of the colon/rectum
 - Adjuvant 5-FU-based therapy allowed if disease progression occurred >6 months after completion; prior oxaliplatin not allowed
 - Measurable disease
 - Paraffin-embedded 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)

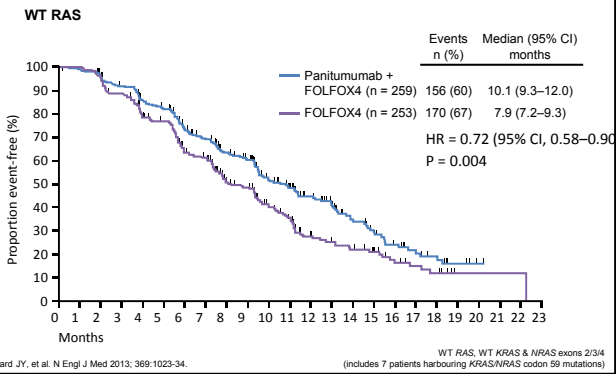


Panitumumab in 1st-line mCRC

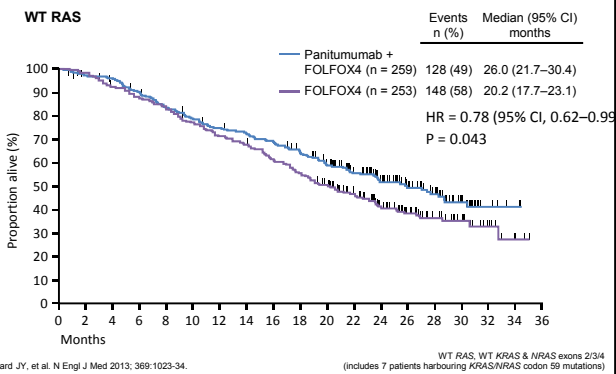
The PRIME study: Panitumumab + FOLFOX4 treatment in WT RAS mCRC



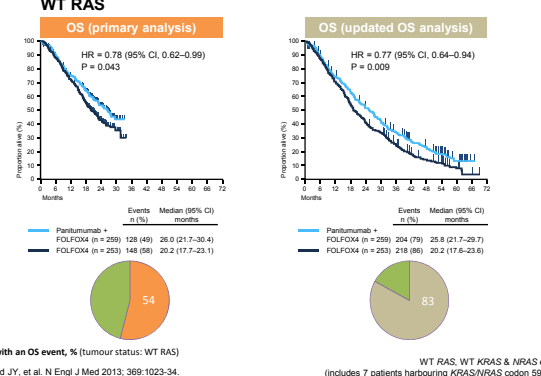
PRIME study RAS analysis PFS (primary analysis)



PRIME study RAS analysis OS (primary analysis)



PRIME study RAS analysis OS (primary & updated OS analyses)



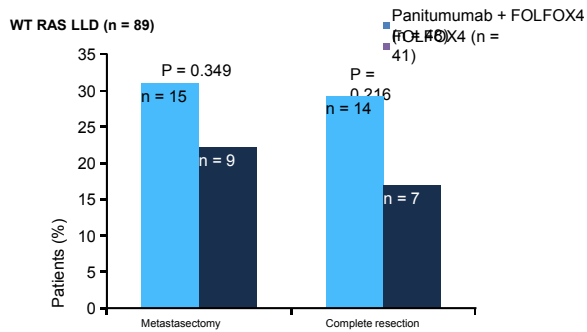
PRIME study RAS analysis Summary of adverse events (primary analysis)

Adverse event	WT RAS			MT RAS		
	Panitumumab + FOLFOX4 (n = 256)	FOLFOX4 (n = 250)	Total (n = 506)	Panitumumab + FOLFOX4 (n = 258)	FOLFOX4 (n = 278)	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

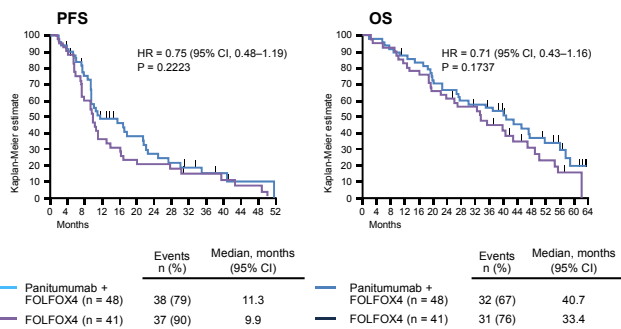
PRIME study RAS analysis Metastectomy and complete resection rates (LLD patients, updated analysis)



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

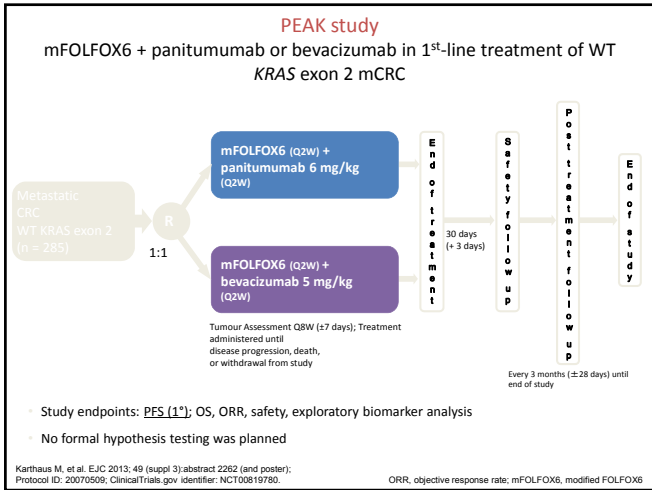
LLD, liver-limited disease

PRIME study RAS analysis PFS, OS (LLD patients, updated analysis)



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

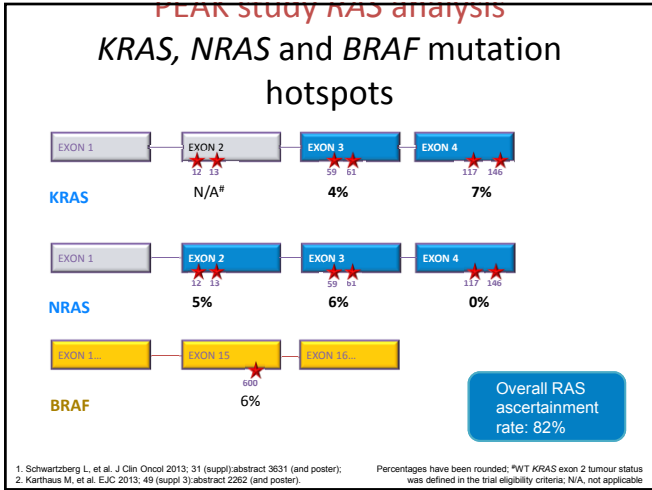
LLD, liver-limited disease



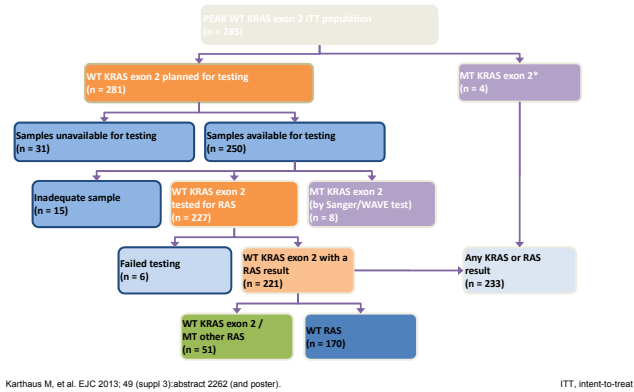
PEAK study *RAS* analysis
Biomarker testing methodology

- 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

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



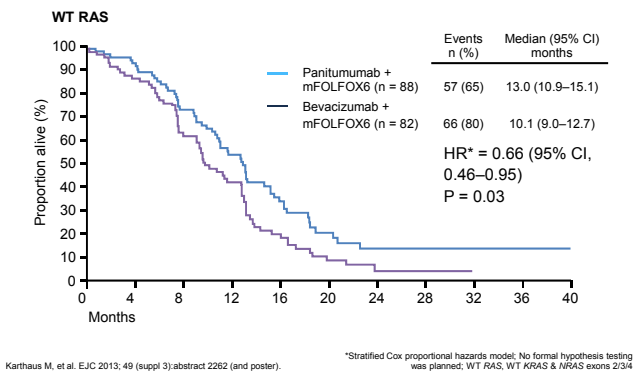
PEAK study RAS analysis RAS testing



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

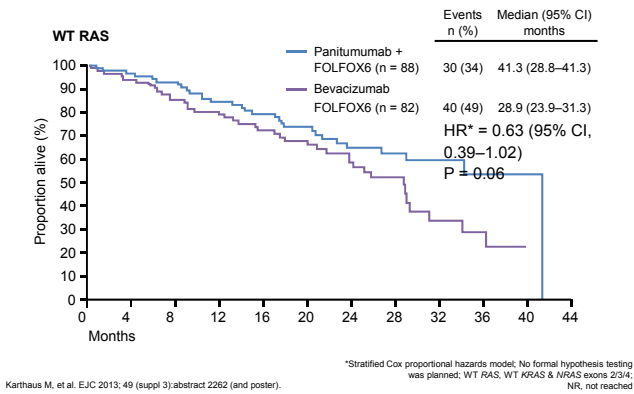
ITT, Intent-to-treat

PEAK study RAS analysis PFS (longer follow-up analysis)



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

PEAK study RAS analysis OS (longer follow-up analysis)



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

PEAK study RAS analysis

Efficacy data (longer follow-up analysis)

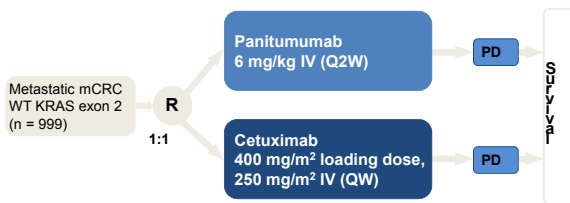
	WT KRAS exon 2 ¹		WT RAS ²	
	Panitumumab + mFOLFOX6 (n = 142)	Bevacizumab + mFOLFOX6 (n = 143)	Panitumumab + mFOLFOX6 (n = 88)	Bevacizumab + mFOLFOX6 (n = 82)
Median PFS, months (95% CI)	10.9 (9.7-12.8)	10.1 (9.0-12.0)	13.0 (10.9-15.1)	10.1 (9.0-12.7)
Hazard ratio (95% CI)	0.84 (0.64-1.11) P = 0.22		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 9631 (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^o); 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.

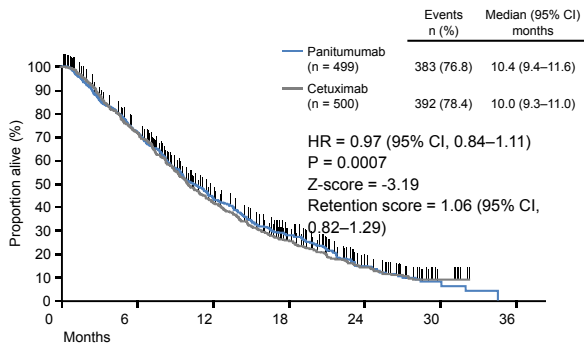
WT KRAS, WT KRAS in codons 12/13

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 intolerance 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

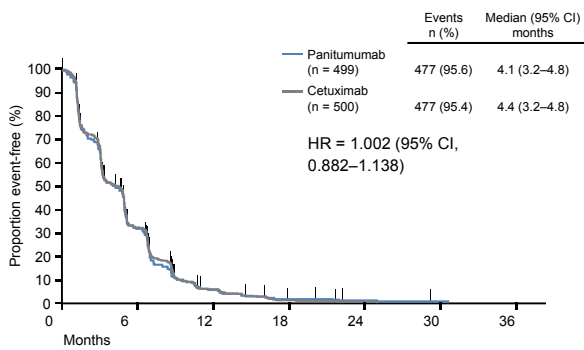
Price T, et al. EJC 2013; 49 (suppl 3):LBA 18 (and oral presentation);
Protocol ID: 20080763; ClinicalTrials.gov Identifier: NCT01001377.

ASPECCT study OS (primary analysis)



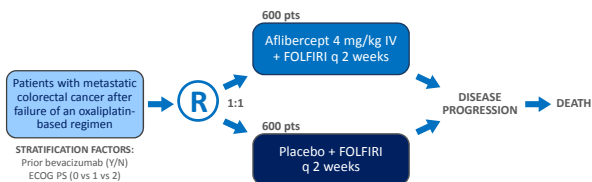
Price T, et al. EJC 2013; 49 (suppl 3):LBA 18 (and oral presentation).

ASPECCT study PFS (primary analysis)



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

VELOUR: Afibercept Phase III Trial in Previously Treated mCRC

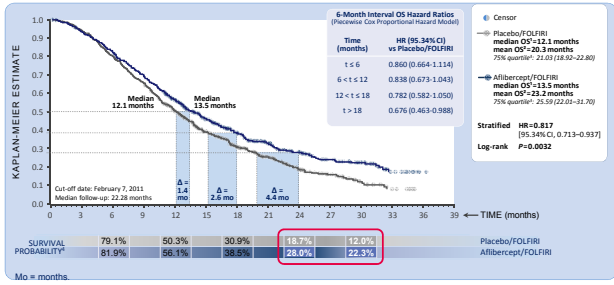


FIRST PATIENT IN: November 2007
ENROLLMENT COMPLETED:
1226 randomized, 1216 treated
Final analysis at 863 OS events

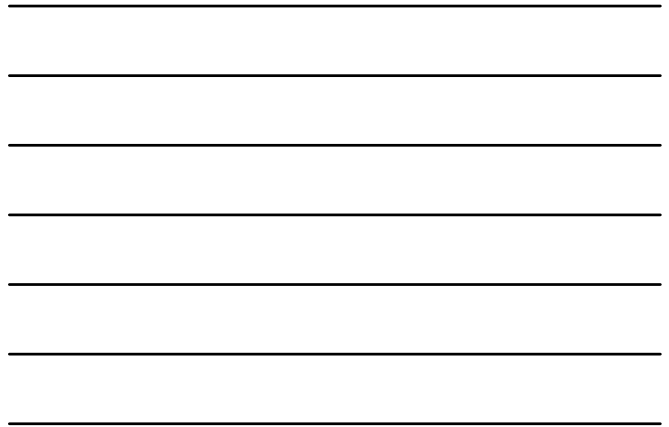
PRIMARY ENDPOINT: OS
SECONDARY ENDPOINTS:
ORR, PFS, safety, PK

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

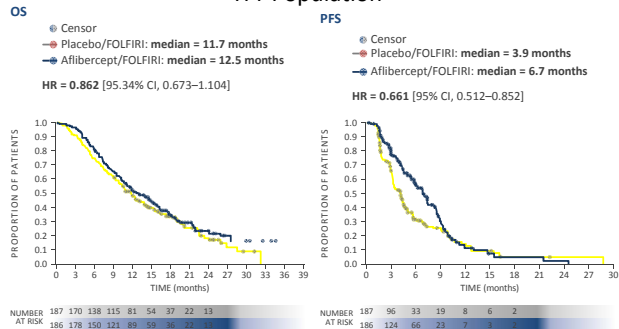
EVALUABLE POPULATION* (%)	PLACEBO (N=530)	AFLIBERCEPT (N=531)
BEST OVERALL RESPONSE		
Complete response	0.4	0
Partial response	10.8	19.8
Stable disease	64.9	65.9
Progressive disease	21.5	10.4
Not evaluable	2.5	4.0
OVERALL RESPONSE RATE		
CR or PR	11.1	19.8
95% CI	8.5-13.8	16.4-23.2
P-value**		0.0001

*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

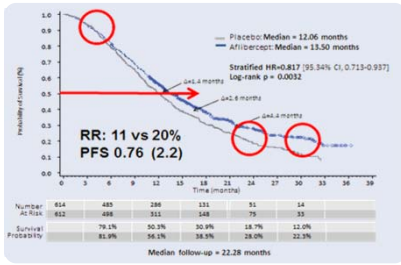


Not powered for direct comparisons (stratification factor)

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%

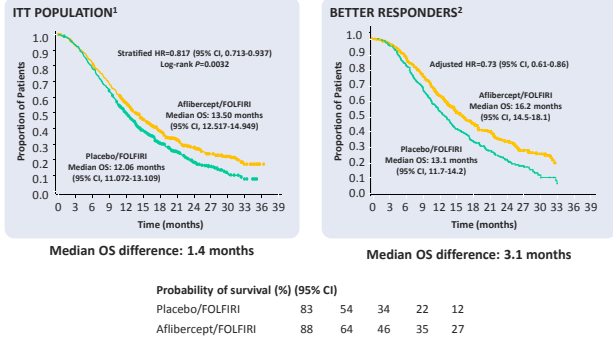
SOURCE: Ruff et al. Eur J Cancer. 2015 Jan;51(1):18-26; Van Cutsem et al. J Clin Oncol. 2012;30:3499-3506.

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.

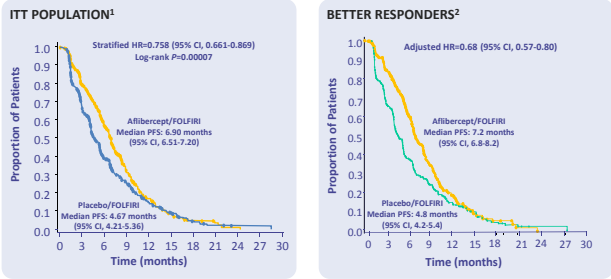
Results: OS in VELOUR ITT Population and Better Responders Subgroup



Probability of survival (%) (95% CI)					
Placebo/FOLFIRI	83	54	34	22	12
Aflibercept/FOLFIRI	88	64	46	35	27

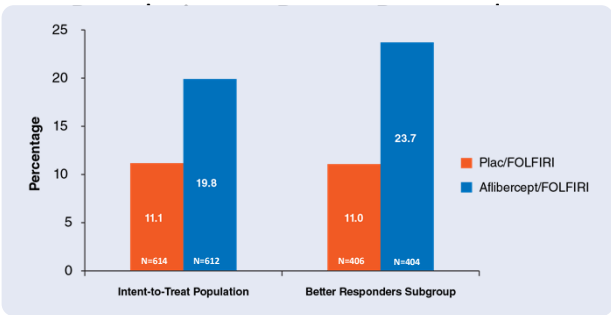
1. Van Cutsem et al. J Clin Oncol. 2012;30:3499-3506. 2. Chau et al. BMC Cancer. 2014;14:605.

