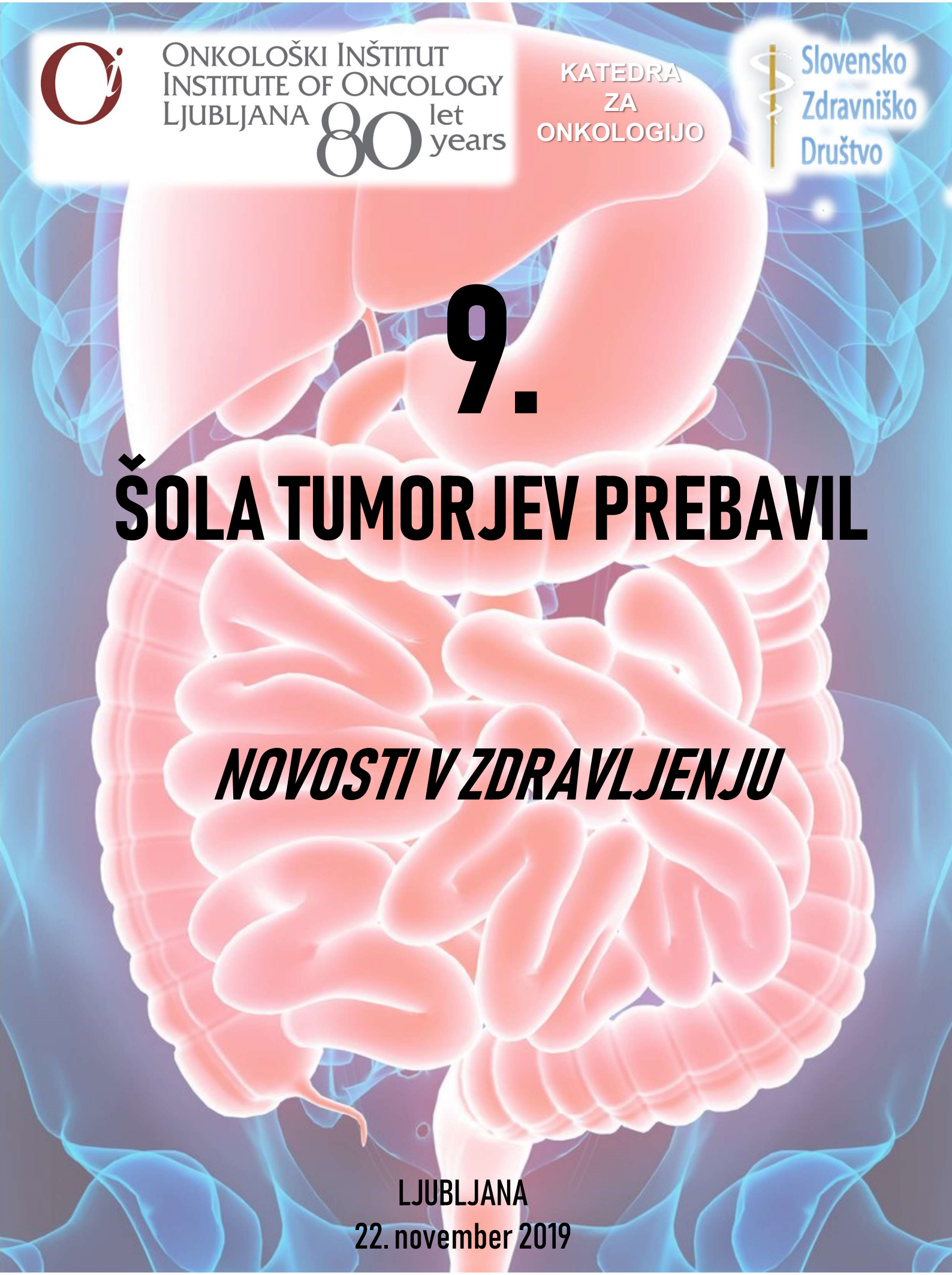

ONKOLOŠKI INŠTITUT
INSTITUTE OF ONCOLOGY
LJUBLJANA 80 let years

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Slovensko
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Društvo

9.

ŠOLA TUMORJEV PREBAVIL

NOVOSTI V ZDRAVLJENJU

LJUBLJANA
22. november 2019

Strokovni odbor:
izr. prof. dr. Janja Ocvirk, dr.med.
doc. dr. Martina Reberšek, dr.med.
mag. Zvezdana Hlebanja, dr.med.
dr. Neva Volk, dr.med.
dr. Tanja Mesti, dr.med.
Marko Boc, dr.med.

Organizacijski odbor:
izr. prof. dr. Janja Ocvirk, dr.med.
doc. dr. Martina Reberšek, dr.med.
mag. Zvezdana Hlebanja, dr.med.
dr. Neva Volk, dr.med.
dr. Tanja Mesti, dr.med.
Marko Boc, dr.med.
Lidija Kristan

Uredniki zbornika:
Marko Boc, dr.med.
izr. prof. dr. Janja Ocvirk, dr.med.
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Organizator in izdajatelj (založnik):
Onkološki inštitut Ljubljana
Sekcija za internistično onkologijo
Katedra za onkologijo

Ljubljana, november 2019

KAZALO

NOVOSTI V ZDRAVLJENJU RAKA DEBELEGA ČREVESA IN DANKE

MULTIDISCIPLINARNI PRISTOP K ZDRAVLJENJU BOLNIKA Z JETRNIMI ZASEVKI RAKA DEBELEGA ČREVESA IN DANKE

MULTIDISCIPLINARNI PRISTOP K ZDRAVLJENJU BOLNIKA S KARCINOMOM TREBUŠNE SLINAVKE

MULTIDISCIPLINARNI PRISTOP K ZDRAVLJENJU BOLNIKA Z KARCINOMOM ŽELODCA

MULTIDISCIPLINARNI PRISTOP K ZDRAVLJENJU BOLNIKA S HCC

MULTIDISCIPLINARNI PRISTOP K ZDRAVLJENJU BOLNIKOV Z RAKI PREBAVIL – PRIKAZI PRIMEROV

PROGRAM SREČANJA: **PETEK, 22.11.2019**

07.00-08.00 **REGISTRACIJA**

Moderatorja: izr. prof. Janja Ocvirk, dr.med., asist. dr. Martina Reberšek, dr.med.

08.00-10.50 **NOVOSTI V ZDRAVLJENJU RAKA DEBELEGA ČREVESA IN DANKE**

Hlebanja Z.: Napredovali rak debelega črevesa in danke – klinična dobrobit v zdravljenju v tretji in kasnejših linijah
Volk N.: Individualen pristop k odmerjanju zdravil v poznih linijah zdravljenja napredovalega raka debelega črevesa in danke
Reberšek M.: Novosti na področju biomarkerjev in personalizacije zdravljenja raka debelega črevesa in danke
Ignjatović M.: Adjuvantno sistemsko zdravljenje raka debelega črevesa
Velenik V.: Kompletno neoadjuvantno zdravljenje raka danke
Brecelj E.: Rehabilitacija kirurških bolnikov z rakom debelega črevesa in danke
Razprava

10.50-11.00 Odmor

11.00-12.45 **MULTIDISCIPLINARNI PRISTOP K ZDRAVLJENJU BOLNIKA Z JETRNIMI ZASEVKI RAKA DEBELEGA ČREVESA IN DANKE**

Ocvirk J.: Pomen sistemskega zdravljenja pri jetrnih zasevkih
Trotovšek B., Oblak I., Nina B.: Kirurgija in drugi načini zdravljenja jetrnih zasevkov raka debelega črevesa in danke

12.45-13.00 **SATELITNO PREDAVANJE 1**

13.00-13.45 Odmor za kosilo

13.45-14.00 **SATELITNO PREDAVANJE 2**

Moderatorji: prof. dr. Stojan Potrč, dr.med., asist. mag. Zvezdana Hlebanja, dr.med., izr. prof. dr. Irena Oblak, dr.med.

14.00-15.45 **MULTIDISCIPLINARNI PRISTOP K ZDRAVLJENJU BOLNIKA S KARCINOMOM TREBUŠNE SLINAVKE**

Ocvirk J.: Vloga neoadjuvantnega sistemskega zdravljenja
Potrč S.: Vloga kirurškega zdravljenja
***Oblak I.*:** Vloga radioterapije
***Hlebanja Z.*:** Vloga sistemske terapije pri napredovalem karcinomu trebušne slinavke
Šečerov-Ermenc A.: Primer bolnika s karcinomom trebušne linavke – SBRT

15.45-16.00 Odmor

Moderatorji: prof. dr. Mirko Omejc, dr.med., dr. Neva Volk, dr.med., izr. prof. dr. Irena Oblak, dr. med.

16.00-17.30 **MULTIDISCIPLINARNI PRISTOP K ZDRAVLJENJU BOLNIKA Z KARCINOMOM ŽELODCA**

Marko B.: Vloga perioperativnega in adjuvantnega sistemskega zdravljenja
Omejc M.: Vloga kirurgije
Oblak I.: Vloga radioterapije
Volk N.: Zdravljenje metastatskega karcinoma želodca
Hribernik N.: Novosti v sistemskem zdravljenju raka želodca in GEP – prikaz primera bolnika
Razprava

17.30-17.40 Odmor

Moderatorji: doc. dr. Blaž Trotovšek, dr.med., asist. dr. Tanja Mesti, dr.med., doc. dr. Peter Popović, dr.med.