Results: PFS in VELOUR ITT Population and Better Responders Subgroup



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

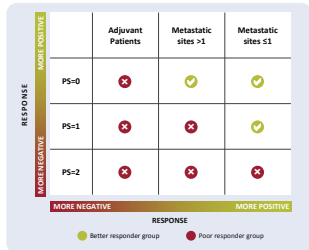
Results: ORR* in VELOUR ITT



*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:
 - At 12 months the probability of survival 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)



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

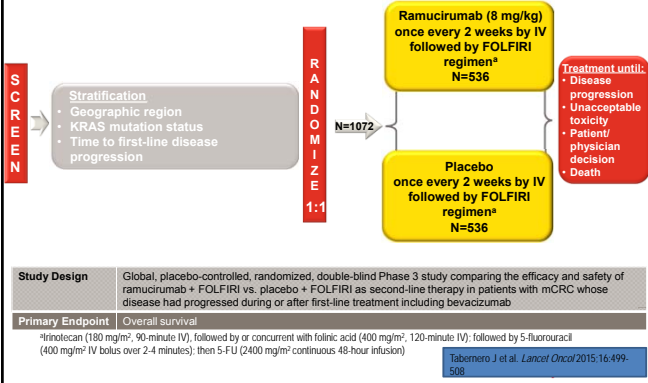
GOOD RESPONDER PATIENTS	PLACEBO + FOLFIRI (N=406) [95% CI]	AFLIBERCEPT + FOLFIRI (N=404) [95% CI]	Δ	HR
Median OS (months)	13.11 [11.70; 14.19]	16.23 [14.49; 18.14]	3.12	0.718 [0.605; 0.851]
Mean OS (months)	18.62	24.83	6.21	-
Median PFS (months)	4.76 [4.24; 5.42]	7.16 [6.77; 8.21]	2.4	0.678 [0.572; 0.803]
WITH PRIOR BEV (N=133) WITH PRIOR BEV (N=132)				
Median OS (months)	12.29 [10.32; 14.26]	15.67 [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.

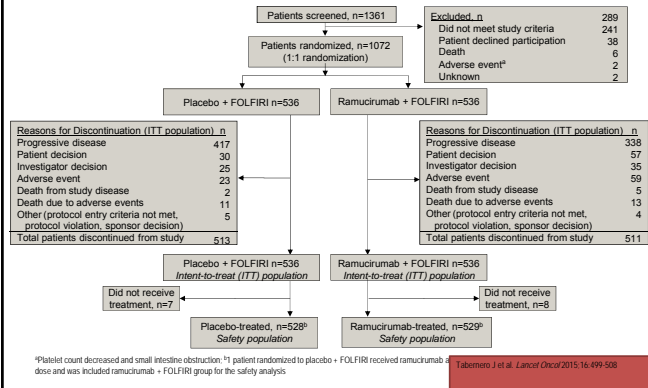
SOURCE: Chau et al. BMC Cancer. 2014 Aug 20;14:605.

88

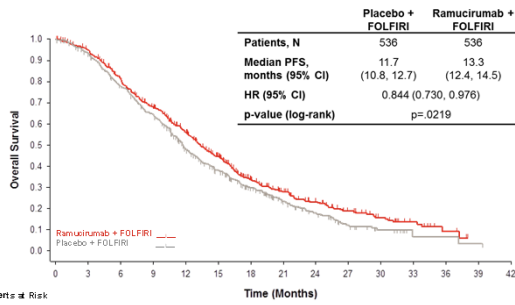
RAISE: Study Design



RAISE: Patient Disposition



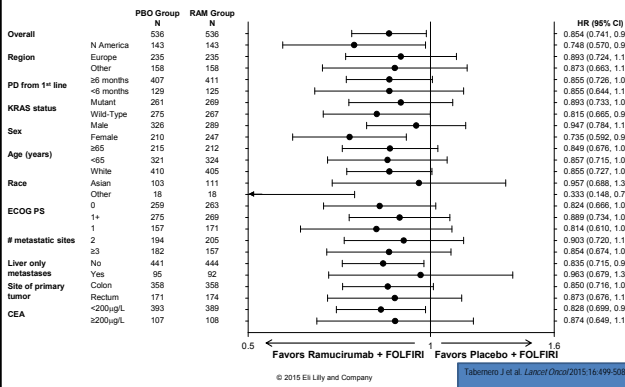
RAISE: Primary Endpoint – Overall Survival of ITT Population



Patients at Risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42
Ramucicromab + 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

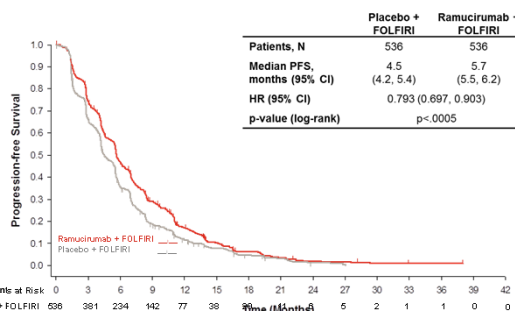
RAISE: Forest Plot – Overall Survival



© 2015 Eli Lilly and Company

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

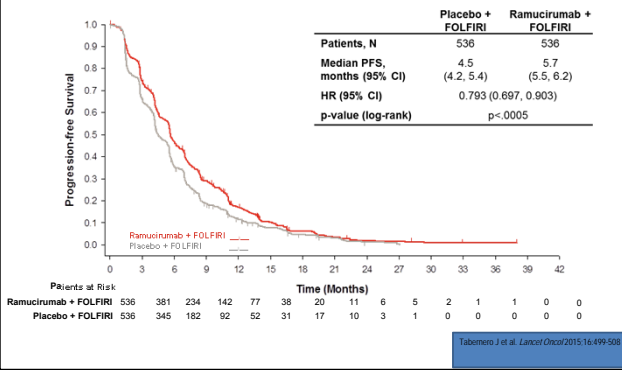
RAISE: Secondary Endpoint – PFS of ITT Population



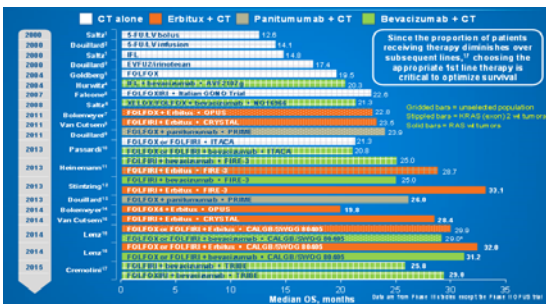
Patients at Risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42
Ramucicromab + FOLFIRI	536	381	224	142	77	38	17	10	3	1	0	0	0	0	0
Placebo + FOLFIRI	536	345	182	92	52	31	17	10	3	1	0	0	0	0	0

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

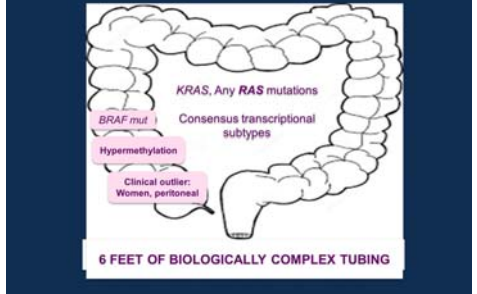
RAISE: Secondary Endpoint – PFS of ITT Population

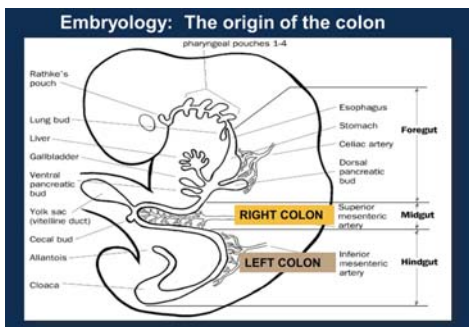


Podatki iz randomiziranih raziskav 1. reda zdravljenja



Metastatic Colorectal Cancer: Patient Selection





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!

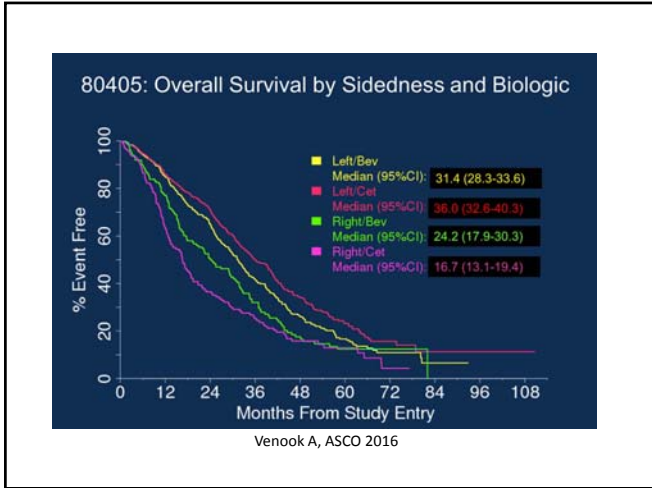
Venook A, ASCO 2016

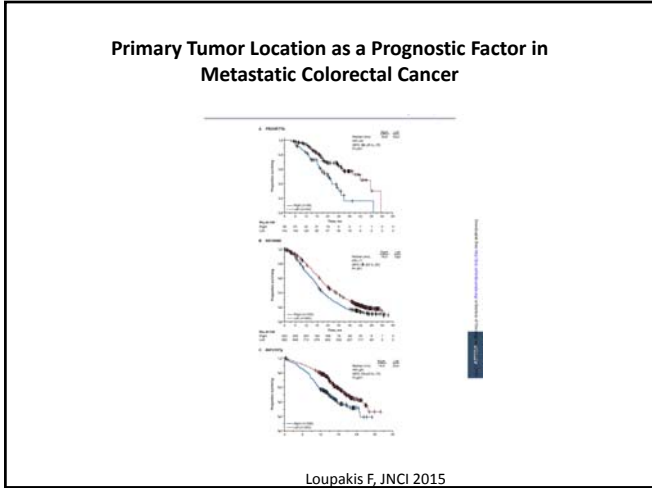
Median OS by Sidedness: 80405 and FIRE-3*

		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

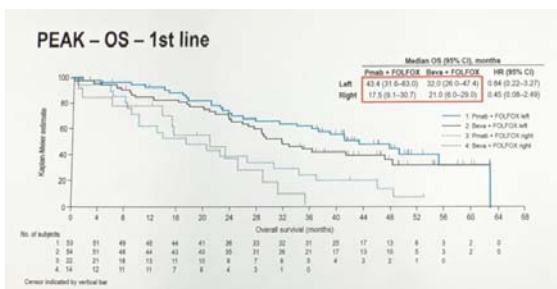




Results – distribution and patients

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

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)
	<i>percent</i>			
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 tednih²
- Gradiranje³

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

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

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

	Nadaljevanje th.	Prilagoditev odmerka?
Gradus 1	nadaljevanje z enakim odmerkom	nadaljevanje z enakim odmerkom
Gradus 2	1. manifestacija 2. manifestacija 3. manifestacija 4. manifestacija	100% 75% 50% -
Gradus 3	1. manifestacija 2. manifestacija 3. manifestacija	75% 50% -
Gradus 4	1. manifestacija	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 B₆
 - topični kortikosteroidi
 - pri paronihijah (okužba)
 - antibiotična mazila
 - peroralni AB

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

DRISKA

- ☐ Srednji čas do pojava G₂₋₄ 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 (Suppl. 1): 47-50.

2. Abushullah S et al. 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
 - Pičje nesladkanih, hladnih in bistrnih sokov
 - Pičje 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 pectoris
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 boleznj

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 simptom¹
 - 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 nujno³)
 - mehanizem: konstrikcija vaskularnih gladkih mišic preko aktivacije protein kinaze C



- prenehanje zdravljenja

- reindukcija
 - ponovitev v 82-100%⁴
 - 18% smrtnost⁵

1. Meydan N, et al. Jpn J Clin Oncol, 2005; 35: 285-70.
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.

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 oslabeledost
 - 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. coli → 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
 - Paralični 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-đimer 10840
Bill 161/138
AST 19,4
ALT 7,99
LDH 30
CRP 158
PCT 30

HVALA ZA POZORNOST



LAČN SM FUL DRUGAČNI!

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.

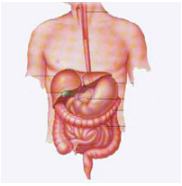
Namen uporabe zdravil v obravnavi raka prebavil:

- ozdravitev
- **preživetje**
- zmanjšanje simptomov

Toksičnost tarčnih zdravil pri zdravljenju tumorjev prebavil 2

Toksičnost tarčnih zdravil pri zdravljenju tumorjev prebavil 3

Uporaba tarčnih zdravil - ESMO/NCCN guidelines



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

Toksičnost tarčnih zdravil pri zdravljenju tumorjev prebavil

4

KARDIOTOKSIČNOST



GASTROINTESTINALNA TOKSIČNOST



LEDVIČNA TOKSIČNOST



KOŽNA TOKSIČNOST



Toksičnost tarčnih zdravil pri zdravljenju tumorjev prebavil

5

KARDIOTOKSIČNOST



- ARTERIJSKA HIPERTENZIJA**
- DIASTOLNA DISFUNKCIJA**
- PODALJŠANJE QTc DOBE**
- TROMEMBOLIČNI ZAPLETI**

Toksičnost tarčnih zdravil pri zdravljenju tumorjev prebavil

6



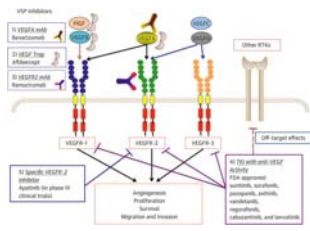
KARDIOTOKSIČNOST

ARTERIJSKA HIPERTENZIJA
DIASTOLNA DISFUNKCIJA
PODALJŠANJE QTc DOBE
TROMEMBOLIČNI ZAPLETI



ARTERIJSKA HIPERTENZIJA

- Najpogosteje pri zdravih, 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 (afibercept)
 - monoklonsko telo, ki se veže na VEGFR-2 in blokira njegovo aktivacijo (ramicirumab)
 - TKI male molekule (sorafenib, regorafenib,...)

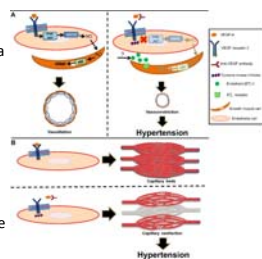




ARTERIJSKA HIPERTENZIJA

MEHANIZEM:

- VEGF zvišuje delovanje endoteljske NO sintetaze 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 krvni tlak.
- VEGF inhibicija moti zaznavo baroreceptorjev in zvišuje tonus žilja.
- Zmanjšan razvoj arteriol in kapilar, „otrdelost“ ožilja zvišuje periferni odpor
- Zmanjšanje izločanje Na in s tem povečanje srčnega afterloada



ARTERIJSKA HIPERTENZIJA



Definicija:

Gradus	Opis stanja	Kritični pogoji
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; urgent intervention indicated

CTCAE4.02

ARTERIJSKA HIPERTENZIJA



POGOSTOST (SMPC):

	vsi gradusi	gradus 3/4	opombe
bevacizumab	42%	do 17% (do 1%)	brez JO25567
afibercept	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	Concomitant/interaction 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	Concomitant/interaction 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, diltiazem/verapamil)	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

Toksičnost terčnih zdravil pri zdravljenju tumorjev prebavi

13

KARDIOTOKSIČNOST

ARTERIJSKA HIPERTENZIJA
DIASTOLNA DISFUNKCIJA
PODALJŠANJE QTc DOBE
TROMBOLIČNI ZAPLETI



Toksičnost terčnih zdravil pri zdravljenju tumorjev prebavi

14

TROMBOLIČNI ZAPLETI (TEZ)

PROTOTIP: BEVACIZUMAB

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



Toksičnost terčnih zdravil pri zdravljenju tumorjev prebavi

15

TROMEMBOLIČNI ZAPLETI (TEZ)

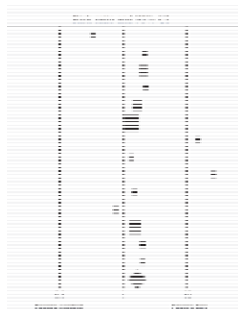


PROTOTIP: BEVACIZUMAB

- Arterijski tromembolični dogodki
 - pri bolnikih, ki prejema 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 utрпи 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)

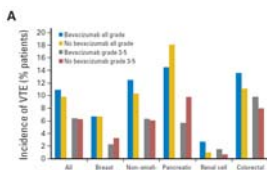
62% ↑ tveganje za ATE

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

TROMEMBOLIČNI ZAPLETI (TEZ) - BEVACIZUMAB



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

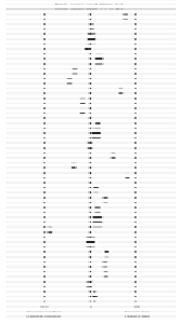


Pooled analysis 10 RCT
6055 bolnikov

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 Randomized Controlled Trials

Toksičnost tarčnih zdravil pri zdravljenju tumorjev prebavil

TROMEMBOLIČNI ZAPLETI (TEZ)

	all TE	ATE	VTE	opombe
bevacizumab	10%	2,3%	8% (G3-4: 6%)	
afibercept	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%)			

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

Toksičnost tarčnih zdravil pri zdravljenju tumorjev prebavil

GASTROINTESTINALNA TOKSIČNOST



- DRISKA
- GIT KRVAVITVE/PERFORACIJE
- CELJENJE RAN
- HEPATOTOKSIČNOST
- DVIG ENCIMOV TREBUČNE SLINAVKE

Toksičnost tarčnih zdravil pri zdravljenju tumorjev prebavil

GASTROINTESTINALNA TOKSIČNOST

Diarrhea	Increase of ≥ 4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 8 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; leading 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	$\leq 2.5 \times \text{ULN}$	$\geq 2.5 - 5.0 \times \text{ULN}$	$\geq 5.0 - 20.0 \times \text{ULN}$	$\geq 20.0 \times \text{ULN}$	-
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	$\leq 3.0 \times \text{ULN}$	Asymptomatic with AST $\leq 3.0 - 5.0 \times \text{ULN}$; $\geq 3 \times \text{ULN}$ with the appearance of worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia	$\geq 5.0 - 20.0 \times \text{ULN}$ for ≥ 2 weeks	$\geq 5 \times \text{ULN}$	$\geq 20.0 \times \text{ULN}$

Toksičnost zdravil pri zdravljenju tumorjev prebavi

GASTROINTESTINALNA TOKSIČNOST

DRISKA

GIT KRVAVITVE/PERFORACIJE
CELJENJE RAN
HEPATOTOKSIČNOST
DVIG ENCIMOV TREBUČNE SLINAVKE

Toksičnost zdravil pri zdravljenju tumorjev prebavi

GASTROINTESTINALNA TOKSIČNOST - DRISKA

MEHANIZEM:

- driska ob zdravljenju 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 absorpcijo Na
- Inhibicija EGFR zato vodi v sekretijsko 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

Toksičnost zdravil pri zdravljenju tumorjev prebavi

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 CZS in učinka na bolečino)
- razmisli o prilagoditvi odmerka (zlasti 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 angiogeneze.
- 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 PERFORACIJI:** 2,4%
- Pri tem gre za življenje ogrožajoče stanje – smrtnost 30%
- Prepoznavanje:
 - abdominalne bolečine, zaprtje, bruhanje



MEHANIZEM: neznan

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



LEDVIČNA TOKSIČNOST

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

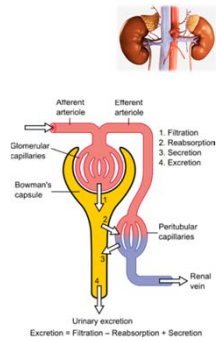


LEDVIČNA TOKSIČNOST

- Najpogosteje pri zdravih, 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 proteinurijo.



LEDVIČNA TOKSIČNOST



Monoklonska protitelesa

BEVACIZUMAB	Proteinurija
	Nefrontski sindrom
	Glomerulonefritis
	Intersticijski nefritis
	Trombotična mikroangiopatija
CETUKSIMAB	Hipomagnezemija
PANITUMUMAB	Hipomagnezemija
TKI	
SORAFENIB	Intersticijski nefritis

Toksičnost tardnih zdravil pri zdravljenju tumorjev prebavil

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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 nefritis)
- poškodbe zaradi motenj v prekrvavitvi (trombotična mikroangiopatija)

Toksičnost tardnih zdravil pri zdravljenju tumorjev prebavil

32

LEDVIČNA TOKSIČNOST - PROTEINURIJA



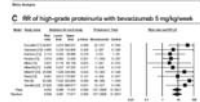
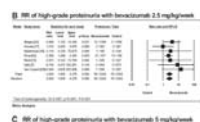
Adverse Event	Grade				
	1	2	3	4	5
Proteinuria	1+ proteinuria; urinary protein $\geq 0.3\text{ g/24 hrs}$	Adults: 2+ proteinuria; urinary protein 1.0 – 3.4 g/24 hrs; Pediatric: urine P/C (Protein/Creatinine) ratio 0.5 – 1.9	Adults: urinary protein > 3.5 g/24 hrs; Pediatric: urine P/C > 1.9		

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

Toksičnost tardnih zdravil pri zdravljenju tumorjev prebavil

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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

Toksičnost tardnih zdravil pri zdravljenju tumorjev prebavi



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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.

Toksičnost tardnih zdravil pri zdravljenju tumorjev prebavi



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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)

Toksičnost tardnih zdravil pri zdravljenju tumorjev prebavi



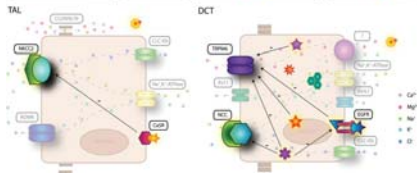
36

LEDVIČNA TOKSIČNOST – TUBULARNA ACIDOZA



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

Diuretika osmotic diuretics loop diuretics thiazide-type diuretics	EGF inhibitors cetuximab erlotinib PPiA ?	Antimicrobials aminoglycoside antibiotics pentamidine rapamycin amphotericin B ? fosfarnet	Calcineurin inhibitors cyclosporin A FK506 Cytostatics cisplatin
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Anke L. LAMERIS et al. Drug-induced alterations in Mg²⁺ homeostasis.

Toksičnost tarčnih zdravil pri zdravljenju tumorjev prebavil

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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.

Toksičnost tarčnih zdravil pri zdravljenju tumorjev prebavil

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KOŽNA TOKSIČNOST



TOKSIČNOST EGFR ZDRAVIL

TOKSIČNOST TKI ZDRAVIL

Toksičnost tarčnih zdravil pri zdravljenju tumorjev prebavil

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KOŽNA TOKSIČNOST

TOKSIČNOST EGFR ZDRAVIL

TOKSIČNOST TKI ZDRAVIL





Toksičnost tarčnih zdravil pri zdravljenju tumorjev prebavil

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KOŽNA TOKSIČNOST – EGFR ZDRAVILA

Kožne spremembe:

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

Toksičnost tarčnih zdravil pri zdravljenju tumorjev prebavil

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KOŽNA TOKSIČNOST

TOKSIČNOST EGFR ZDRAVIL

TOKSIČNOST TKI ZDRAVIL



Toksičnost tarčnih zdravil pri zdravljenju tumorjev prebavil

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KOŽNA TOKSIČNOST – TKI ZDRAVILA

Kožne spremembe:

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



Toksičnost tarčnih zdravil pri zdravljenju tumorjev prebavil

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Pharmacy



"Each capsule contains your medication,
plus a treatment for each of its side effects."

HVALA!

Maja Ebert Moltara
Onkološki Inštitut Ljubljana
mebert@onko-i.si



Toksičnost tarčnih zdravil pri zdravljenju tumorjev prebavil

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

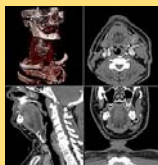
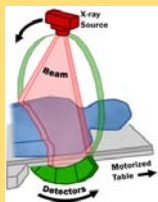
Snemanje večjega števila rentgenskih posnetkov
pod različnimi koti okoli ene osi rotacije



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.

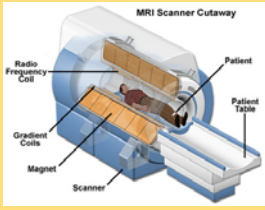


Digitalno geometrijsko procesiranje.

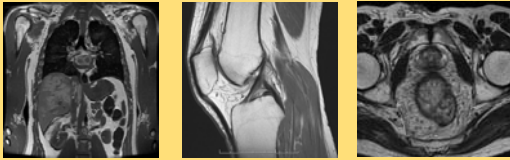


Tomografski posnetki („virtualne rezine“) struktur v notranjosti telesa z možnostjo prikaza v različnih ravninah in 3-D rekonstrukcijo.

MRI



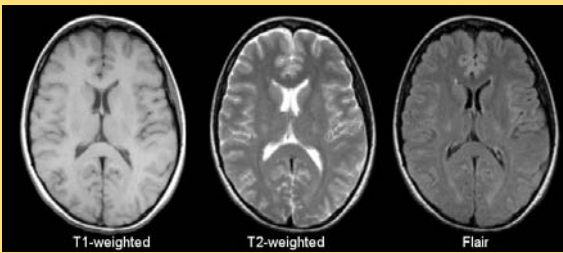
→ Digitalno geometrijsko procesiranje



MRI sekvenca

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

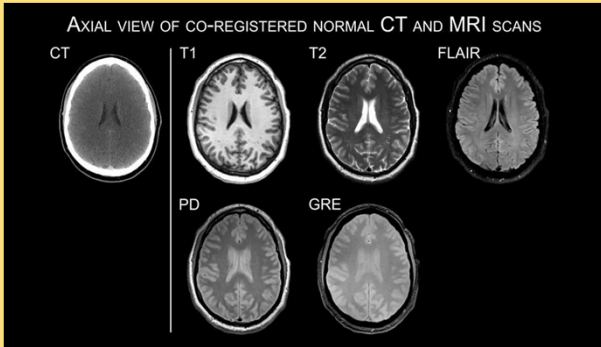
Vsaka sekvenca vsebuje različno število parametrov, več sekvenc pa združujemo v MRI protokole za posamezne anatomske lokalizacije.



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 ,...

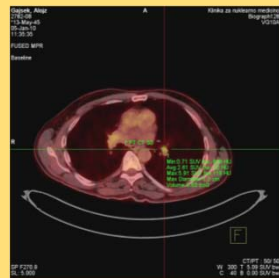
PET-CT

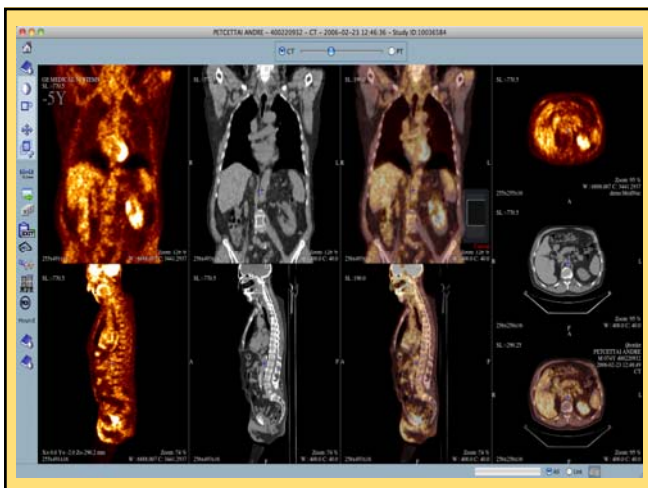
- ^{18}F -FDG (2-deoksi-2-[^{18}F]fluoro-D-glukoza) se v telesu obnaša enako kot glukoza
- ^{18}F -FDG-6-fosfat (FDG-6-P) je metabolit ^{18}F -FDG, ki se kopiči v celicah in prikaže porabo glukoze v organih in tkivih telesa (maligne celice imajo povečano izražanje glukoznega prenašalca GLUT-1)
- ^{18}F
 - 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. onkologija:

- postavitve 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. infektologija:

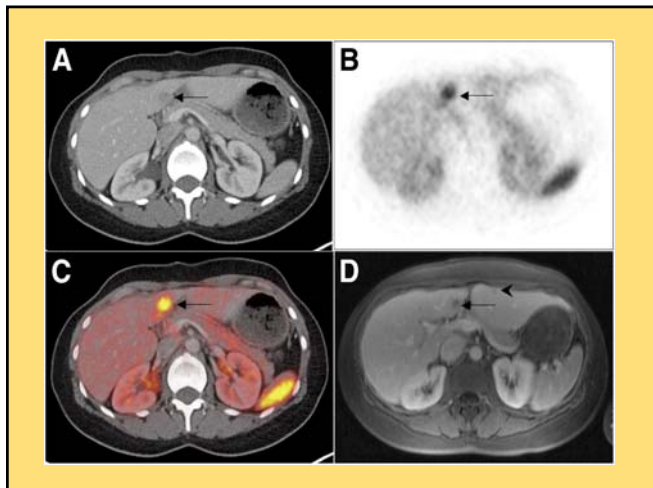
- prikaz vnetja, vročina neznanega izvora, kronična vnetna bolezen črevesja (aktivnost, razširjenost)

3. nevrologija:

- opredeljevanje demenc, določitev mesta epileptogenega žarišča,...

4. kardiologija:

- ocena viabilnosti miokarda



NAČRTOVANJE OBSEVANJA

Zaporedje postopkov, s katerimi bolnika pripravimo na obsevanje

1. Postavitve indikacije za obsevanje



2. Simulacija obsevanja



Multidisciplinarni konzilij



CT simulator (radiološki inženir v sodelovanju z radioterapevtom)

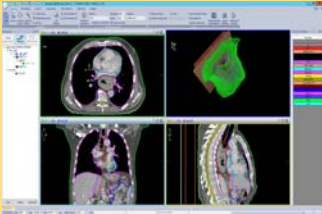


1. pravilna namestitve bolnika z uporabo fiksacijskih pripomočkov
2. po potrebi aplikacija kontrastnega sredstva (po, iv ali intrakavitarno)
3. preslikava določenega dela telesa

NAČRTOVANJE OBSEVANJA



3. Vrsovanje tarčnih struktur



Vrsovalnica (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)

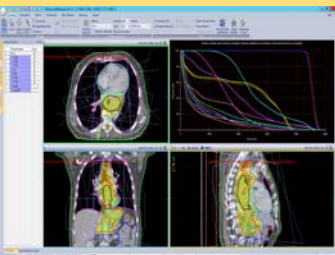


1. določitev števila, vstopnih kotov in energije žarkov ter postavitev zaščit za zdrava tkiva
2. evaluacija izdelanega obsevalnega načrta:
 - ustrezna doza in pokritost tarčnih volumnov
 - ocena doze znotraj rizičnih organov

NAČRTOVANJE OBSEVANJA



5. Pregled in potrditev obsevalnega načrta



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

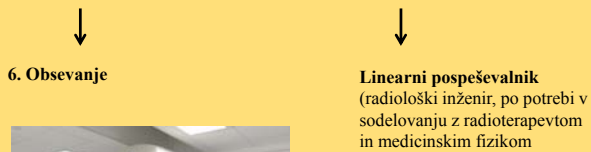


- Evaluacija izdelanega obsevalnega načrta glede na namen obsevanja in klinično sliko:
- ustrezna absorbirana doza znotraj vrisanih tarčnih volumnov
 - ne presežena tolerančna doza v zdravih tkivih

NAČRTOVANJE OBSEVANJA



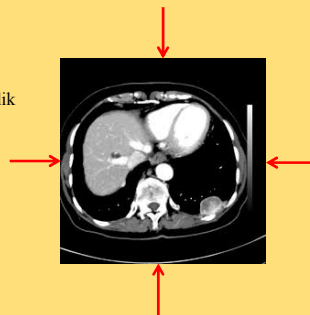
NAČRTOVANJE OBSEVANJA



NAČRTOVANJE OBSEVANJA – računanje absorbirane doze

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

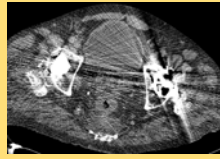
→ informacije pridobljene iz seta CT slik



NAČRTOVANJE OBSEVANJA – računanje absorbirane doze

Težave pri:

1. CT slikah z veliko artefakti



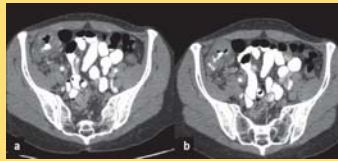
MAR – „metal artifact reduction“



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 absorpcija
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

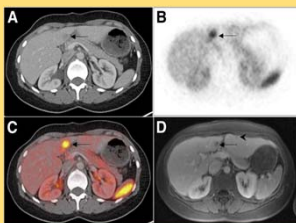
Zakaj?

- 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!!!)

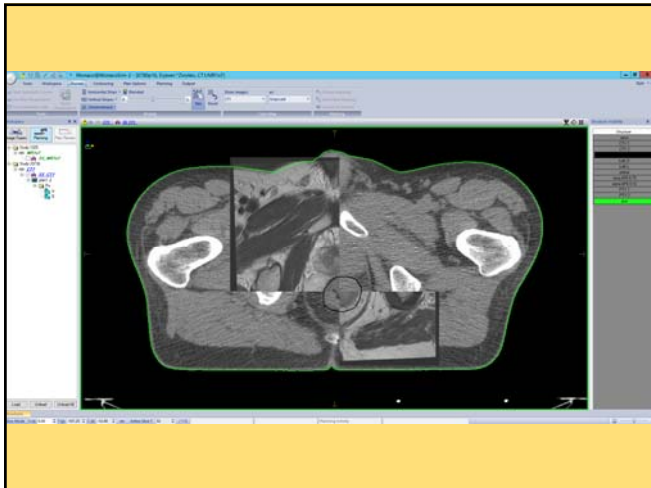


Za potrebe načrtovanja obsevanja posnamemo le določene sekvence (postopek je krajši od diagnostičnega MRI)

NAČRTOVANJE OBSEVANJA S POMOČJO MRI

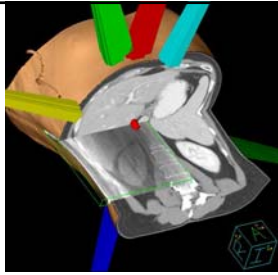
Problemi:

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

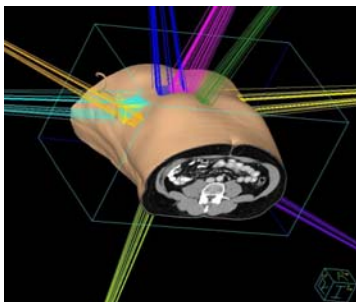
	MRI	PET-CT
GIT	Spodnja 1/3 rektuma	Analni kanal, požiralnik, kardija želodca
GUT	TRT: prostata, mehur, (cervix) BRT: prostata, cervix, nožnica	/
Pljuča	(Pancoastovi tumorji)	Pljuča
Glava&vrat	Obnosne votline, žrelo	/
LPS	Možgani, hrbtenica (sarkomi)	/
Dojka	/	/



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);
- Predpogoj:
 - a) Linearni akceleratorji novejših generacij, ki omogočajo tehniko SBRT (IGRT);
 - b) Kontrola respiratorne gibljivosti med RT;
 - c) Natančna imobilizacija bolnika.