17.40-18.50 **MULTIDISCIPLINARNI PRISTOP K ZDRAVLJENJU BOLNIKA S HCC**
Mesti T.: Vloga sistemskega zdravljenja
Trotovšek B.: Vloga kirurgije
Popović P.: Vloga interventne radiologije

18.50-20.20 **MULTIDISCIPLINARNI PRISTOP K ZDRAVLJENJU BOLNIKOV Z RAKI PREBAVIL – PRIKAZI PRIMEROV**

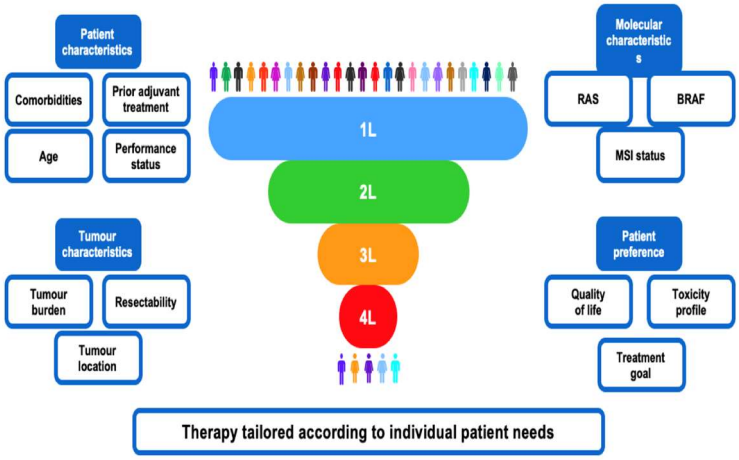
20.20-20.50 **SKLEPI IN ZAKLJUČEK SREČANJA**

NAPREDOVALI RAK DEBELEGA ČREVESA IN DANKE - KLINIČNA DOBROBIT ZDRAVLJENJA V III. IN KASNEJŠIH LINIJAH

asist. mag. Zvezdana Hlebanja, dr.med.
Zdravnica specialistka internistične onkologije

NAČIN ZDRAVLJENJA MCRC

- Določajo 4 glavne kategorije:
  - značilnosti bolnika,
  - značilnosti tumorja,
  - molekularne značilnosti tumorja,
  - bolnikove preference
- Terapija mora biti individualno prilagojena

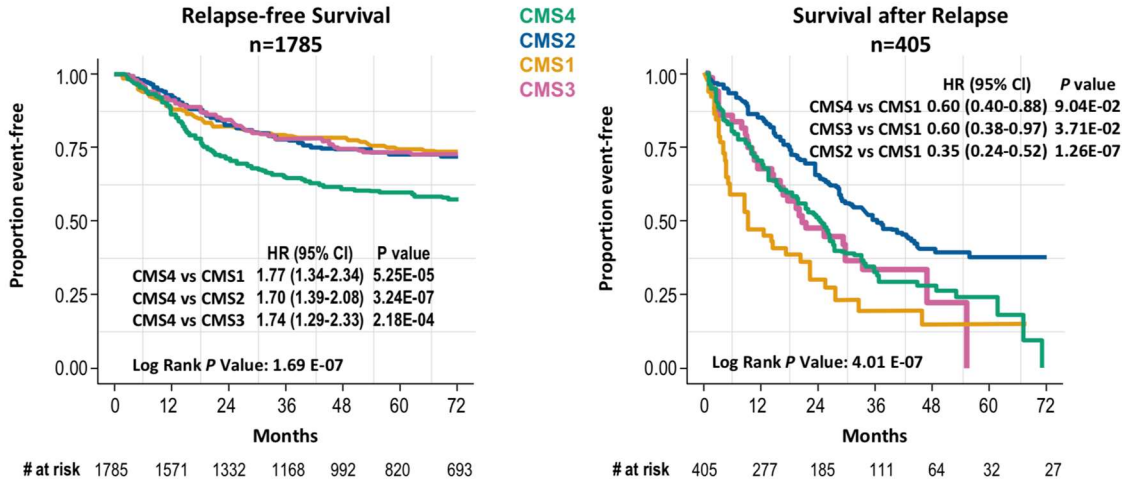


KOLOREKTALNI RAK JE VEČ KOT ENA BOLEZEN: BOLNIKE Z METASTATSKIM KOLOREKTALNIM RAKOM DELIMO V 4 MOLEKULARNE PODTIPE, KI IMAJO RAZLIČNE POTEKE:

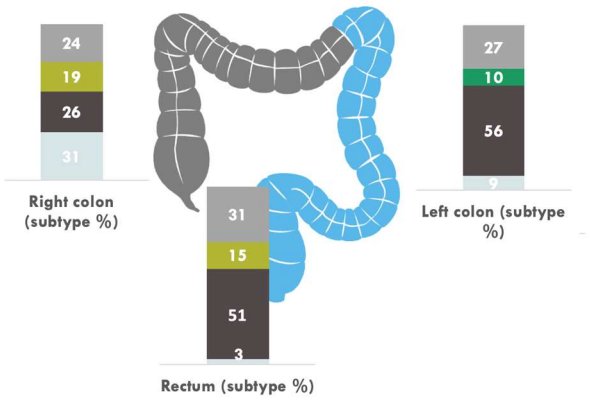
Key Features of the Consensus Molecular Subtypes (CMS)

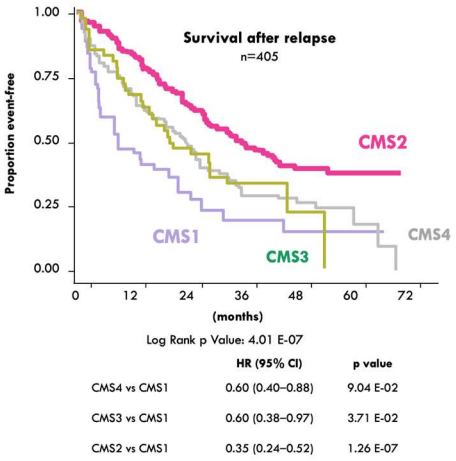
CMS1 MSI Immune	CMS2 Canonical	CMS3 Metabolic	CMS4 Mesenchymal
14%	37%	13%	23%
MSI, CIMP high Hypermutation	SCNA high	Mixed MSI status SCNA low, CIMP low	SCN high
BRAF mutations		*KRAS* mutations	
Immune infiltration and activation	WNT and MYC activation	Metabolic deregulation	Stromal infiltration TGF beta activation Angiogenesis
Worse survival after relapse	Better survival after relaspe		Worse relapse-free and overall survival

MOLEKULARNI PODTIPI MCRC NAPOVEDUJEJO DOLŽINO PREŽIVETJA IN ODGOVOR NA ZDRAVLJENJE



NAJBOLJŠO PROGNOZO IMAJO LEVO LEŽEČI TUMORJI ČREVESA S CMS2 MOLEKULARNO ZASNOVO!





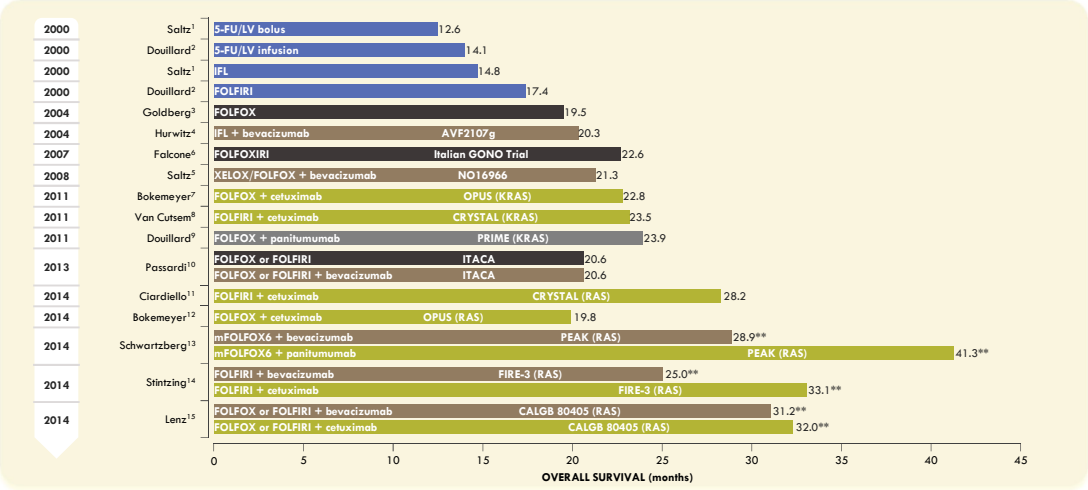
IZBIRA PRVOLINIJSKEGA ZDRAVLJENJA ODLOČILNO VPLIVA NA DOLŽINO CELOKUPNEGA PREŽIVETJA

Parameter*	**1st line[1–4]**	**2nd line[5–7]**	**Later lines[8,9]**
Response rate	**35–69%**	16–41%	1–22%
PFS	**8–14 months**	4–9 months	2–4 months
OS	**19–42 months**	11–21 months	6–10 months