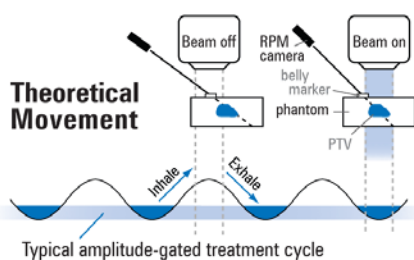
Linearni akcelerator (aparat 8)



SBRT hrbtenice na novem aparatu 4



Dihalno proženje



RPM = Real-time Position Management

Kontrola respiratorne gibljivosti



Stereotaktična radioterapija

- Moderna tehnika obsevanja;
- Omogoča \uparrow D na TU (ablativno);
- 1 do nekaj frakcij (\downarrow 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: LC₃ 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 (Jerezek-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)

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NCCN Guidelines Version 2.2016 Hepatocellular Carcinoma

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CLINICAL PRESENTATION	SURGICAL ASSESSMENT ^{1,2}	TREATMENT	SURVEILLANCE
Potentially resectable or transplantable, operable by performance status or comorbidity	<ul style="list-style-type: none"> • Child-Pugh Class A, B¹ • No portal hypertension • Suitable tumor location • Adequate liver reserve • Suitable liver remnant 	<ul style="list-style-type: none"> • Resection, if feasible (preferred)^{3*} or Locoregional therapy See Principles of Locoregional Therapy (HCC-C) • Ablation⁴ • Arterially directed therapies • External-beam radiation therapy (EBRT) (conformal or stereotactic)⁵ (category 2B) • Transplant 	<ul style="list-style-type: none"> • Imaging⁶ 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 • Refer to a hepatologist for a discussion of antiviral therapy for carriers of hepatitis
	<ul style="list-style-type: none"> • UNOS criteria¹⁴ • Patient has a tumor ≤5 cm in diameter or 2-3 tumors ≤3 cm each • No macrovascular involvement • No extrahepatic disease 	<ul style="list-style-type: none"> • If ineligible for transplant • If eligible for transplant, refer to liver transplant center¹⁴ • Consider bridge therapy as indicated¹⁴ 	

¹Discussion of surgical treatment with patient and determination of whether patient is amenable to surgery.
²Patients with Child-Pugh Class A liver function, who fit UNOS criteria (www.unos.org) and are resectable could be considered for resection or transplant. There is controversy over which initial strategy is preferable to treat such patients. These patients should be evaluated by a multidisciplinary team.
³See Principles of Resection (HCC-B).
⁴Highly selected Child-Pugh Class B patients with limited resection.
⁵Some patients beyond the Milan criteria can be considered for transplantation. Extended criteria/downstaging protocols are available at selected centers and through UNOS.
⁶Hopwood V, Reynolds J, Cook JR, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med*. 1992;326(11):1303-10.
⁷Many transplant centers consider HCC-B patients for transplantation. (See Discussion).
⁸See Principles of Surgery (HCC-D).
⁹In well-selected patients with small, properly located tumors, ablation should be considered as definitive treatment in the context of a multidisciplinary review. (Feng K, Yan J, Li X, et al. A randomized controlled trial of radiofrequency ablation and surgical resection in the treatment of small hepatocellular carcinoma. *J Hepatol*. 2012;57(4):776-82. and Chen MS, Li JZ, Zhou Y, et al. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. *Ann Surg*. 2009;249(3):321-326).
¹⁰Case series and single-arm studies suggest safety and possible efficacy of radiation therapy in selected cases. (See Principles of Locoregional Therapy (HCC-C))
¹¹SBRT or multi-phase CT scans for liver assessment are recommended. Consider chest imaging as clinically indicated.

Note: 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.

For relapse, see Initial Workup (HCC-A)

HCC-6

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CLINICAL PRESENTATION

Unresectable
 • Inadequate hepatic reserve¹⁸
 • Tumor location

→ Evaluate whether patient is a candidate for transplant (See UNOS criteria under Surgical Assessment [HCC-5])¹⁸

TREATMENT

Transplant candidate → Refer to liver transplant center
 • Consider bridge therapy as indicated¹⁸

Not a transplant candidate → Options:^{18,20}
 • Locoregional therapy preferred^{18, 20}
 • Ablation
 • SBRT (conformal or stereotactic)²¹ (category 2B)
 • Systemic therapy
 • Sorafenib (Child-Pugh Class A [category 1] or B)^{18,22}
 • Chemotherapy²³
 • Systemic intra-arterial
 • Clinical trial
 • Best supportive care

SURVEILLANCE

• Imaging² 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

18Mazzillaro V, Regalla E, Doo 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. (See Discussion.)
 19Case series and single-arm studies suggest safety and possible efficacy of radiation therapy in selected cases. (See Principles of Locoregional Therapy [HCC-5].)
 20Meta or multi-phase CT scans for liver assessment are recommended. Consider chest imaging as clinically indicated.
 21Moss, Data-Pugh Score (MSS-D-P).
 22Chen does not indicate preference. The choice of treatment modality may depend on extent/location of disease, hepatic reserve, and institutional capabilities.
 23Use of chemoradiation has also been supported by randomized controlled trials in selected populations. (See Best Supportive Care [L3-2], Nigam V, The NCC, et al. Randomized controlled trial of transarterial lipiodol chemoradiation for unresectable hepatocellular carcinoma. Hepatology 2002;35:1164-1171 and Luvett JM, Reul M, Mantala X, et al. Arterial embolization or chemoradiation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomized controlled trial. Lancet 2002;359:1734-1739.)
 24There are limited data supporting the use of chemotherapy, and its use in the context of a clinical trial is preferred.
 Note: All recommendations are category 2A unless otherwise indicated.
 Clinical Trials: NCCN believes that the best management of any cancer patient is a clinical trial. Participation in clinical trials is especially encouraged.
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National Comprehensive Cancer Network
NCCN Guidelines Version 1.2017 Rectal Cancer

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similarly that carefully selected patients might benefit from this approach.¹⁵

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.^{16, 17} In a more recent retrospective analysis of 43 patients who underwent repeat hepatectomy for recurrent disease, 5-year overall and DFS rates were reported to be 73% and 22%, respectively.¹⁸ A recent meta-analysis of 27 studies including >7000 patients found that those with longer disease-free intervals, those whose recurrences were solitary, smaller, or unifocal, and those lacking extrahepatic disease derived more benefit from repeat hepatectomy.¹⁹ Panel consensus is that re-resection of liver or lung metastases can be considered in carefully selected patients.^{15, 19, 20}

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).¹⁵

Local Therapies for Metastases

The standard of care for patients with resectable metastatic disease is surgical resection. If resection is not feasible, image-guided ablation²¹ or stereotactic body radiation therapy (SBRT; also called stereotactic ablative radiotherapy [SABR])²²⁻²⁴ 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 margins²⁵ or safely treated by SBRT. In select patients with liver- or liver-dominant metastatic disease that cannot be resected or ablated arthroscopically, other locally directed treatment options may be offered.²⁵⁻²⁷

A meta-analysis of 60 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.²⁸ Local therapies are described in more detail below. The role of non-surgical 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.^{16, 17} 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.^{16, 17} 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.²⁹ 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		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 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
Rushoven 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	ORGAN	Dose-Volume omejitve	Drugo
Standardna D	25Gy	3	75 Gy	Zdrava jetra	> 700 cc pri < 15 Gy v 3 fr	Volumen zdravih jeter= 1000 cc
Zmanjšanje D 10%	22.5 Gy	3	67.5 Gy	Hrbtnjača	< 18 Gy v 3 fr	
				Ledvica (R+L)	V15 Gy < 35%	
Zmanjšanje D 20%	20.63 Gy	3	61.89 Gy	želodec, duodenum, tanko črevo	< 21 Gy v 3 fr	Bolniki z GTV < 3 mm od srca, želodca, duodenuma in tankega črevesa so izključeni
Zmanjšanje D 30%	18.75 Gy	3	56.25 Gy	Srce	< 30 Gy v 3fr	

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

Bolniki		Predpisana D	Št. lezij
Št. bolnikov	57	75 Gy	63 (82%)
Starost	67 (39 – 85) let	67,5 Gy	5 (7%)
Spol (M:Ž)	35:22	61,89 Gy	5 (7%)
Št. lezij	77	56,25 Gy	4 (4%)
Št. lezij na bolnika	1 pri 43 bolnikih (74%) 2 pri 11 bolnikih (19%) 3 pri 4 bolnikih (7%)	Skupaj	77 (100%)
Preiskava za definiranje TU	57 CT 32 CT-PET 2 MRI		

Rezultati

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

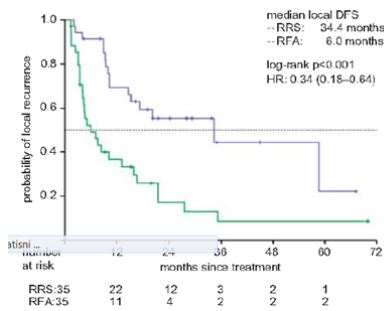
Odgovor	Lezije (5t%)
CR	25 (52%)
PR	15 (31%)
SD	5 (11%)
PD	3 (6%)
Total	48 (100%)

AKUTNA TOKSIČNOST:

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

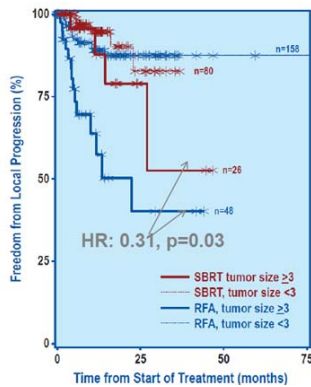
LC 94%

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



Stintzing, 2013:

SBRT vs RFA



SBRT > RFA pri
 $TU \ge 3\text{ cm}$

Michigan, 2013

Kriteriji za SBRT

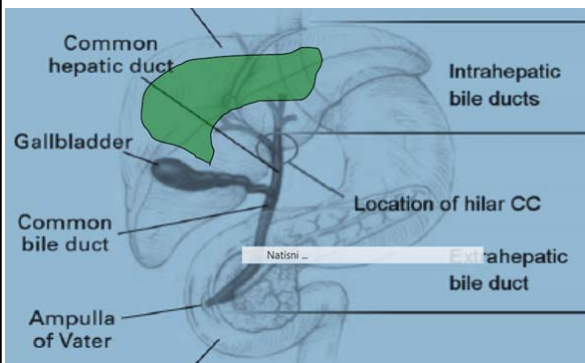
- Velikost: ≤ 6 cm
- Št. lezij: ≤ 5
- Brez aktivne ekstrahepatične bolezni
- >700 cc zdravih jeter
- Fokalni TU
- >5 mm od lumna črevesja

Ugotovitve nekaterih raziskovalcev

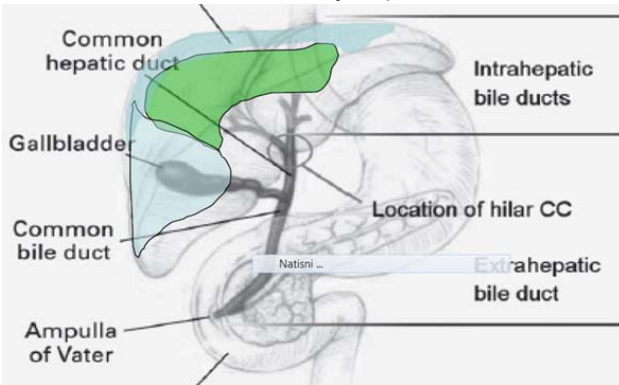
- **Lee, 2009:** 68 bolnikov z neresektabilnimi zasevki v jetrih CRC raka, raka dojke, žolčnika,...
- rak dojke ima daljše preživetje v primerjavi z ostalimi raki*
- **Swaminath, 2011:**
- nekateri bolniki z 1-5 zasevkov v jetrih po SBRT živijo 5-10 let brez bolezni*
- **Scorsetti, 2013:** 57 bolnikov z 77 zasevki v jetrih CRC raka dojke, 36% bolnikov stabilno ekstrahepatično bolezen
- LC 94%, mediano preživetje 19 mesecev**

Najnižja stopnja tveganja za SBRT

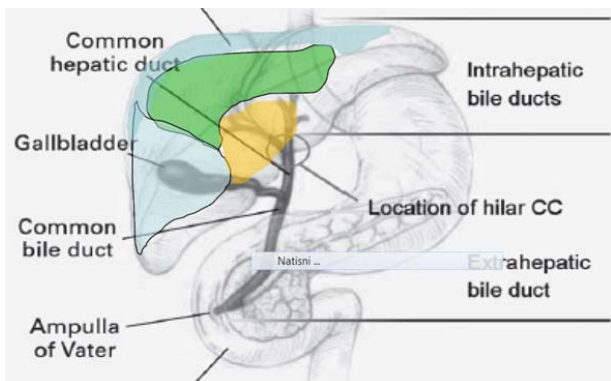
(centralno: stran od črevesja, reber, biliarnega trakta)



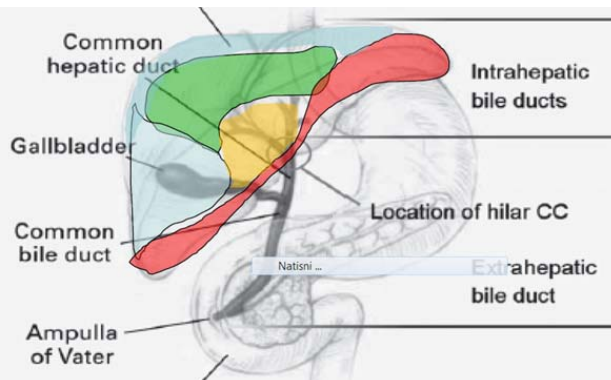
Nizka stopnja tveganja za SBRT (zgornja lateralna jetra)



Srednja stopnja tveganja za SBRT (centralne lezije, ob biliarnem traktu)



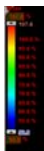
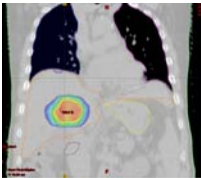
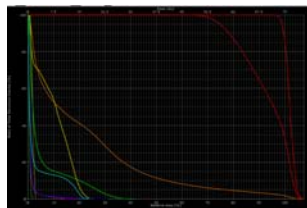
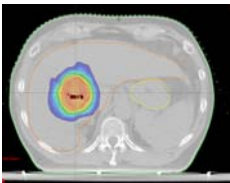
Visoka stopnja tveganja za SBRT (bližina želodca, črevesja)



PAZLJIVOST

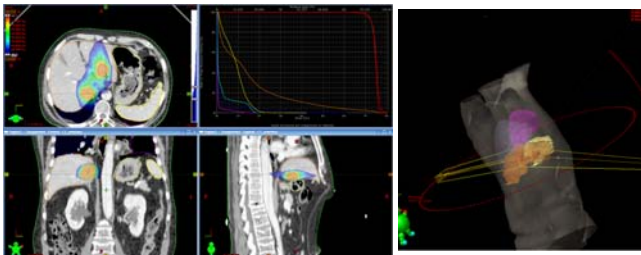
- Centralne lezije: večja toksičnost
- Prehodno prekini sistemske terapije
- Pazljivost pri antiangiogeni terapiji

SBRT JETER : 25Gy x 3;



Instituto clinico humanitas, Milano

SBRT JETER: 25Gy x 3

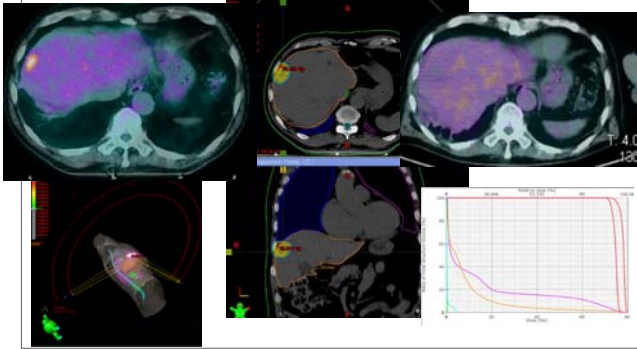


Instituto clinico humanitas, Milano

SBRT JETER: 25Gy x 3

PET pred zdravljenjem

PET po 6 mesecih



SBRT INOPERABILNEGA CA PANKREASA

2013



RESEARCH

Open Access

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

Angelo Tozzi¹, Tiziana Comito¹, Filippo Alongi^{1,2}, Pierina Naviana¹, Cristina Ifode¹, Pietro Mancosu¹, Giacomo Reggioni¹, Elena Clerici¹, Lorenza Rimassa¹, Alessandro Zerbi¹, Antonella Fogliata¹, Luca Cozzi¹, Stefano Tomatis¹ and Maria Scognetti¹

- Januarjem 2010 - oktober 2011
- **30 bolnikov z inoperabilnim ali recidivnim adenocarcinomom pankreasa**
- 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

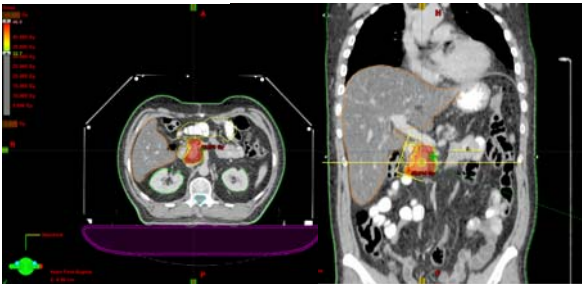
MEDULA	D1cc<18 Gy
LEDVICA	V15Gy <35%
DUODENUM	V36Gy<1cc
ŽELODEC	V36Gy<1cc
TANKO ČREVO	V36Gy<3cc
JETRA	(Vcc) jetra – V21Gy>700cc

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

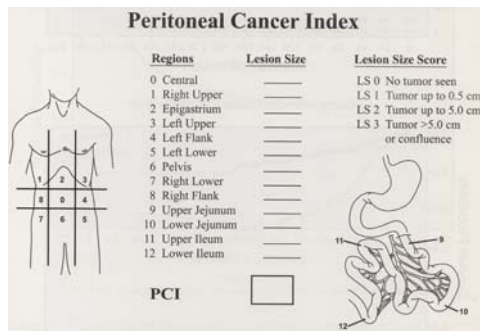
- CT trebuha
- CT toraksa
- PET-CT
- MR trebuha



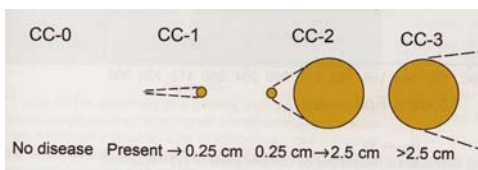
Kvantitativni prognostični kazalci

- 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)

Opređeli 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

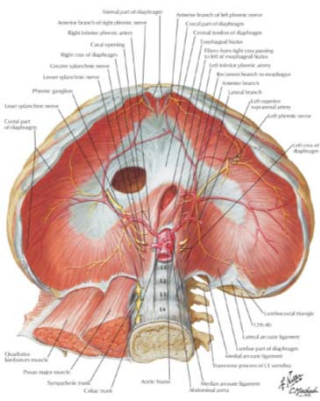
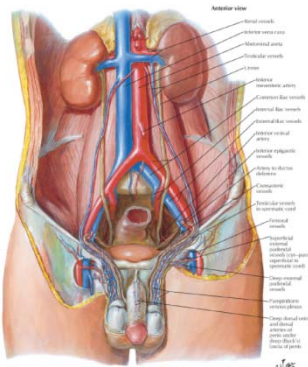
Posegi pri CRS

Peritonektomija

- Anteriorna parietalna peritonektomija
- Peritonektomija L zg. kvadranta
- Peritonektomija D zg. kvadranta
- Pelvična peritonektomija
- Omentalna bursektomija

Resekcije

- Kožna brazgotina, epigastrično maščevje
- Omentektomija in splenektomija
- Kapsulektomija jeter
- Histerektomija z ovariektomijo
- Resekcija rektosigmoidnega kolona
- Holecistektomija



Indikacije

standardno zdravljenje:

- peritonealni psevdomiksom
- peritonealni mezoteliom
- kolorektalni rak z omejeno karcinozo

v fazi raziskovanja:

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Elias et al. EJC, 2014

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- kolorektalni rak z omejeno karcinozo

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



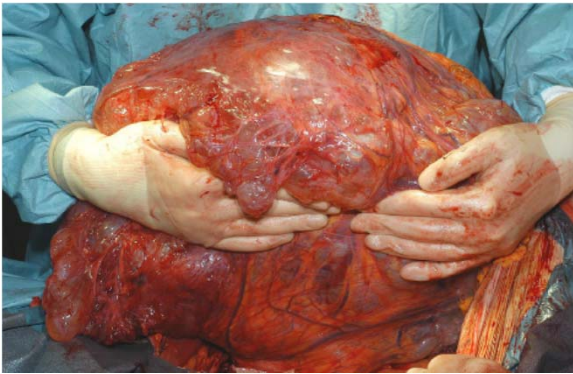
Mukokela slepiča



Mukokela slepiča

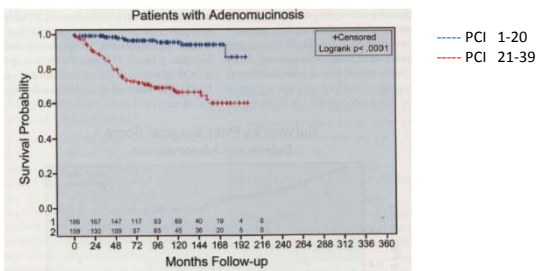


Omental cake



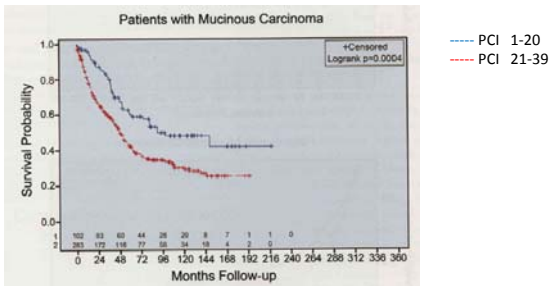
Mucinska cista

Preživetje glede na PCI



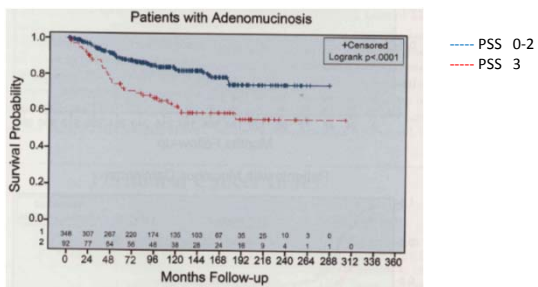
Sugarbaker, Cancer J, 2009

Preživetje glede na PCI



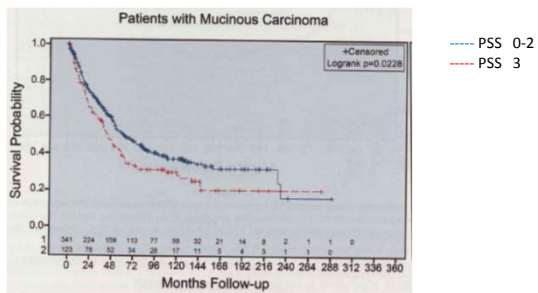
Sugarbaker, Cancer J, 2009

Preživetje glede na PSS



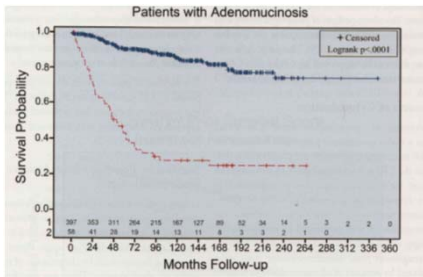
Sugarbaker, J Surg Oncol, 2007

Preživetje glede na PSS



Sugarbaker, J Surg Oncol, 2007

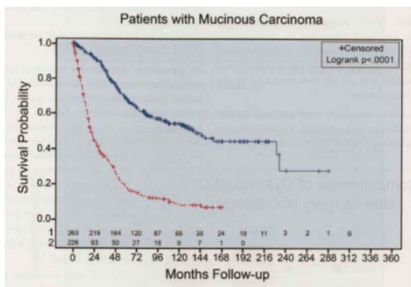
Preživetje glede na CCS



— CCS 0-1
— CCS 2-3

Sugarbaker, J Surg Oncol, 2007

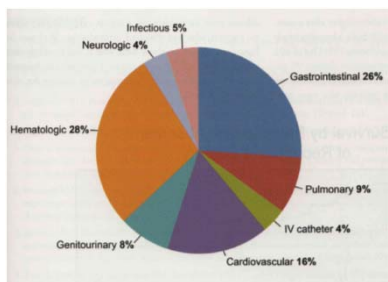
Preživetje glede na CCS



— CCS 0-1
— CCS 2-3

Sugarbaker, J Surg Oncol, 2007

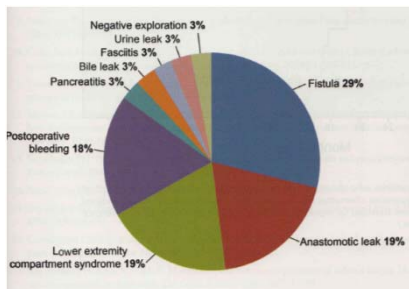
Zapleti



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

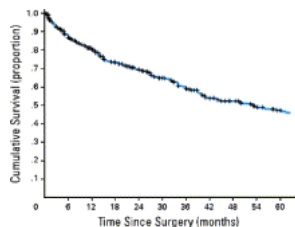
- 0,3-3/1000000
- vloga azbesta(?)
- različni podtipi

- epitelooidni
- 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

Indikacije

standardno zdravljenje:

- peritonealni psevdomiksom
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Elias et al. EJC, 2014

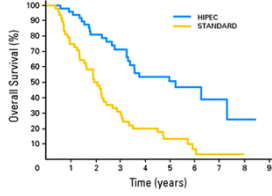
Kolorektalni rak

- 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
Choi (136)	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
Franke (138)	University of Pittsburgh Medical Center, Pittsburgh	2008	III	36	20	85	NR	45	NR
Bjelcic (139)	Washington Cancer Institute, Washington, DC	2008	III	49	33	NR	NR	50	20
Kiamanesh (101)	Louis-Maurier University Hospital, Paris	2007	III	30	38	NR	72	NR	44
Vervaaal (140)	Netherlands Cancer Institute, Amsterdam	2005	III	59	43	54	NR	56	43
Glehen (141)	Multi-institutional	2004	III	377	32	90	NR	55	40
Vervaaal (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

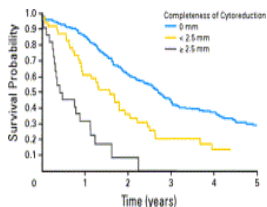
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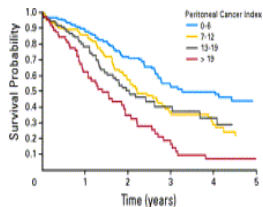
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Total				1084					
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Kolorektalni rak

- CCR in PCI vplivata na prognozo
- PCI > 20 kontraindikacija za operacijo



Elias et al. JCO, 2010



Kolorektalni rak

Karcinoma peritoneja in jetrni zasevki:

- operacija v selektivnih primerih
- PCI < 12
- < 3 jetrni zasevki → 3 letno preživetje 27%
srednje preživetje 40 mesecev

Maggiari 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

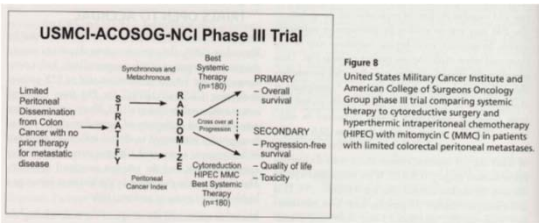


Figure 8
United States Military Cancer Institute and American College of Surgeons Oncology Group phase III trial comparing systemic therapy to cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) with mitomycin C (MIMC) in patients with limited colorectal peritoneal metastases.

Raziskave

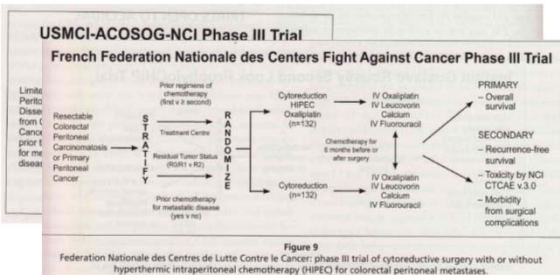
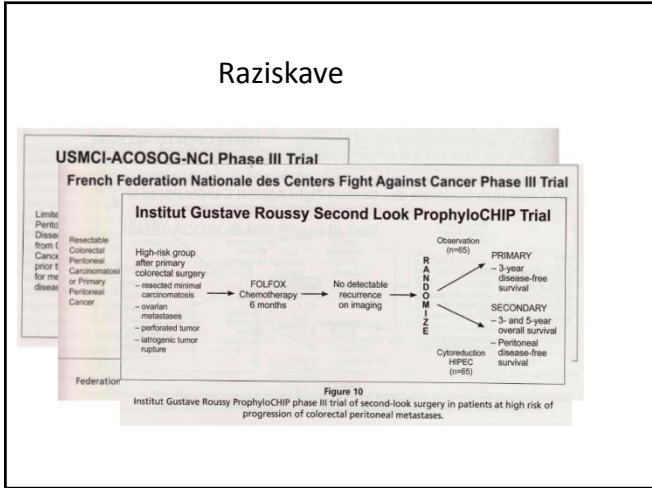
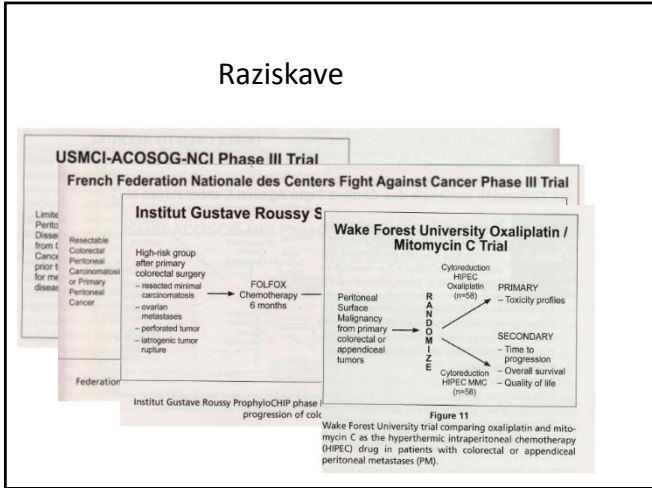


Figure 9
Federation Nationale des Centres de Lutte Contre le Cancer: phase III trial of cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy (HIPEC) for colorectal peritoneal metastases.

Raziskave



Raziskave



Kolorektalni rak – bolniki s tveganjem za razvoj PC

- Perforiran primarni tumor
- Izoliran ovarijski zasevek **>40%**
- Odstranjena lokalizirana karcinoma peritoneja
- T4 tumorji
- Pozitivna peritonealna citologija **8-30%**
- Okluzivni ali krvaveči tumorji

HVALA

Elektrokemoterapija zasevkov v jetrih

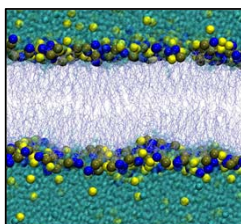
Ibrahim Edhemovic, Erik Brecelj
Institute of Oncology Ljubljana, Slovenia

What is electrochemoterapy?

It is a combination of reversible electroporation and chemotherapy

Electroporation

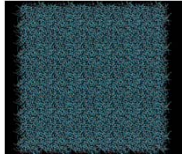
- Electroporation is phenomenon which follows the application of high electric fields on a cell membrane which leads to the cell membrane permeabilization.



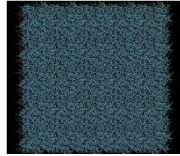
Courtesy of Dr. Mounir Tarek, Theory Modeling and Simulations group, Université de Lorraine, Nancy, France

Electroporation

- Electroporation is phenomenon which follows the application of high electric fields on a cell membrane which leads to the cell membrane permeabilization.



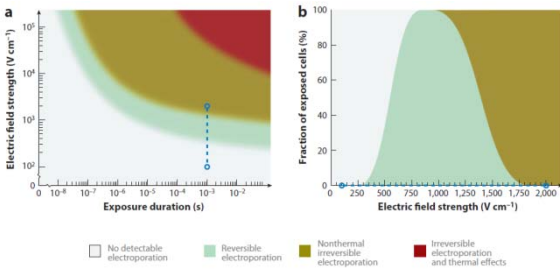
Reversible



Irreversible

Adapted from: Department of molecular dynamics studies. University of Buenos Aires

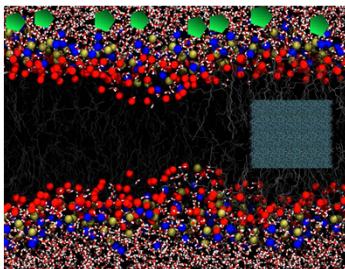
Reversible, Irreversible



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

Reversible electroporation

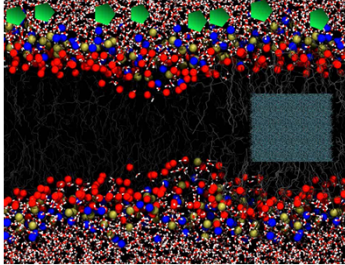
Cell membrane separates the cell from its surrounding environment and provides selective transport.



Adapted from: Department of molecular dynamics studies. University of Buenos Aires

Reversible electroporation

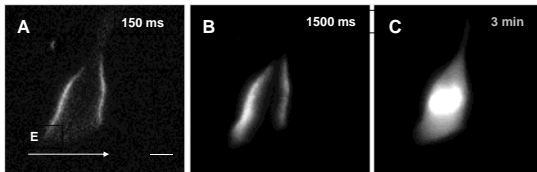
If a cell is exposed to an external electric field, cell membrane permeability is temporarily increased allowing molecules otherwise deprived of transport mechanisms to cross the cell membrane.



As electroporation is a transient phenomenon, after some time the cell membrane reseals and the transported molecules remain trapped inside the cell.

Adapted from: Department of molecular dynamics studies. University of Buenos Aires

Visualization of cell electropermeabilization

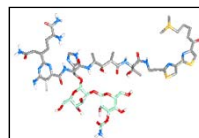


- Fluorescence of the cell; A: 150 ms, B: 1500 ms, and C: 3 min after pulse delivery.
- The images were corrected for background fluorescence and the brightness was automatically enhanced. The cell was exposed to a single 260 V (650 V/cm) rectangular pulse (750 μ s). Propidium iodide (100 μ M) was added to suspension before the pulse was applied to visualize the permeabilized regions. Bar represents 10 μ m.

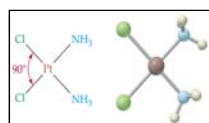
Sersa et al. EJSO 2007

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

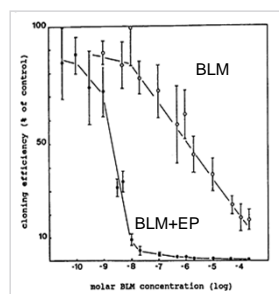
Drugs tested	Potentiation
• Bleomycin	100-5000 -fold
• Cisplatin	3-80 -fold
• Carboplatin	10-13 -fold
• Methotrexate	
• Melphalan	
• Mithramycin	
• Actinomycin D	
• Adriamycin	
• Cyclophosphamide	
• Mitomycin C	
• Doxorubicin	
• 5-fluorouracil	
• Vinblastine	
• Vincristine	
• Paclitaxel	
• Taxotere	

Electroporation allows introduction of hydrophilic and nonpermeant molecules into the cytosol

- Drugs: electrochemotherapy
- Nucleic acids (DNA, siRNA...)
- Proteins
- Small molecules

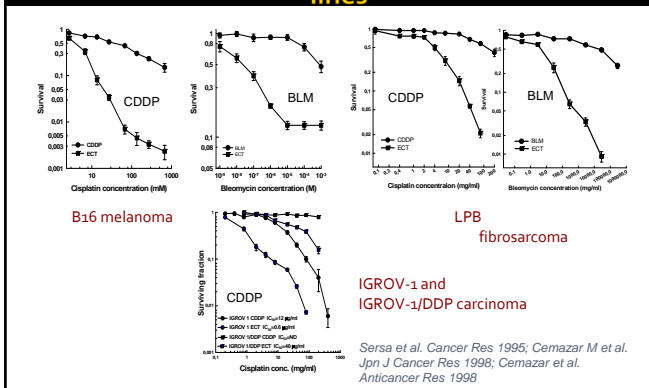
The first in vitro survival curve demonstration that cytotoxicity of BLM is increased by electroporation

- Cell suspension was mixed with drug solution and immediately exposed to electric pulses.
- Cytotoxicity was potentiated ~1000 fold.