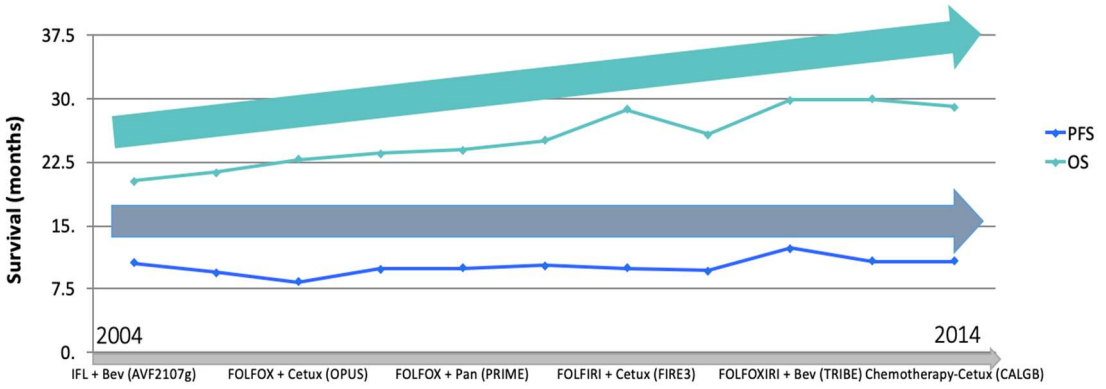
***Range of results for targeted treatment arms of key Phase II and III trials.**

1st line therapy is a critical determinant of OS[1–9]

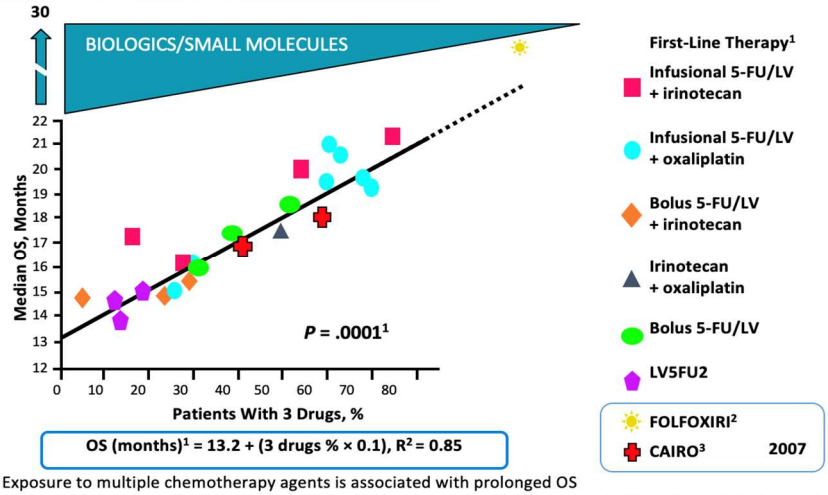
IZBOLJŠAVE V NAČINIH PRVOLINIJSKEGA ZDRAVLJENJA KAŽEJO IZBOLJŠAVO MOS



...VENDAR SE CELOKUPNO PREŽIVETJE MCRC PODALJŠUJE ZLASTI ZARADI UČINKOVITIH TERAPIJ V KASNEJŠIH LINIJAH ZDRAVLJENJA

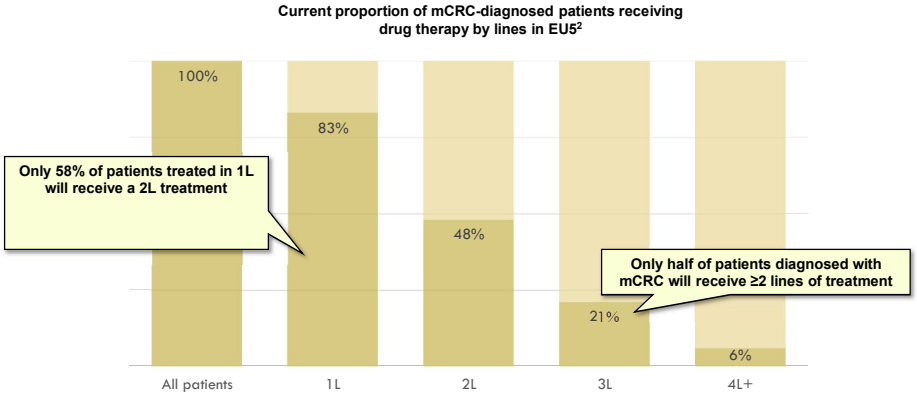


KOMBINIRANJE ZDRAVILNIH UČINKOVIN PODALJŠUJE CELOKUPNO PREŽIVETJE

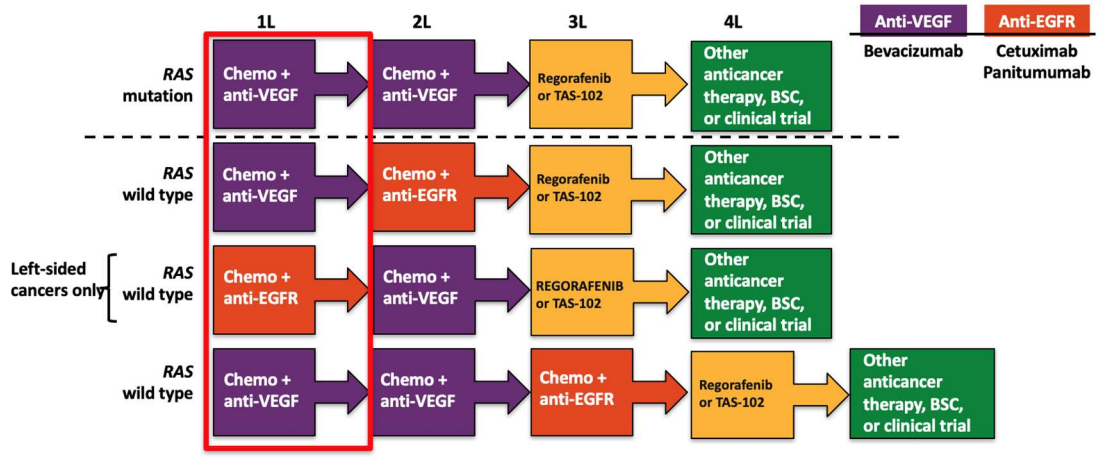


- Exposure to multiple chemotherapy agents is associated with prolonged OS
- Using multiple lines of therapy across a patient's disease course enables several different agents to be used

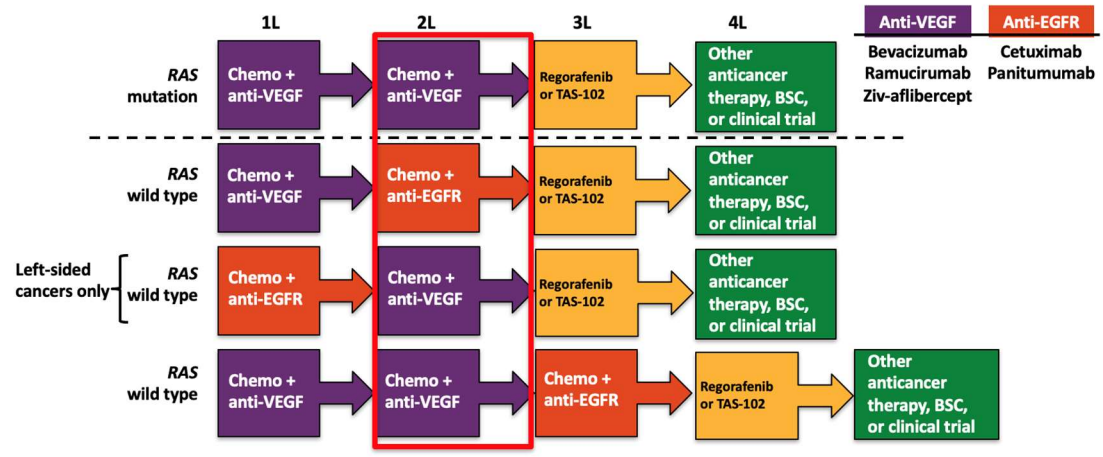
ZA VSAKO NADALJNO LINIJO ZDRAVLJENJA JE PRIMERNIH MANJ KANDIDATOV



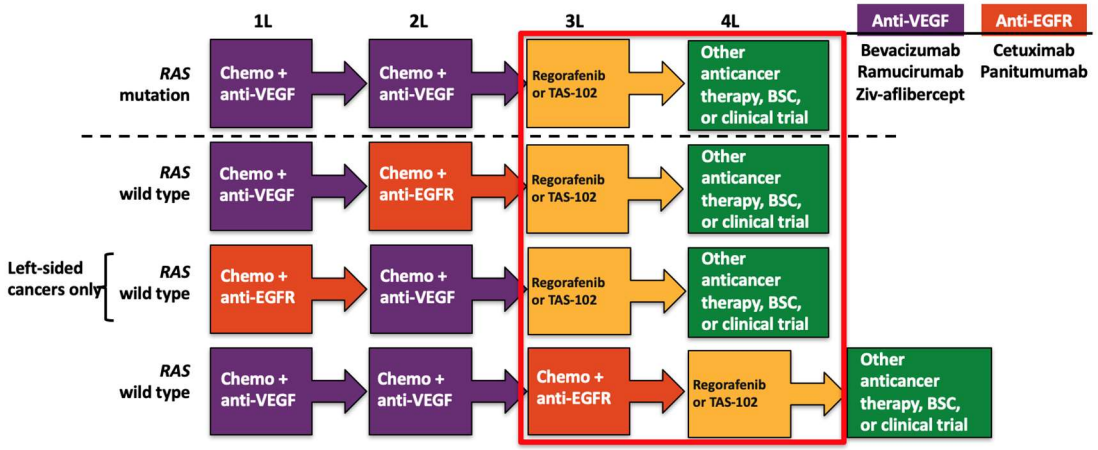
PRIPOROČILA ZA ODLOČITEV O ZDRAVLJENJU MCRC - I. LINIJA



PRIPOROČILA ZA ODLOČITEV O ZDRAVLJENJU MCRC - II. LINIJA



PRIPOROČILA ZA ODLOČITEV O ZDRAVLJENJU MCRC - III. IN NADALJNE LINIJE



ODLOČITEV O ZDRAVLJENJU V III. IN KASNEJŠIH LINIJAH

❖ Odločitev o vrstah zdravljenja metastatskega kolorektalnega raka v III. liniji je odvisno od kondicije bolnika, molekularnih značilnosti tumorja in od vrste predhodnih zdravljenj.