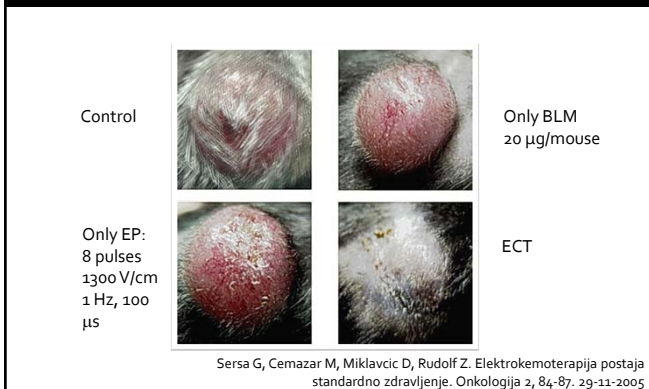


Orlowski et al. Biochem Pharmacol 1988

Electroporation increases cytotoxicity of chemotherapeutic drugs in different tumor cell lines



The effect of the ECT



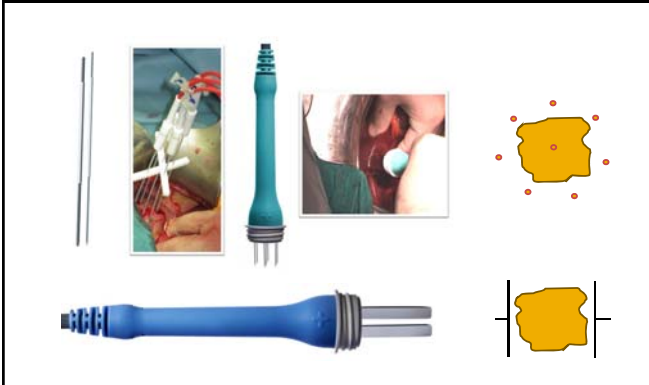
Electrochemotherapy

- 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, Belehradec J, Jr., Paoletti C. Electrochemotherapy potentiation of antitumor 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



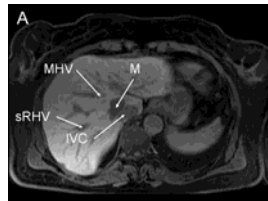
Electric pulse generator – Cliniporator Vitae

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

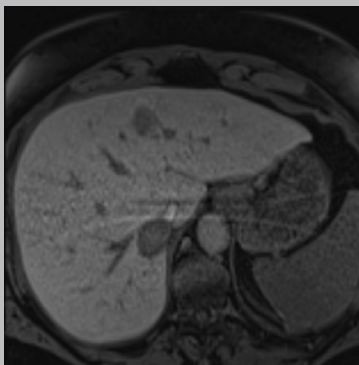
- Single metastasis in Sg1, on the inferior caval vein, between the right hepatic vein and the common trunk treated with ChT and cetiximab – some downsizing achieved.
- Considering specific location RFA could not be effective because of cooling effect of the veins.
- Radical resection was potentially possible with right trisectionectomy (leaving only lateral part of the left liver – too small liver remnant – damage from ChT)



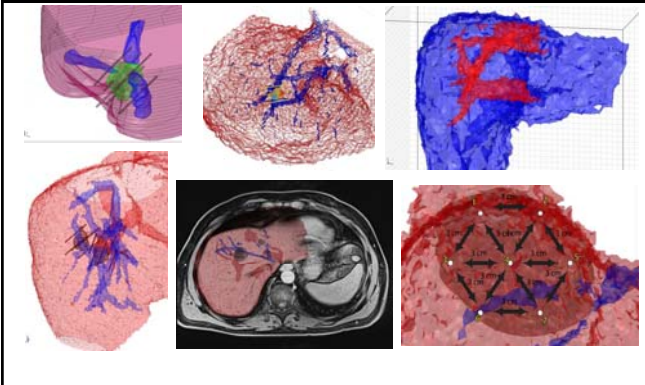
▪ Axial T1W MRI image, showing a hypointense lesion (M) in between inferior vena cava (IVC), superior right hepatic vein (sRHV) and middle hepatic vein (MHV), in late liver phase, 20 min post Gd-EOB-DTPA.

Edhemovic I et al. Technol Cancer Res Treat 2011

Treatment planing – Images importing and analysing

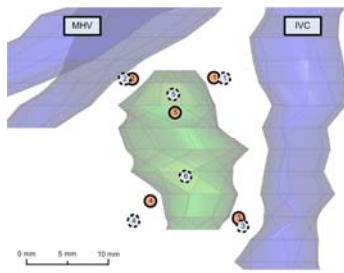
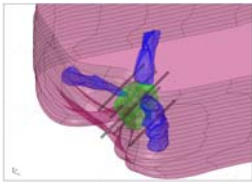


Segmentation



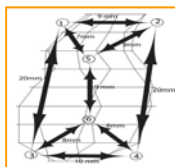
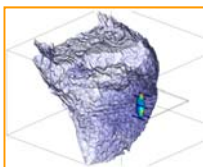
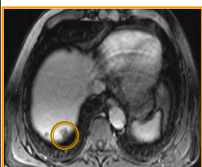
Numerical treatment planning

- 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



Edhemovic I et al. Technol Cancer Res Treat 2011

Treatment planning and executing

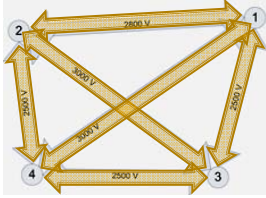


Electrode pair	Voltage according to plan [V]	No. of pulses according to plan	Predicted current [A]	Delivered voltage [V]	Delivered no. of pulses	Measured current [A]
1,5	2100	8	31	1900	10	32,3
1,6	2100	8	26	2100	8	45,2
1,5	2100	8	26	1700	21	44,7
1,6	2100	8	35	2100	8	48,3
1,5	2100	8	25	2100	8	48,9
1,6	2100	8	29	1900	8	48,8
1,5	2100	8	28	2100	8	47,5
1,6	2100	8	33	1700	16	41,1
1,6	1700	8	40	1700	8	48,9
TOTAL		72			105	

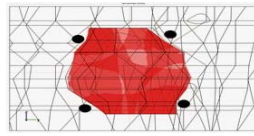


electrodes with fixed gel

Treatment planning



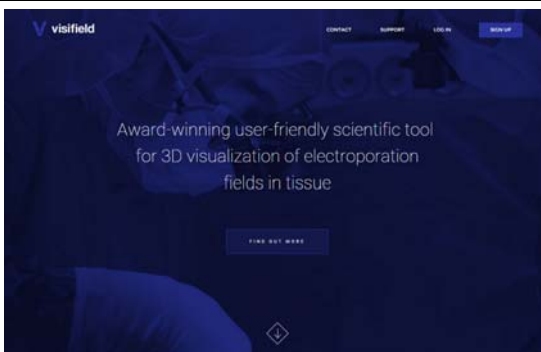
Voltage between electrode pairs



Tumor coverage

Miklavcic et al. Towards treatment planning and treatment of deep-seated solid tumors by Electrochemotherapy. BioMedical Engineering OnLine 2010, 9:10

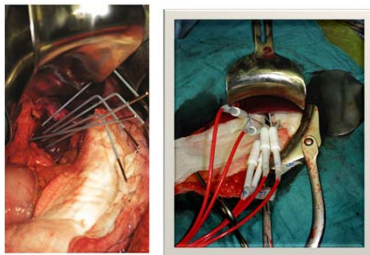
Online treatment planning



www.visifield.com

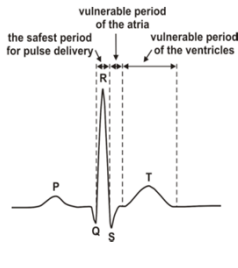
Identification of metastasis and preparatory procedures needed before delivery of electric pulses

- 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)



Edhemovic I et al. Technol Cancer Res Treat 2011

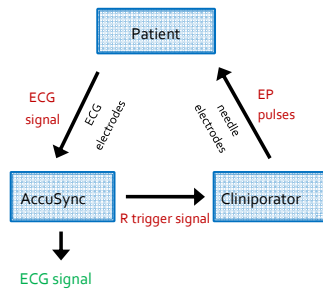
ECG synchronization



Edhemovic I et al. Technol Cancer Res Treat 2011

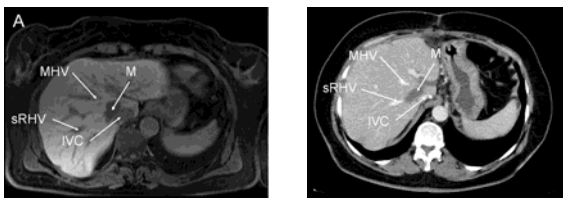
Delivery of electric pulses and ECG synchronization

- 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



Edhemovic I et al. Technol Cancer Res Treat 2011

Post-treatment follow up

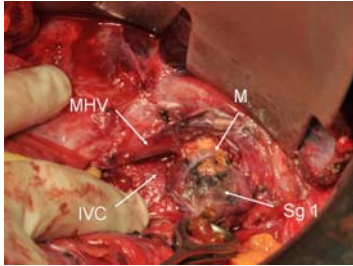


- Two months after electrochemotherapy CT was performed
- No change in size of the metastasis treated
- CT image showed that margins were blurred, which demonstrated that treatment had some effect
- Reoperation planned

Edhemovic I et al. Technol Cancer Res Treat 2011

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.

Edhemovic I et al. Technol Cancer Res Treat 2011

ECT of liver metastases

- The patient is 5 yrs. without recurrent disease

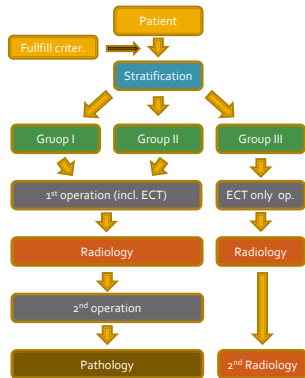


Professor Eldar M. Gadzijev

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

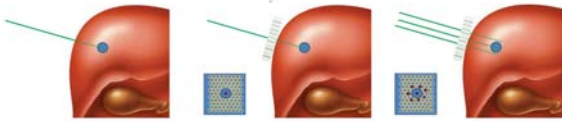


Longe needle electrodes (left) with variable geometry and electrodes with fixed geometry (right)

Electrochemotherapy

- **Agent:**
 - Bleomycin – BLM: Bleomycinum, Heinrich Mack Nachf. GmbH & Co. KG, Illertissen, Germany
 - Dosage: 15 mg/m²
 - 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

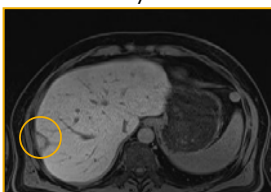


Results – Patients and Metastases

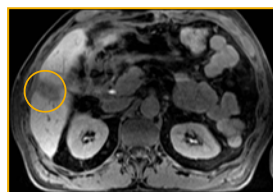
- 16 pts. (12 males, 4 females)
- Median age 60,3 (36,6 – 69,1)
- Response evaluable on 15 patients
- 27 evaluable metastases out of 29 treated
- 21 evaluable metastases treated with long needle electrodes and 6 with fixed geometry electrodes
- Median diameter of the metastases: 18 mm (6 – 29mm)
- 13 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

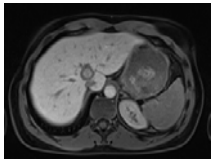


PR

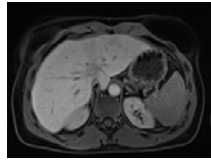


CR

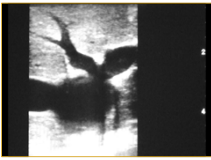
Successful ECT



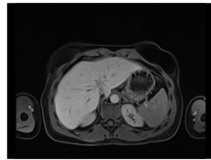
Before ECT



2 months after ECT



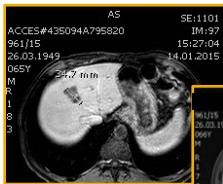
Intraop. US



6 months after ECT

Institute of Oncology Ljubljana

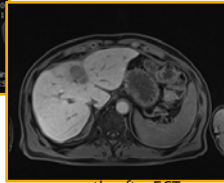
Unsuccessful ECT



Before ECT



1 months after ECT

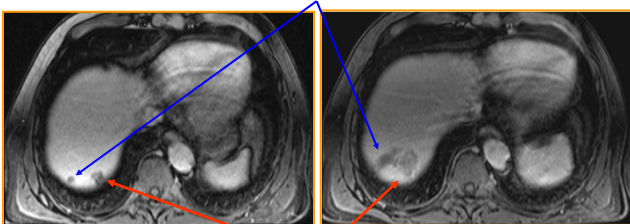


2 months after ECT

Institute of Oncology Ljubljana

Radiology

ECT treated metastasis regressed,
visible are changes similar than after RFA



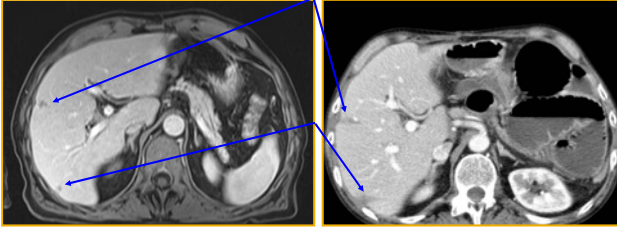
MRI before ECT

MRI after ECT

Non treated metastasis has grown

Radiology

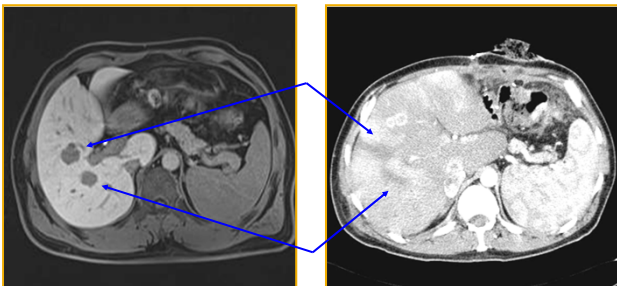
ECT treated metastases in Sg. V and VI regressed, changes are similar to those after RFA



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
1 st	19	15 (79%)	4 (21%)	0 (0%)
2 nd	19	14 (73%)	0 (0%)	5 (26%)

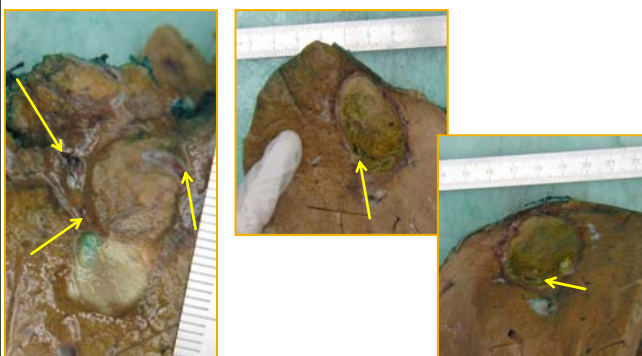
Results - Radiology

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%)

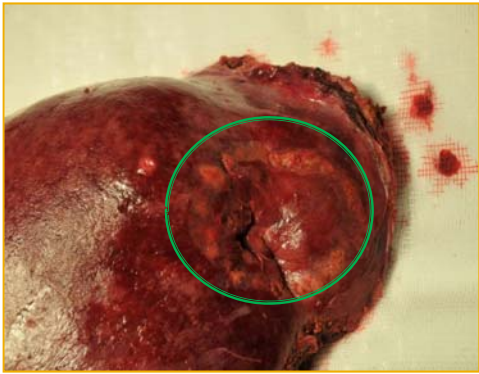
Chi-square test: $p = 1$

Preserved structures within electroperated field

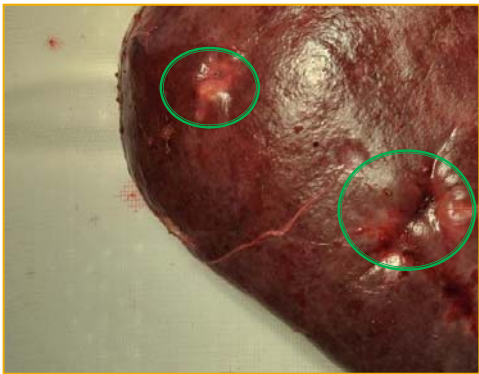


Courtesy of Gorana Gasljevic, Institute of Oncology Ljubljana

Macroscopic appearance

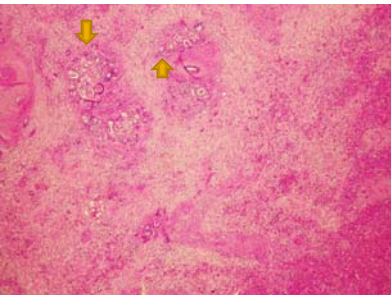


Macroscopic appearance



How we measured - Pathology

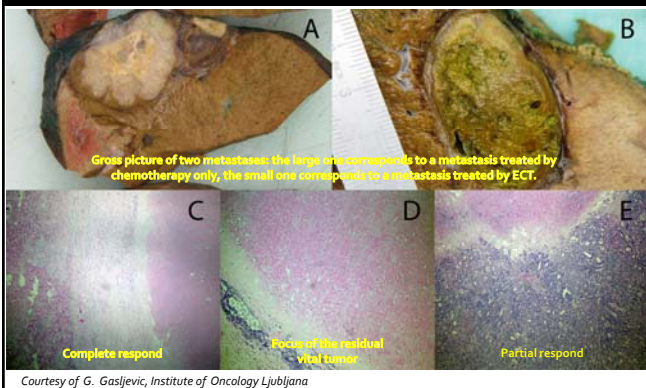
Percent of viable tumor tissue



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



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				All
	Compl. (0-1%)	Major(1-25%)	Medium(26-50%)	Minor (>51%)	
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, Breclj et al. Electrochemotherapy of the liver metastases, *JSO*, 2104