❖ Glede na priporočila prihajajo v poštev v III. liniji zdravljenja:

- TAS-102 (Lonsurf),
- Regorafenib (Stivarga),
- Za RAS nemutirane bolnike v izrazito dobri kondiciji pa tudi reindukcijsko zdravljenje z antiEGFR zdravili

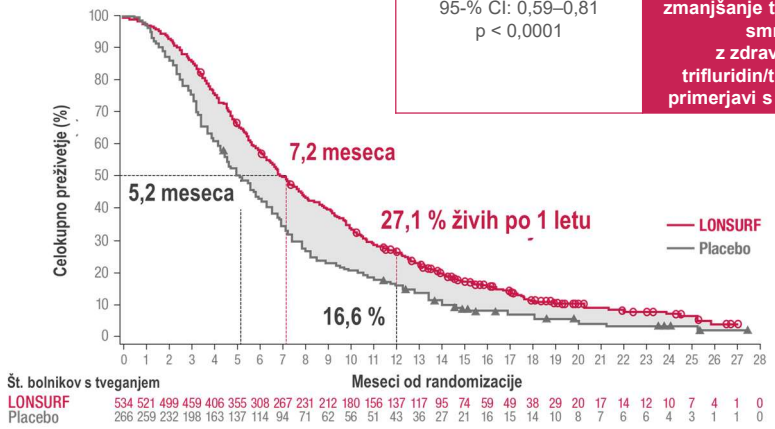
❖ TAS-102 (Lonsurf):

- Zdravilni učinkovini: trifluridin/tipiracil
- Je oralni citostatik iz skupine antimetabolitov
- Primeren za zdravljenje bolnikov v III. liniji, ki niso sposobni za intenzivno citostatsko zdravljenje
- Primeren tudi za srčne bolnike, saj ne povzroča koronarnih vazospazmov

TRIFLURIDIN/TIPIRACIL – POMEMBNO IZBOLJŠANJE MEDIANE OS PRI BOLNIKIH Z MKRR V III. LINIJI

HR 0,69
95-% CI: 0,59–0,81
p < 0,0001

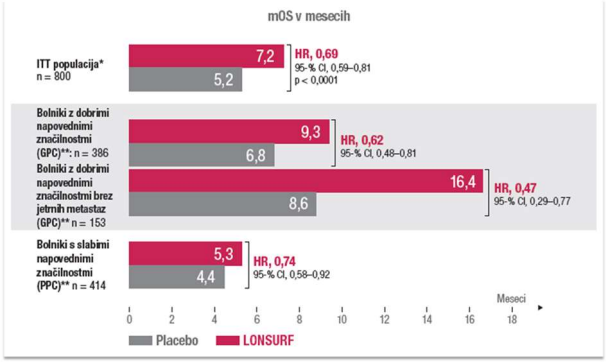
31-%
zmanjšanje tveganja za smrt z zdravilom trifluridin/tipiracil v primerjavi s placebom

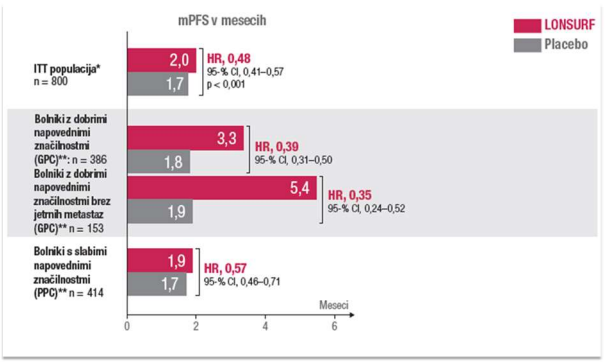


Izboljšanje mediane OS za 2 meseca
(7,2 meseca z zdravilom trifluridin/tipiracil v primerjavi s 5,2 meseca s placebom v posodobljeni analizi OS, 89 % dogodkov)[2]

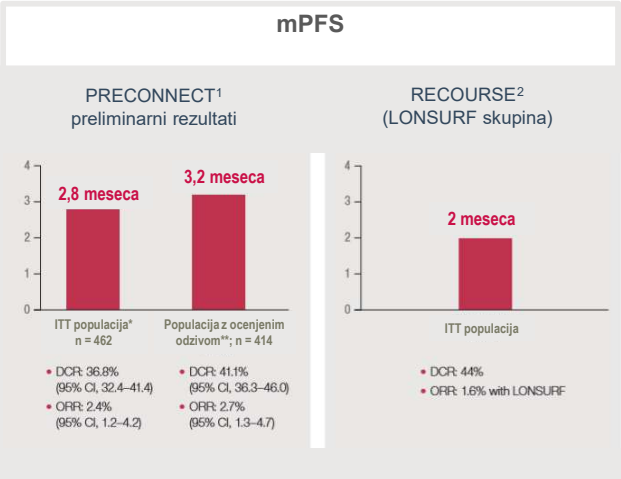
TRIFLURIDIN/TIPIRACIL – POMEMBNO PODALJŠA OS IN PFS PRI BOLNIKIH Z METASTATSKIM KOLOREKTALNIM RAKOM

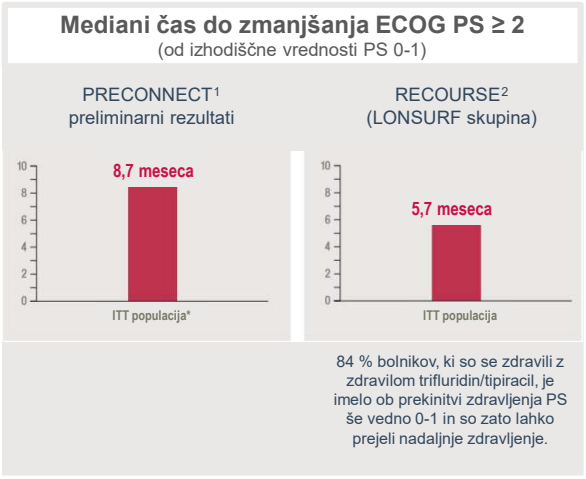
- Učinkovitost zdravila trifluridin/tipiracil je bila dokazana pri vseh podskupinah bolnikov z mKRR





RAZISKAVA PRECONNECT - DODATNI DOKAZI O UČINKOVITOSTI ZDRAVILA TRIFLURIDIN/TIPIRACIL

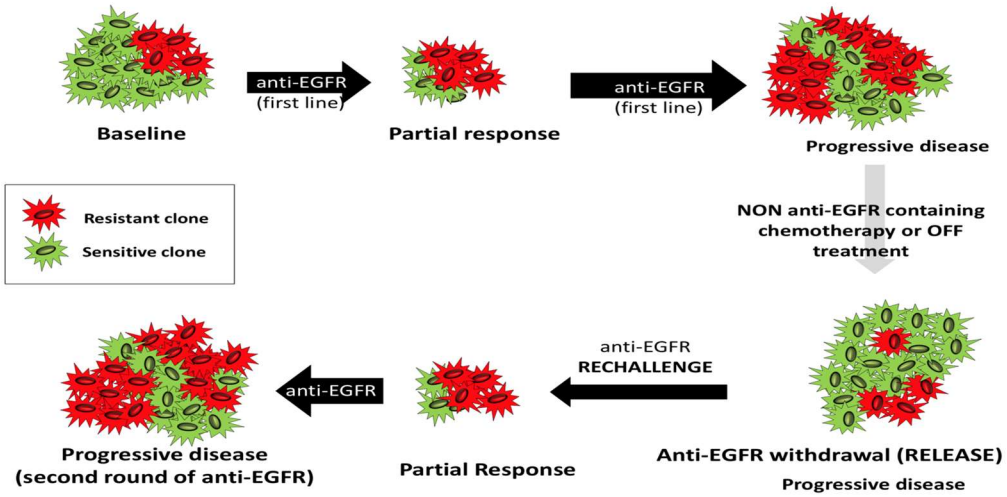




REINDUKCIJSKO ZDRAVLJENJE Z ANTI-EGFR ZDRAVILI

- Za RAS nemutirane bolnike v izrazito dobri kondiciji, brez hujših pridruženih bolezni, prihaja v III. liniji zdravljenja v poštev reindukcijsko zdravljenje z antiEGFR zdravili
- Tovrstno zdravljenje je smiselno pri bolnikih, ki so izrazito dobro odgovorili na prvolinijsko zdravljenje z antiEGFR zdravili, in so v II. liniji prejeli zdravljenje z drugačnim citostatikom +- drugačnim biološkim zdravilom
- Njihov RAS status mora ostati nemutiran

HIPOTEZA KLONALNE DINAMIKE MED ZDRAVLJENJEM Z ANTI-EGFR ZDRAVILI

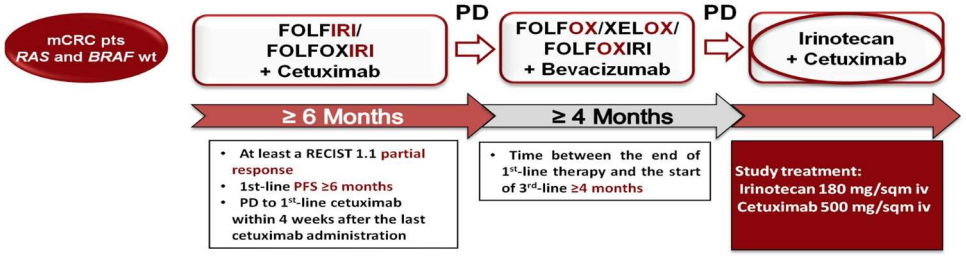


CRICKET ŠTUDIJA - DOKAZI O UČINKOVITOSTI REINDUKCIJE Z ANTI-EGFR ZDRAVILI

Phase II, non comparative, study

Target accrual: 27 pts

CRICKET



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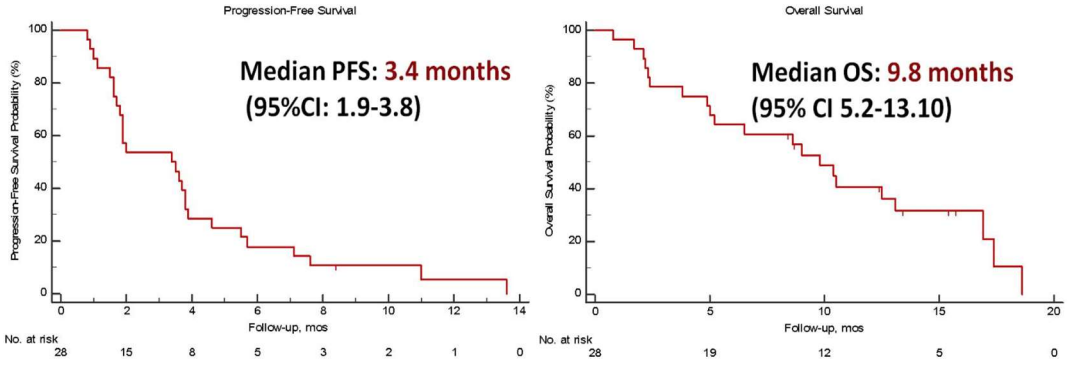
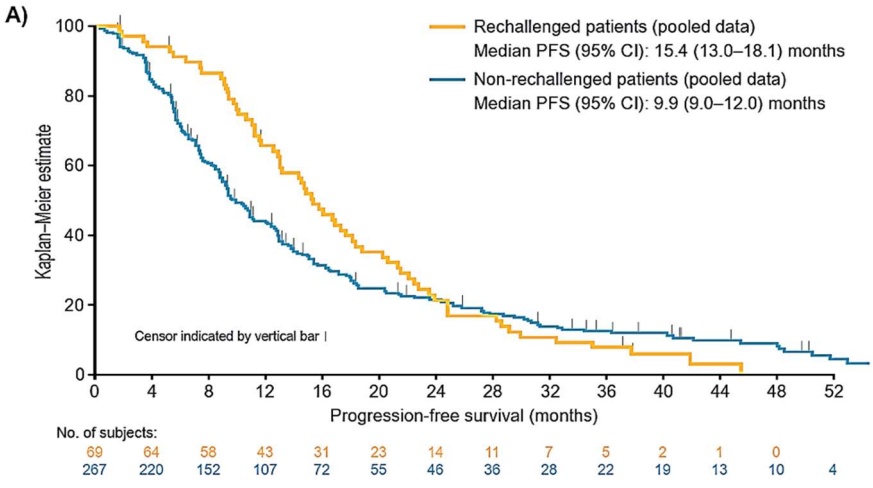
CRICKET ŠTUDIJA - DOKAZI O UČINKOVITOSTI REINDUKCIJE Z ANTI-EGFR ZDRAVILI

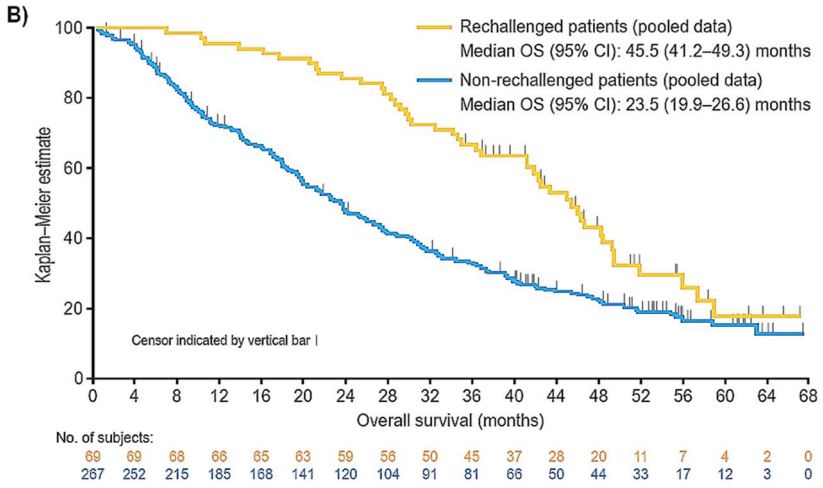


Presented By Daniele Rossini at 2018 ASCO Annual Meeting

PFS BOLNIKOV REINDUKCIJSKO ZDRAVLJENIH Z ANTI-EGFR (PRIME, PEAK - RETROSPEKTIVNA ANALIZA)

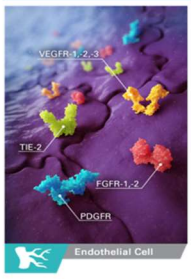


OS BOLNIKOV REINDUKCIJSKO ZDRAVLJENIH Z ANTI-EGFR (PRIME, PEAK - RETROSPEKTIVNA ANALIZA)



MULTITARČNI TIROZIN KINAZNI INHIBITOR REGORAFENIB IMA ŠTEVILNE PROTITUMORSKE ZNAČILNOSTI

ANTIANGIOGENIC

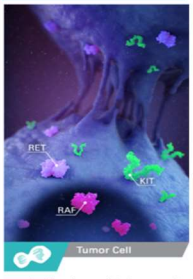


Inhibits key angiogenic receptors **VEGFR-1, -2, -3, TIE-2, PDGFR, and FGFR-1 and -2** via kinase inhibition[2,3]

ANTI-IMMUNOSUPPRESSIVE

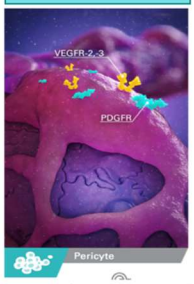
Disrupts tumor immunity by inhibiting **CSFR-1**, a receptor important for tumor-associated macrophage differentiation and recruitment[4,5]

ANTIPROLIFERATIVE



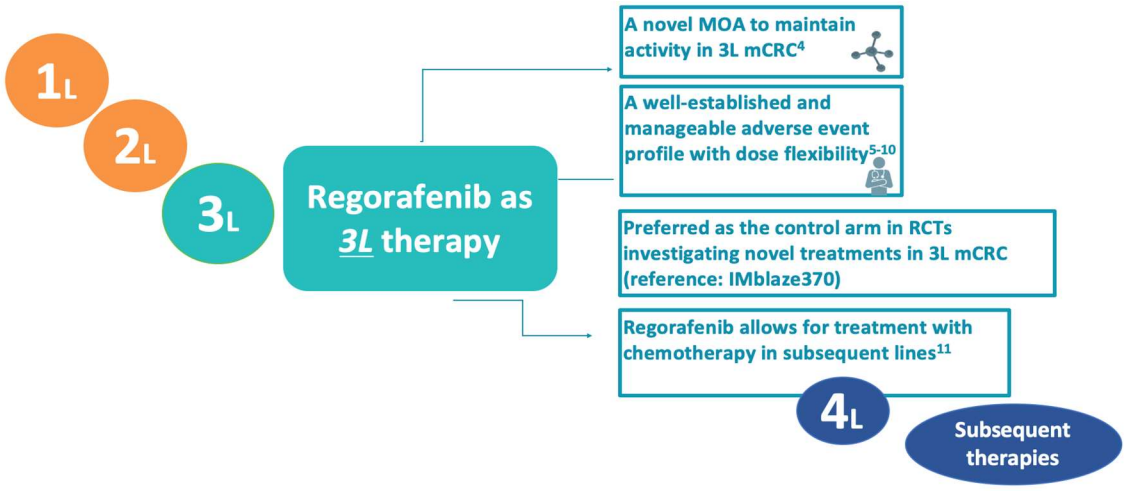
Potently blocks multiple protein kinases, including **KIT, RAF, and RET**, which are important in cell proliferation[2,3,6]