Thermal vs. Non-Thermal

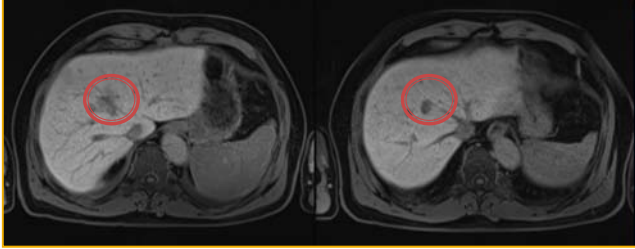
RFA

- Thermal injury of surrounding tissue
- Non – selective
- Takes longer
- Cooling effect
- Relasing of different tissue products

Electroporation

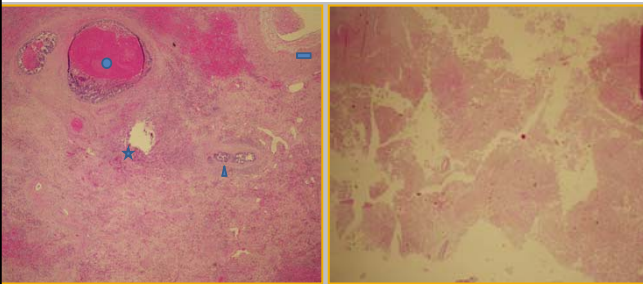
- No thermal injury
- Selective
- Takes less time
- No cooling effect

Preserved major vessels



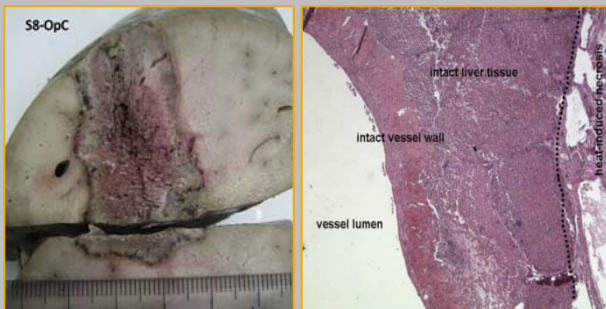
Courtesy of Maja Music, Institute of Oncology Ljubljana

ECT vs. RFA



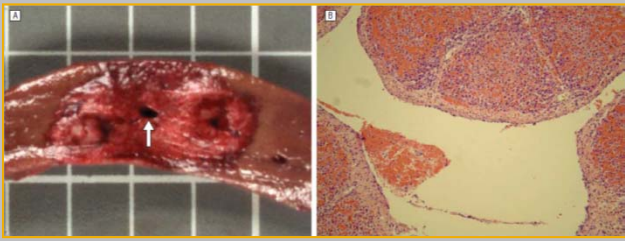
Star – fibroseous nodus (regressiv changes) after ECT
Circle – residual, partially necrotic tumor
Triangle – preserved biliar duct within fibroseous nodus
Rectangle – preserved, somehow edematoseous blood cesselles within fibroseous nodus
Courtesy of Gorana Gasljevic, Institute of Oncology Ljubljana

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



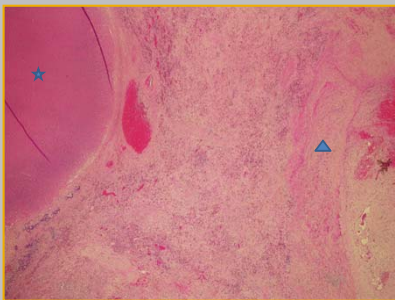
Irreversible Electroporation for the Ablation of Liver Tumors. Are We There Yet? Kevin P. Charpentier, MD. ARCH SURG/VOL 147 (NO. 11), NOV 2012

Preserved structures within electroperated field



Courtesy of Gorana Gasljevic, Institute of Oncology Ljubljana

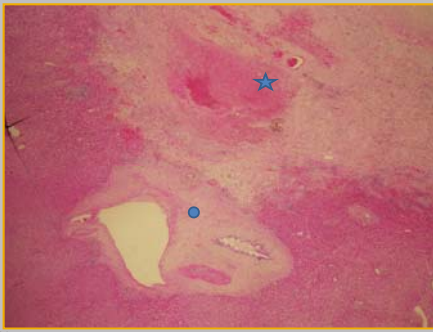
Preserved blood vessel close to the tumor



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	Groups	ID	Complications
I (two stage)	01	SIRS (1)	III (one operation)	09	Ascites (2) Infection NOS (1)
	02	•		10	Supravent. tachycard. (2)
	03	Atrial fibrillation (2) Colon perforation (3)		11	Small bowel obstr. (3) Infection NOS (1)
	04	•		12	Ascites (2) Colon perforation (3) Pleural effusion (2)
	05	•		13	Abd. abscess (3)
	06	Infection NOS (1)		14	•
II (two operat.)	07	Abd. abscess (3) Pneumonia (1) Wound infection (2)		15	Cholestatic icterus (2) Infection NOS (1) Biliary fistula (3) Transient liver failure (2) Transient renal failure (3) Pleural effusion (2)
	08	Transient liver failure (2)		16	Infection NOS (1) Biliary fistula (3)

12 pts. with complications
4 pts. with no complications

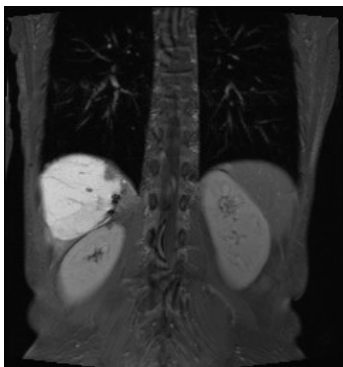
ECG analysis

- 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)

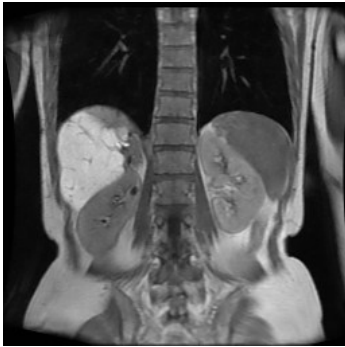
Electrode – related complications

- 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.

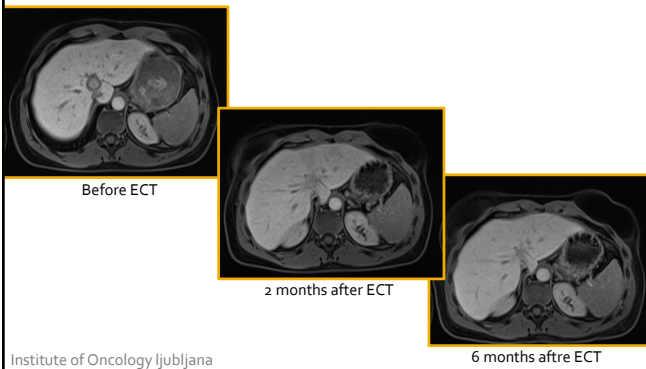
Before treatment



After treatment



Metastatic breast cancer



Conclusions

- Electrochemotherapy is safe and efficient treatment modality
- It is widely accepted in national guidelines for various skin tumors
- In liver, it was shown that ECT has 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 Brečelj - 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 your attention!



30.11.Ljubljana



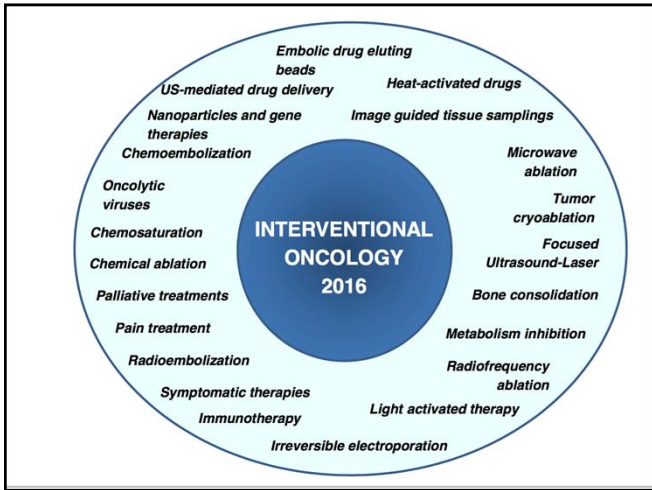
Medicinska fakulteta
Univerza v Ljubljani, Slovenija

Perkutano lokalno zdravljenje jetrnih lezij

Popovič Peter
Nina Boc

Klinični Inštitut za radiologijo, UKC Ljubljana
Oddelek za radiologijo, Onkološki Inštitut Ljubljana
Medicinska Fakulteta, Univerza v Ljubljani,



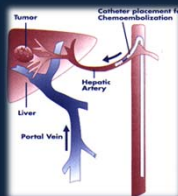


Intraarterijska lokoregionalna terapija

• Transarterijska kemoembolizacija –

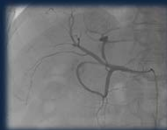
“conventional” cTACE (lipiodol)

“Drug-eluting Microspheres” TACE
Doxorubicin - DEBDOX
Irinotecan - DEBIRI

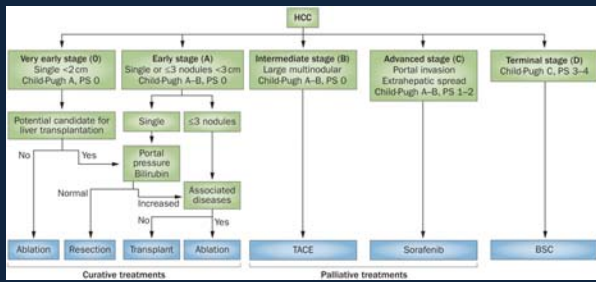


• Radioembolizacija

(SIRT): Yttrium 90 radioaktivni mikrodelci (<30 mikronov)



BCLC klasifikacija



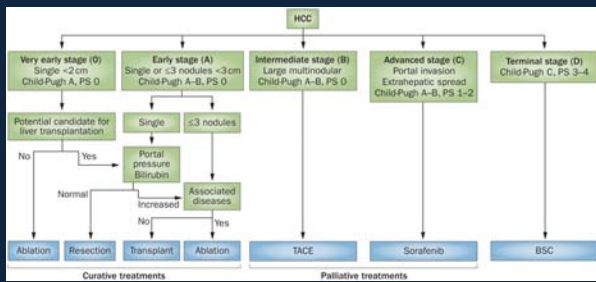
Fomer, A. et al. (2014) Treatment of intermediate-stage hepatocellular carcinoma. *Nat. Rev. Clin. Oncol.*

UKC Ljubljana

- Register raka 2009
- 133 HCC/leto*
- Januar 2011- december 2012 (144 bol)
 - > kirurgija 20 bol
 - > TX jeter 3 bol
 - > RFA 4 bol
 - } (18,8%)
 - > DEBDOX 70 bol
 - > Radioembolizacija 5 bol
 - > DEBDOX+sorafenib 11 bol
 - } (59,7%)
 - > sorafenib 31 bol
 - } (21,5%)

*www.onko-i.si/rss

BCLC klasifikacija



Fomer, A. et al. (2014) Treatment of intermediate-stage hepatocellular carcinoma. *Nat. Rev. Clin. Oncol.*

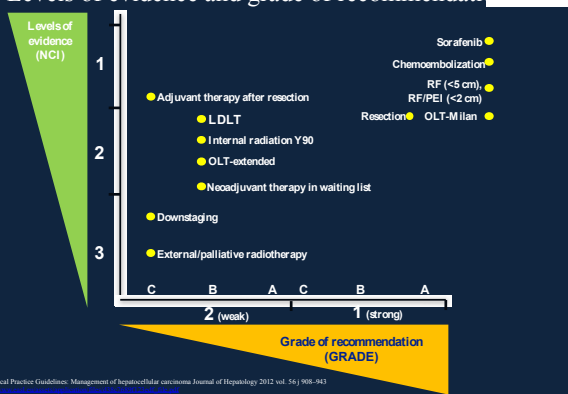
Srednji štadij HCC: Proгноza - EASL, EORTC



- srednje preživetje 11-16 mesecev
- multidisciplinarni pristop

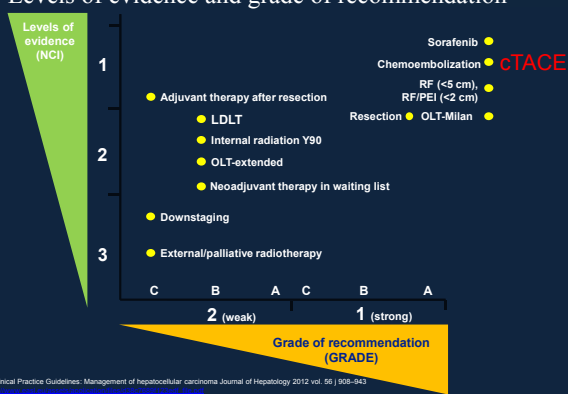
EASL-EORTC Clinical Practice Guidelines. Management of hepatocellular carcinoma Journal of Hepatology 2012; vol. 56 | 908-943

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 | 908-943

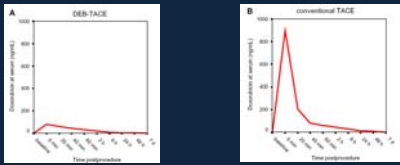
Intermediate stage HCC: Levels of evidence and grade of recommendation



EASL-EORTC Clinical Practice Guidelines. Management of hepatocellular carcinoma Journal of Hepatology 2012; vol. 56 | 908-943

Chemoembolization of hepatocellular carcinoma with drug eluting beads: Efficacy and doxorubicin pharmacokinetics

María Varela¹, María Isabel Real², Marta Burrel², Alejandro Forner¹, Margarita Sala¹, Mercè Brunet³, Carmen Ayuso², Lluís Castells⁴, Xavier Montañá², 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

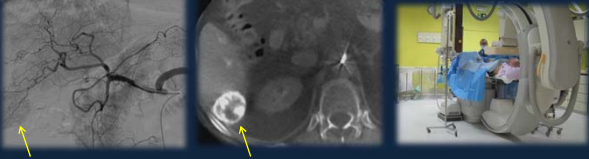
Contents lists available at ScienceDirect
Cancer Treatment Reviews
 journal homepage: www.elsevierhealth.com/journals/ctrv

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

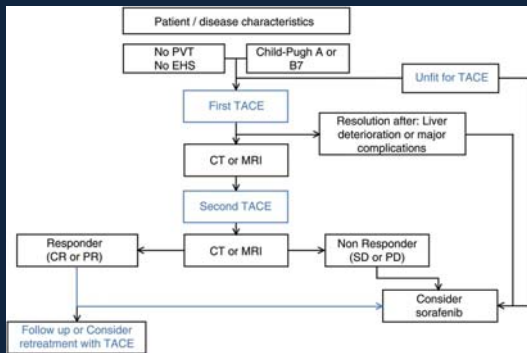
DEBDOX TACE-standardizirana metoda

- 75 -100 μ ,100-150 mgDoxorubicin
- Superselektivni pristop (mikrokater) pod kontrolo CBCT
- mRECIST
- "On demand"



Iwazawa, J., et al. Eur. J. rad., 2012
 *Popović 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 appearance 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

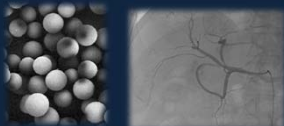
Radioembolizacija (SIRT)

(selektivna notranja radioterapija, hepatična brahiterapija)

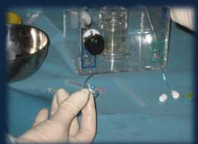
selektivna intraarterijska aplikacija zelo visoke doze sevanja v tumorje v jetrih, ob prejeti majhni dozi sevanja normalnega jetrnega tkiva

Mikrodelci (20-40 um) Y-90

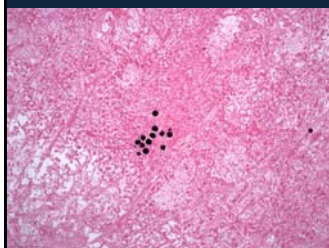
Y-90: Beta sevanje
 povprečna razdalja: 2,5 mm
 največja razdalja: 11 mm
 doza do 3 GBq
 120 Gy



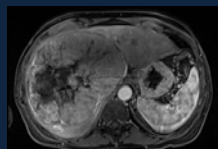
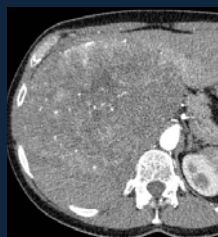
raspolovni čas: 64 h



51 let, Ž, HCC 18 cm, brez ciroze

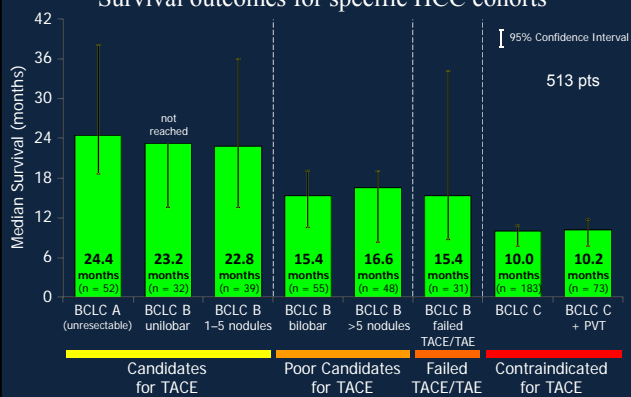


nekroza



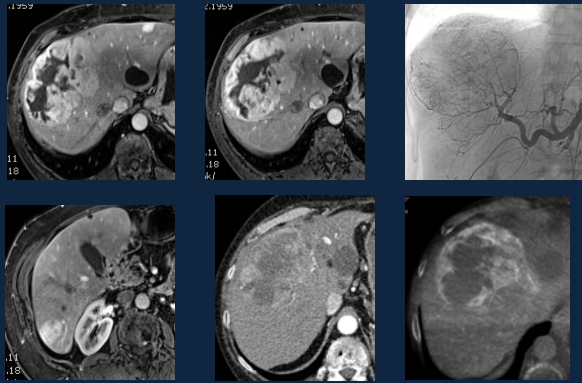
hcc

ENRY Study of SIR-Spheres microspheres in HCC: Survival outcomes for specific HCC cohorts



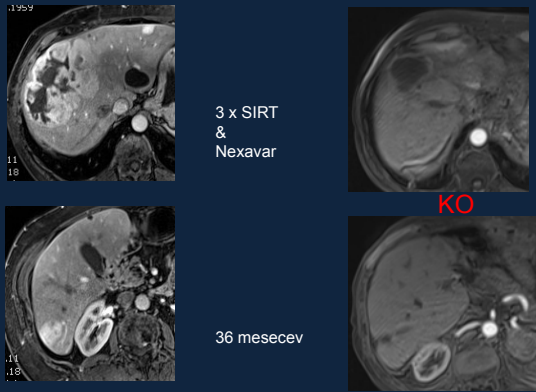
Sangro et al. Hepatology 2011; 54: 868-878. Ettorre et al. ASCO Annual Meeting, J Clin Oncol 2011; 29 (Suppl): Abs. 4099.