ANTIMETASTATIC

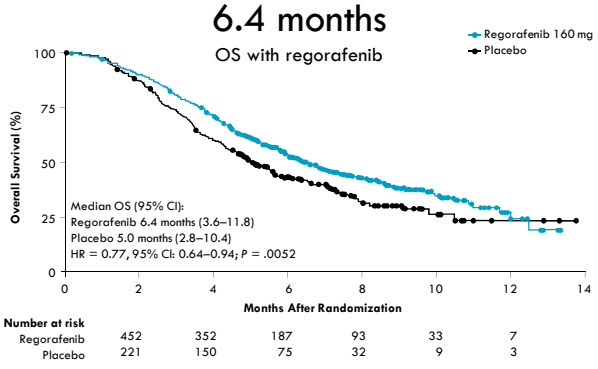


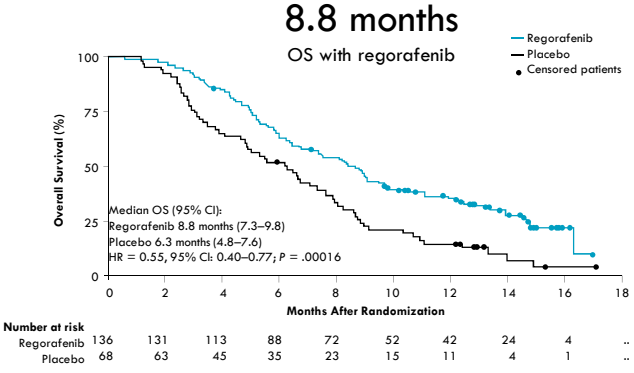
Inhibits **VEGFR-2 and -3**, important mediators involved in endothelial cell proliferation and migration
Blocks **PDGFR**, believed to play a role in cancer-associated fibroblast-induced metastasis[2,7,8]

PRIPOROČILA SVETUJEJO REGORAFENIB V III. LINIJI ZDRAVLJENJA, ZA DOVOLJ FIT BOLNIKE, **NE** GLEDE NA RAS STATUS



REGISTRACIJSKI ŠTUDIJI ZA REGORAFENIB: CORRECT IN CONCUR

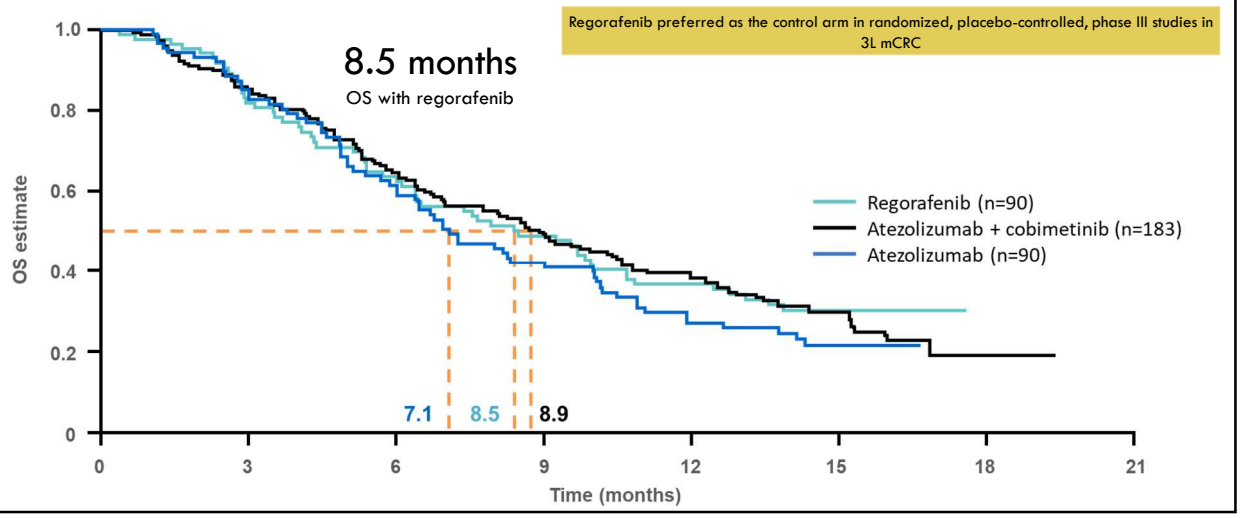




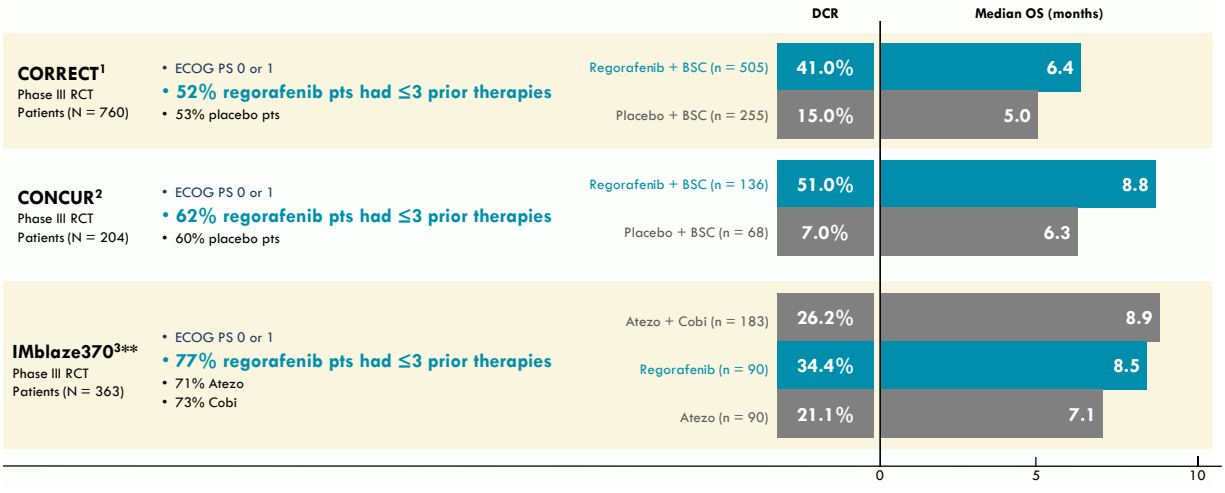
CORRECT[1]: **23% reduction in the risk of death** (primary endpoint)

CONCUR[2]: **45% reduction in the risk of death** (primary endpoint)

REZULTATI NOVEJŠE RAZISKAVE FAZE III BOLNIKOV ZDRAVLJENIH Z REGORAFENIBOM: IMBLAZE370

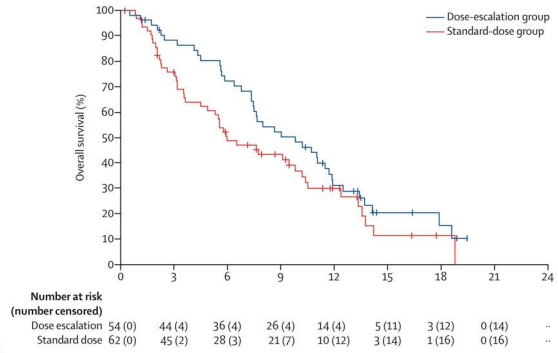


DOBROBIT ZDRAVLJENJA Z REGORAFENIBOM JE VEČJA PRI BOLNIKIH Z MANJ PREDHODNIMI LINIJAMI ZDRAVLJENJA

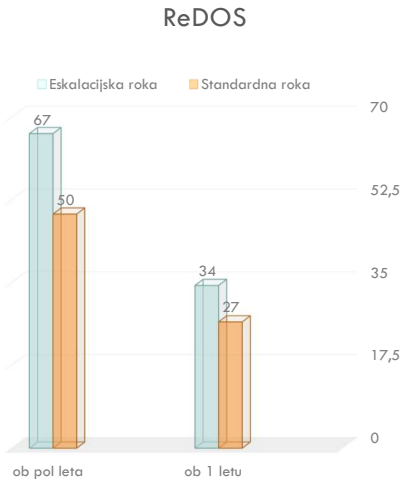


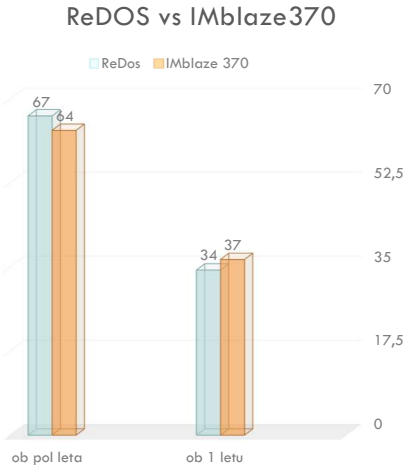
NAJNOVEJŠA KLINIČNA RAZISKAVA BOLNIKOV ZDRAVLJENIH Z REGORAFENIBOM - REDOS

- Študija ReDOS je ob skrbnem uvajanju odmerkov regorafeniba dokazala še daljša preživetja.
- Dokazali so, da je smiselno zdravljenje z regorafenibom začeti s polovičnim odmerkom (80mg), ter le tega postopno zviševati, v kolikor so bolniki to prenesli.
- V primerjavi z bolniki, ki so začeli zdravljenje s polnim odmerkom (160mg), so imeli bolniki v eskalacijski roki daljše mOS.
- mOS za eskalacijsko roko je 9.8 meseca, za standardno roko pa 6 mesecev



PREŽIVETJE PRI POL LETA IN ENEM LETU!





ZAKLJUČEK

- Napredovali kolorektalni rak ni ena bolezen
- Molekularni podtipi napovedujejo potek bolezni, kot tudi odgovor na zdravljenje, tako s citostatiki kot z biološkimi zdravili
- Boljša preživetja teh bolnikov so posledica novih načinov zdravljenja, predvsem pa posledica več linijskega zdravljenja
- Število bolnikov primernih za sistemsko zdravljenje se z vsako nadaljnjo linijo zdravljenja zmanjšuje
- Prvolinijsko zdravljenje prinese največ k celokupnemu preživetju (običajno dvojček ali trojček citostatikov + biološko zdravilo)
- Drugolinijsko zdravljenje (običajno zamenjamo tako citostatik v dvojčku kot biološko zdravilo)

ZAKLJUČEK

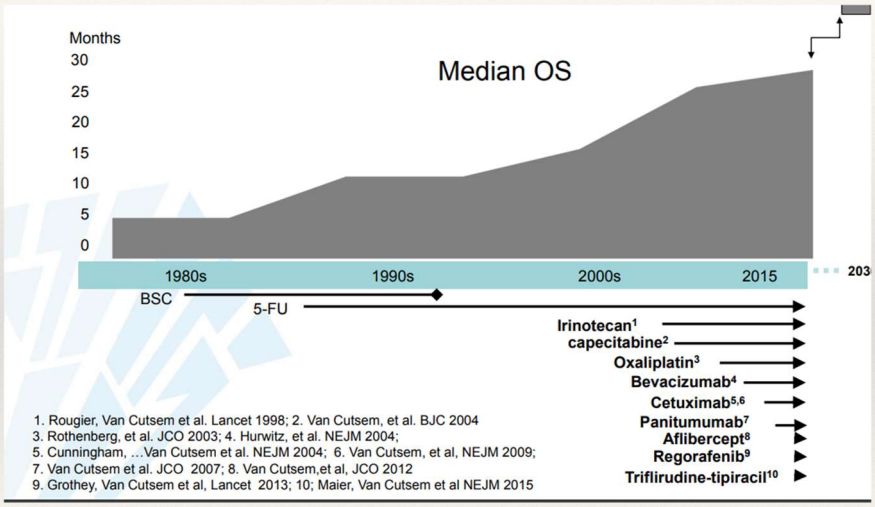
- V III. liniji zdravljenja bolnikov z metastatskim kolorektalnim rakom je le to odvisno od PS bolnika, pridruženih bolezni, ciljev zdravljenja, preferenc bolnika in narave tumorja
- Na voljo je reindukcijsko zdravljenje z antiEGFR zdravili za bolnike v odlični kondiciji, z RAS nemutiranimi tumorji
- Dva nova agensa: TAS-102 in regorafenib, sta primerna v III. liniji zdravljenja predvsem za bolnike z refraktarnimi tumorji in običajno vodita v stabilizacijo bolezni
- TAS-102 / Lonsurf je citostatik (kombinacija trifluridin/tipiracila), je peroralno zdravilo, primerno za bolnike, ki niso sposobni za intenzivno citostatsko zdravljenje in tiste s pridruženo srčno boleznijo
- Regorafenib / Stivarga je multitarčni tirozin kinazni inhibitor, peroralno zdravilo, primeren za bolnike v dobri kondiciji (PS>2), ne glede na RAS status
- Preživetja bolnikov zdravljenih z regorafenibom se glede na zadnje študije podaljšujejo, ker bolnikom prilagajamo uvajalno dozo, ker zdravilo dobijo bolniki v dobri kondiciji, v zgodnejših linijah zdravljenja, ter zaradi boljšega obvladovanja toksičnih sopojavov

Individualen pristop k odmerjanju zdravil v poznih linijah zdravljenja napredovalega raka debelega črevesa in danke

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

9. šola tumorjev prebavil, 22.11.2019

Sistemsko zdravljenje mRDČD skozi čas



Tretja linija zdravljenja metastatskega raka debelega črevesa in danke

- Po progresu na KT z fluoropirimidini, oksaliplatinom in irinotekanom, v kombinaciji z tarčnimi zdravili (anti VEGF, anti EGFR) v EU dodatne možnosti zdravljenja:

regorafenib (EMA 2013)

trifluridin tipiracil hidroklorid (EMA 2016)

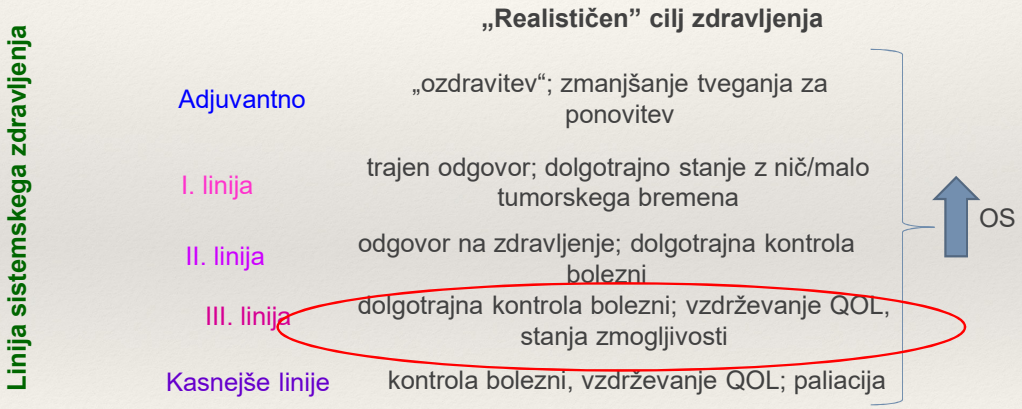
pa tudi „rechallenge“ koncept: sekvenca?

Table 7. Systemic therapy choices according to the Zurich treatment algorithm for patients with unresectable metastatic disease (excluding those with oligometastatic disease)[a]

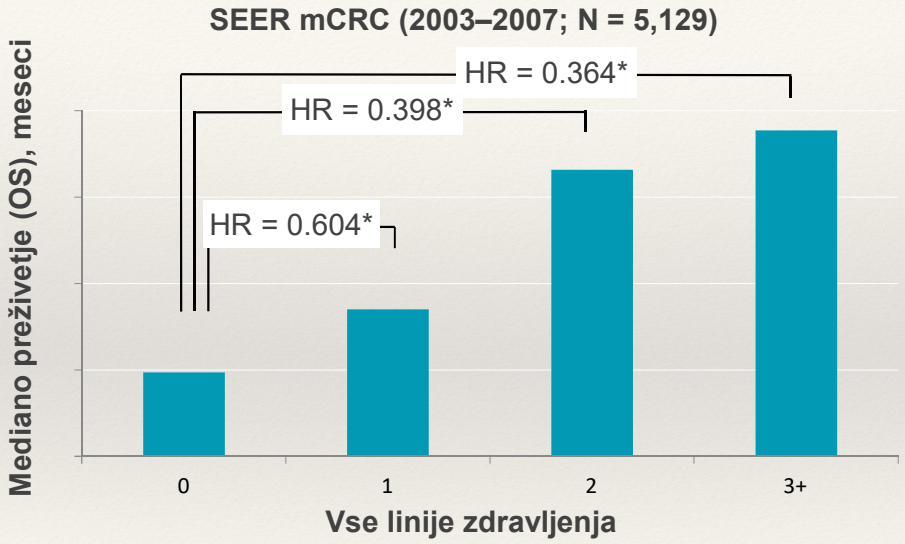
Category	Fit patients[b]					
Treatment goal	Cytoreduction (tumour shrinkage)			Disease control (control of progression)		
Molecular profile	*RAS* wt	*RAS* mt	*BRAF* mt	*RAS* wt	*RAS* mt	*BRAF* mt
Third line						
Preferred choice (s)	CT doublet + EGFR antibody[c,d] or irinotecan + cetuximab[f]	Regorafenib or trifluridine/ tipiracil	Regorafenib or trifluridine/ tipiracil	CT doublet + EGFR antibody[f] or irinotecan + cetuximab	Regorafenib or trifluridine/tipiracil	Regorafenib or trifluridine/tipiracil
Second choice	EGFR antibody monotherapy[f]			EGFR antibody monotherapy[f]		
Third choice	Regorafenib or trifluridine/ tipiracil			Regorafenib or trifluridine/ tipiracil		

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

Cilji zdravljenja se spreminjajo glede na linijo zdravljenja

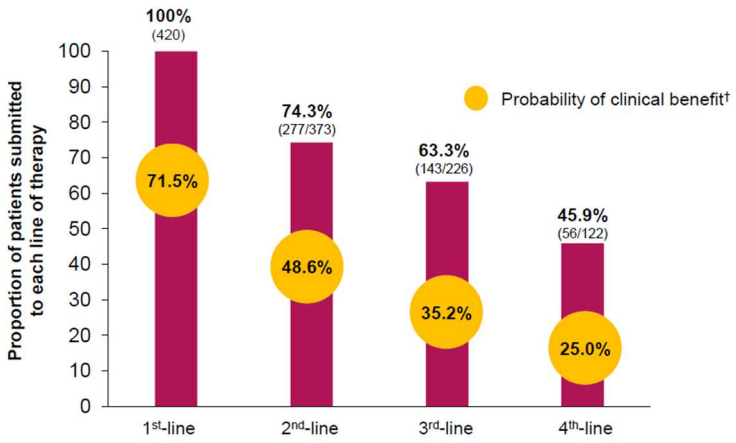


Več linij zdravljenja – daljše preživetje



HR, hazard ratio; SEER, Surveillance, Epidemiology, and End Results.
Hanna N, et al. *J Clin Oncol.* 2014;32(suppl 3):abstract 559.