54 let, Ž, multifokalni HCC 12 cm, BCLC B, Child A



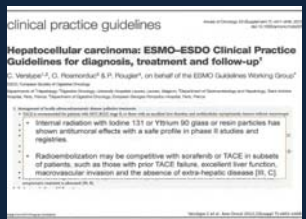
JUNI 2013

54 let, Ž, multifokalni HCC 12 cm, BCLC B, Child A



Juni 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

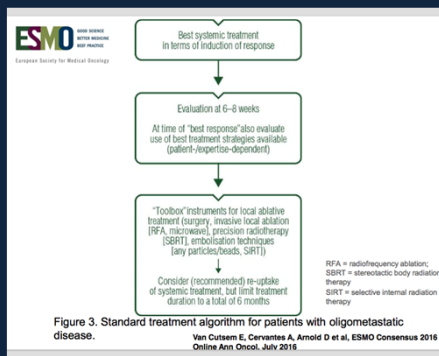
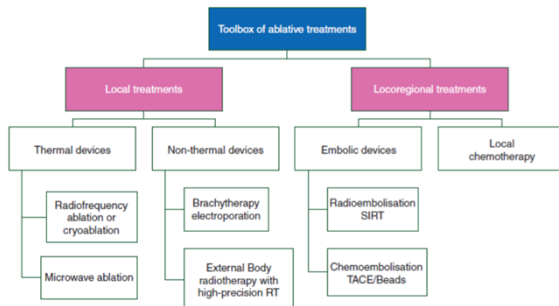


Figure 1: toolbox of ablative treatments



Van Cutsem E, Cervantes A, Arnold D et al, ESMO Consensus 2016
Online Ann Oncol, July 2016

ESMO consensus guidelines for the management of patients with metastatic colorectal cancer

E. Van Cutsem^{1*}, A. Cervantes², R. Adam³, A. Sobrero⁴, J. H. Van Krieken⁵, D. Aderka⁶, E. Aranda Aguilar⁷, A. Bardelli⁸, A. Benson⁹, G. Bodoky¹⁰, F. Ciardiello¹¹, A. D'Hoore¹², E. Diaz-Rubio¹³, J.-Y. Douillard¹⁴, M. Ducreux¹⁵, A. Falcone^{16,17}, A. Grothey¹⁸, T. Gruenberger¹⁹, K. Haustermans²⁰, V. Heinemann²¹, P. Hoff²², C.-H. Köhne²³, R. Labianca²⁴, P. Laurent-Puig²⁵, B. Ma²⁶, T. Maughan²⁷, K. Muro²⁸, N. Normanno²⁹, P. Österlund^{30,31}, W. J. G. Oyen³², D. Papamichael³³, G. Pentheroudakis³⁴, P. Pfleiffer³⁵, T. J. Price³⁶, C. Punt³⁷, J. Ricke³⁸, A. Roth³⁹, R. Salazar⁴⁰, W. Scheithauer⁴¹, H. J. Schmoll⁴², J. Taberner⁴³, J. Taieb²⁵, S. Tejpar¹, H. Wasan⁴⁴, T. Yoshino⁴⁵, A. Zaanan²⁵ & D. Arnold⁴⁶

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	Embolitic 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
EICHLER (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; FOLFOX: 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.

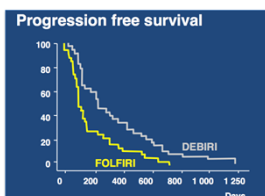
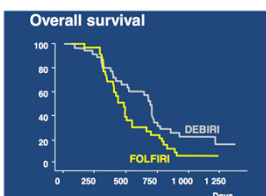
13,3-25 mesecev

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*, CARLEO ALIBERTI*, MASSIMO TILI*, LUCA MELAZZANI*, FRANCESCO GRAGNANO*, PIROLO GIORGIANI*, ANDREA MAMBROTTI*, FRANCESCO MONTAGNANI*, PIROLO ALESSANDRONI*, VINCENZO CATALANO*, PIROLO COSCHIERA*



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

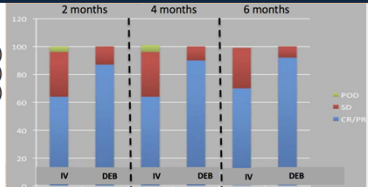
Robert C. G. Martin II, MD, PhD^{1,2}; Charles R. Scoggins, MD, MBA^{1,2}; Marshall Schreeder, MD¹; William S. Rilling, MD¹; Christopher J. Laing, MD³; Clifton M. Tatum, MD³; Lawrence R. Kelly, MD⁴; Ricardo D. Garcia-Monaco, MD⁵; Vivek R. Sharma, MD^{2,8}; Todd S. Crocenzi, MD⁹; and Steven M. Strasberg, MD¹⁰ *In 2015*



• 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 nerezektabilnimi zasevki v jetrih
- neodzivni na kemoterapijo (z/brez irinotekana)
- le jetrni zasevki ali minimalni ekstrahepatični zasevki
- zasevki zajemajo < 70% parenhima
- ustrezna jetрна 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 nadaljnjega zdravljenja v sodelovanju z onkologom (dodatna sistemska terapija ali nadaljevanje lokalnega zdravljenja)

Martin R. Journal of Oncology 2009

mCRC-naše izkušnje

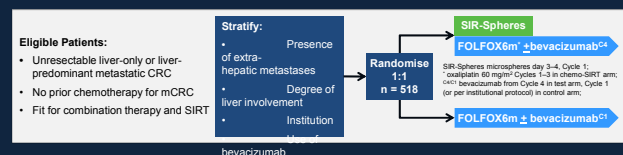
DEBIRI TACE	Spremljanje	Mrtvi	Srednje preživetje celokupno	Srednje preživetje po DEBIRI TACE
21 bol.	35,4 (1-68) mes.	17/21 bol.	43,4 mes. (22,2-64,6 m)	13,9 mes. (9,1-18,6m)

*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)

Secondary endpoints: PFS in liver
Overall survival
Response rate
Quality of life
Recurrence rate
Toxicity
Resection rate

Sponsor: Sirtex

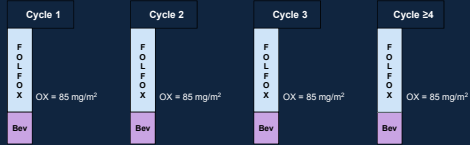
Pis: Prof. Peter Gibbs; Prof. Guy van Hazel

Status: Currently enrolling

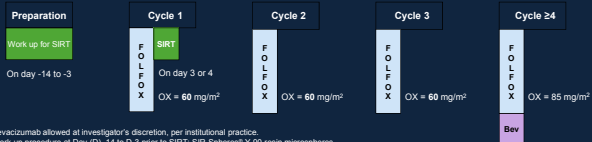
<http://www.sirtex.com> ; www.foxo.com

SIRFLOX - protokol raziskave

Control arm: mFOLFOX6 (+ bevacizumab) ⁽¹⁾



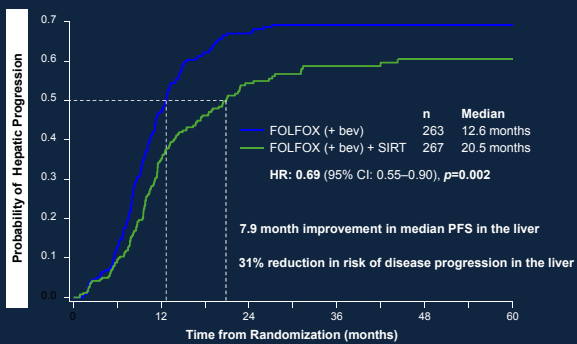
Treatment arm: mFOLFOX6 (+ bevacizumab) ⁽¹⁾ + SIRT ⁽²⁾



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 3592. Van Hazel G et al. J Clin Oncol 2016.

Progression-Free Survival in the Liver



Time from Randomization (months)	0	12	24	36	48	60
Number at risk	263	96	29	9	5	2
FOLFOX	263	108	33	11	5	2
FOLFOX + SIRT	267	106	33	11	5	2

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

Author year	Treatment	Response (RCCO) %				Proportion New lesions	Overall survival					Key points
		CR	PR	SD	PD		Median survival	6 months	1 year	2 years	3 years	
Boyer 05, 2009	TACE	13	33	33	19	19	21	18	11	5	1	Response to TACE is associated with an increase in median number of operations for recurrent CHC
Wang 05, 2007	TACE	10	40	28	22	38	21	10	5	1	1	TACE is safe associated with an increase in median number of operations for recurrent CHC
Wang 05, 2008	TACE + DEBDOX	10	40	28	22	38	21	10	5	1	1	A meta-analysis of TACE, DEBDOX, and SIRT in patients with recurrent CHC
Wang 05, 2008	TACE	0	0	0	0	0	0	0	0	0	0	A meta-analysis of TACE, DEBDOX, and SIRT in patients with recurrent CHC
Wang 05, 2008	SIRT	0	0	0	0	0	0	0	0	0	0	A meta-analysis of TACE, DEBDOX, and SIRT in patients with recurrent CHC
Wang 05, 2008	TACE + SIRT	0	0	0	0	0	0	0	0	0	0	A meta-analysis of TACE, DEBDOX, and SIRT in patients with recurrent CHC
Wang 05, 2008	TACE	0	0	0	0	0	0	0	0	0	0	A meta-analysis of TACE, DEBDOX, and SIRT in patients with recurrent CHC
Wang 05, 2008	SIRT	0	0	0	0	0	0	0	0	0	0	A meta-analysis of TACE, DEBDOX, and SIRT in patients with recurrent CHC
Wang 05, 2008	TACE + SIRT	0	0	0	0	0	0	0	0	0	0	A meta-analysis of TACE, DEBDOX, and SIRT in patients with recurrent CHC
Wang 05, 2008	TACE	0	0	0	0	0	0	0	0	0	0	A meta-analysis of TACE, DEBDOX, and SIRT in patients with recurrent CHC
Wang 05, 2008	SIRT	0	0	0	0	0	0	0	0	0	0	A meta-analysis of TACE, DEBDOX, and SIRT in patients with recurrent CHC
Wang 05, 2008	TACE + SIRT	0	0	0	0	0	0	0	0	0	0	A meta-analysis of TACE, DEBDOX, and SIRT in patients with recurrent CHC
Wang 05, 2008	TACE	0	0	0	0	0	0	0	0	0	0	A meta-analysis of TACE, DEBDOX, and SIRT in patients with recurrent CHC
Wang 05, 2008	SIRT	0	0	0	0	0	0	0	0	0	0	A meta-analysis of TACE, DEBDOX, and SIRT in patients with recurrent CHC
Wang 05, 2008	TACE + SIRT	0	0	0	0	0	0	0	0	0	0	A meta-analysis of TACE, DEBDOX, and SIRT in patients with recurrent CHC
Wang 05, 2008	TACE	0	0	0	0	0	0	0	0	0	0	A meta-analysis of TACE, DEBDOX, and SIRT in patients with recurrent CHC
Wang 05, 2008	SIRT	0	0	0	0	0	0	0	0	0	0	A meta-analysis of TACE, DEBDOX, and SIRT in patients with recurrent CHC
Wang 05, 2008	TACE + SIRT	0	0	0	0	0	0	0	0	0	0	A meta-analysis of TACE, DEBDOX, and SIRT in patients with recurrent CHC
Wang 05, 2008	TACE	0	0	0	0	0	0	0	0	0	0	A meta-analysis of TACE, DEBDOX, and SIRT in patients with recurrent CHC
Wang 05, 2008	SIRT	0	0	0	0	0	0	0	0	0	0	A meta-analysis of TACE, DEBDOX, and SIRT in patients with recurrent CHC
Wang 05, 2008	TACE + SIRT	0	0	0	0	0	0	0	0	0	0	A meta-analysis of TACE, DEBDOX, and SIRT in patients with recurrent CHC

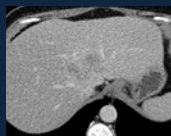
srednje preživetje 13 mesecev

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

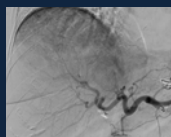


TACE marec 2013

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	preživetje 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, 2018
doi:10.1093/annonc/mdx204

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

J. W. Valle¹, I. Borbath², S. A. Khan³, F. Huguet⁴, T. Gruenberger⁵ & D. Arnold⁶ 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.

**Neuroendocrine gastro-entero-pancreatic tumors:
ESMO Clinical Practice Guidelines for diagnosis,
treatment and follow-up†**

K. Öberg¹, U. Knigge², D. Kwekkeboom³ & A. Perren⁴ on behalf of the ESMO Guidelines Working Group*

¹Department of Endocrine Oncology, University Hospital, Uppsala University, Uppsala, Sweden; ²Department of Surgery, Rigshospitalet, Copenhagen, Denmark; ³Department of Nuclear Medicine, Erasmus Medical Center, Rotterdam, The Netherlands; ⁴Institute of Pathology, University of Bern, Bern, Switzerland

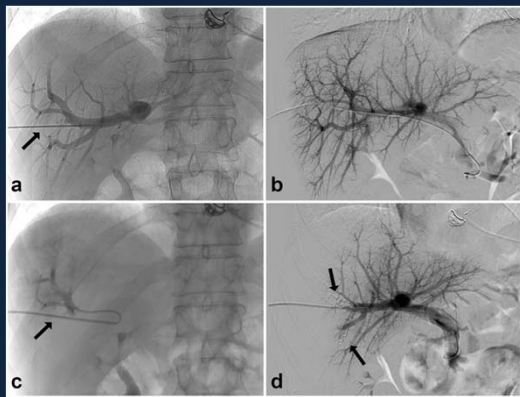
management of advanced/metastatic disease

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

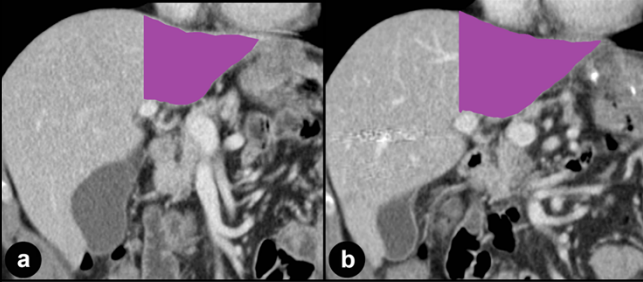


Embozene 250,500, 700, 900, 1300

50 let, m, ca želodca, zasevki v jetrih, KT

Pred embolizacijo

Po embolizaciji

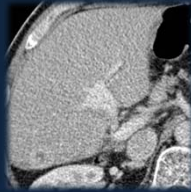


segmenti 1, 2, 3, 4 = 25% FLR

segmenti 1, 2, 3, 4 = 41% FLR

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.

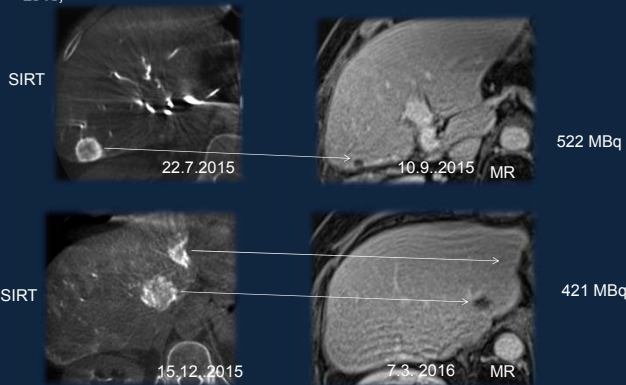
Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

E. C. Smyth¹, M. Verheij², W. Allum³, D. Cunningham⁴, A. Cervantes⁵ & D. Arnold⁶ on behalf of the ESMO Guidelines Committee*

*Department of Gastrointestinal Oncology, Royal Marsden Hospital, London and Surrey, UK; †Department of Radiation Oncology, The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands; ‡Department of Surgery, Royal Marsden Hospital, London and Surrey; ‡Department of Medicine, Royal Marsden Hospital, London and Surrey, UK; ‡Medical Oncology Department, INCLIVA University of Valencia, Valencia, Spain; ‡Instituto Gulbenkian de Oncologia (IGIO), 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
- oktober 2013 ECX, ECF
- 2014 TOF
- 2014 TACE + PVE
- 2014 desna hepatektomija
- 2015 SIRT-julij 2015
- 2015 SIRT – december 2015

- oktober 2016 MR stabilna bolezen

36 months

THE CHANGING FACE OF CLINICAL TRIALS
 Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D., John 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