Deleži bolnikov z mCRC po linijah zdravljenja in verjetnost klinične dobrobiti



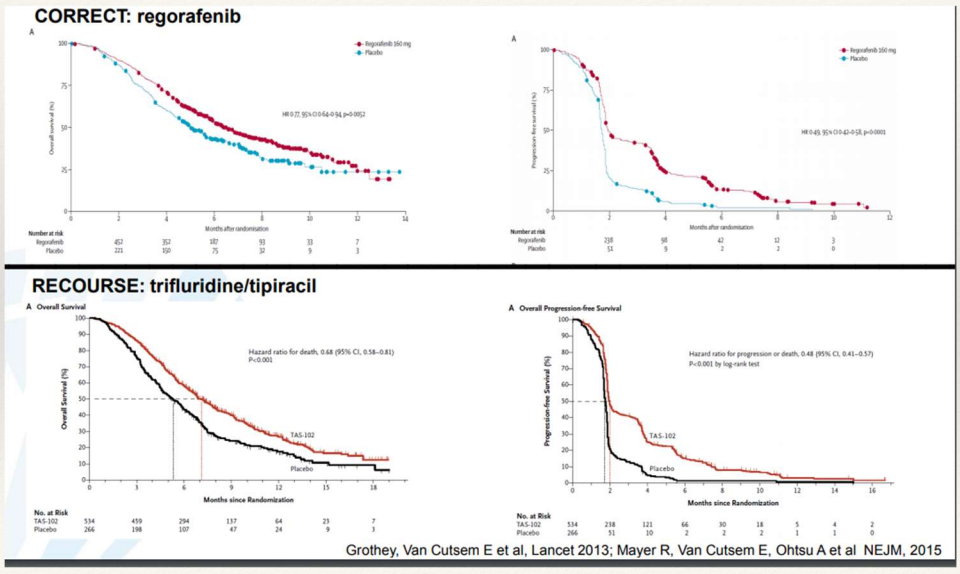
Tampellini M et al. Clin colorectal Cancer 2017; 16. 372-6

Izbor bolnikov za 3. linijo

- Ni posebnih kriterijev za izbor bolnikov – (PS, starost, komorbidnost; cilji zdravljenja in preference bolnika, predhodne linije in posledice….); dejavniki, pomembni za izbor 1. linije >> pomembnejši za izbor 3. in kasnejših linij
- Ni pomemben RAS status, lokacija primarnega tumorja

Bekaii-Saab T et al. Clin Colorectal Cancer, Volume 18, Issue 1, e117 - e129

Regorafenib in trifluridin/tipiracil v zdravljenju mRDČD



Grothey, Van Cutsem E et al, Lancet 2013; Mayer R, Van Cutsem E, Ohtsu A et al NEJM, 2015

Stable Disease Is a Rational Therapeutic Goal with Increasing Lines of Treatment

Phase III trials		Objective Response Rates and Stable Disease	
		ORR = CR + PR, %	SD, %
1L	FOLFIRI ± cetuximab[1,*]	57	NR
	FOLFOX4 ± panitumumab[2,*]	55	NR
	FOLFOX4/XELOX ± bevacizumab[3]	38	NR
2L	FOLFOX4 + bevacizumab[4]	23	NR
	FOLFIRI ± panitumumab[5,*]	35	39
	CT + continued bevacizumab[6]	5	63
	FOLFIRI + aflibercept[7]	20	66
	FOLFIRI + ramucirumab[8,9]	13	61
3–4L	Regorafenib[10]	CORRECT 1%	40%
	Regorafenib[11]	CONCUR 4%	47%
	TAS-102[12]	2	42

Note: Informal comparison as these are not head-to-head clinical trials. *KRAS wild-type subset.

1. Van Cutsem E, et al. *J Clin Oncol.* 2011;29(15): 2011-2019; 2. Douillard, J-Y, et al. *J Clin Oncol.* 2010;28(31):4697-4705; 3. Saltz LB, et al. *J Clin Oncol.* 2008;26(12):2013-2019; 4. Giantonio BJ, et al. *J Clin Oncol.* 2007;25(12)1539-1544; 5. Peeters M, et al. *J Clin Oncol.* 2010;28(31):4706-4713; 6. Bennouna J, et al. *Lancet Oncol.* 2013;14(1):29-37; 7. Van Cutsem E, et al. *J Clin Oncol.* 2012;30(28):3499-3506; 8. Tabernero J, et al. ASCO GI 2015. Abstract 512; 9. Ramucirumab [summary of product characteristics]. Houten, The Netherlands: Eli Lilly Nederland B.V.; 2014; 10. Grothey A, Van Cutsem E, et al. *Lancet*. 2013;381(9863):303-312; 11. Li J, et al. *Lancet Oncol*. 2015;16(6):619-629; 12. Mayer J, et al. *N Engl J Med*. 2015;372(20):1909-1919.

Optimalna sekvenca?

REGORAFENIB → TRIFLURIDIN - TIPIRACIL

TRIFLURIDIN - TIPIRACIL → REGORAFENIB

Varnostni profil različen, ni pa drugih napovednih dejavnikov za izbor, tudi ni posebnih skupin bolnikov, bolj primernih za določeno zdravljenje

Regorafenib

- Dozirna shema 160 mg/dan 3 tedne, nato en teden pavze.
- Toda: samo 20% bolnikov tolerira 160 mg permanentno, potrebne prilagoditve uvajalnega odmereka zaradi NU, zlasti SRN in utrudljivosti[1,2,3]
- **76% bolnikov v študiji CORRECT mora modificirati odmerek[1]**
- **70% bolnikov vsaj enkrat prekine jemanje regorafeniba**

1. Grothey A, Van Custem E, Sobrero A, et al. Lancet. 2013; 381: 303-312
2. Li J, Qin S, Xu R et al. Lancet Oncol. 2015 Jun;16(6):619-29
3. Eng C et al. Lancet Oncol. 2019 Jun;20(6):849-861

Odmerek regorafeniba

- Priporočeni uvodni odmerek regorafeniba – v raziskavah ni primeren za vse bolnike, zato zasnovanih več raziskav o primernejšem režimu uvajanja zdravila
- Izboljšanje prenosljivosti, hkrati obdržati učinkovitost zdravila (prof. Grothey, Mayo) → raziskava ReDOS: začetni odmerek 80mg Stivarge® = 50% odmerek

Bekaii-Saab TS et al. Lancet Oncol. 2019 Aug;20(8):1070-1082

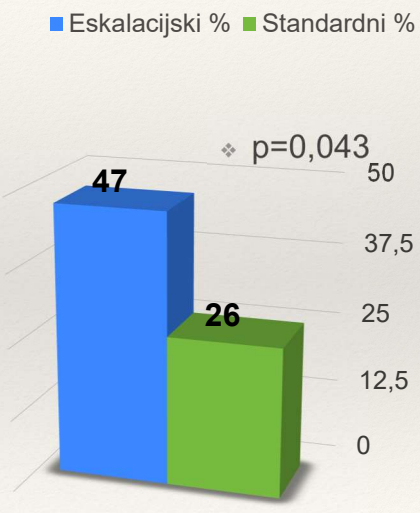
Raziskava ReDOS

- **Randomizirana, odprta faza II**
  - **R.1 eskalacijski** z začetnim polovičnim odmerkom, ki se tedensko zvišuje. **80mg ➞ 120mg ➞ 160mg**
  - **R.2 standardni** način z začetnim priporočenim odmerkom **160 mg**
- Trajanje: 3 tedne, nato teden pavze
- **V obeh rokah se 2. cikel začne z odmerkom, ki se v 1. ciklu pokaže kot maksimalno tolerabilen**
- Pri obeh rokah se odmerek modificira glede na pojav NU

Bekaii-Saab TS et al. Lancet Oncol. 2019 Aug;20(8):1070-1082

ReDOS
Primarni cilj: delež bolnikov, ki je zaključil 2 ciklusa zdravljenja v 8 tednih in vstopil v 3. cikel

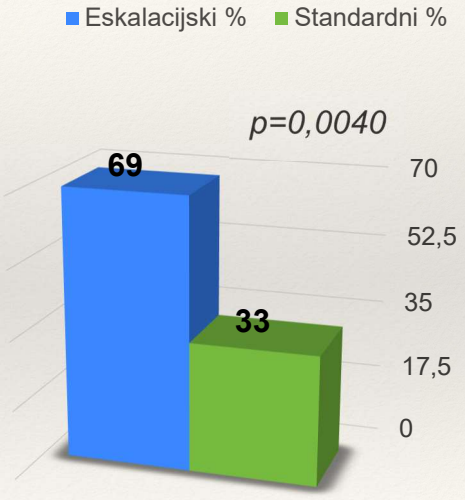
- 116 bolnikov, od tega v 3. cikel vstopi:
- v eskalacijski roki: 23 bolnikov od 54 - **47%**
- v standardni roki: 16 bolnikov od 62 - **26%**
- **Delež bolnikov, ki je začel 3. ciklus zdravljenja značilno višji v eskalacijski roki**



Bekaii-Saab TS et al. Lancet Oncol. 2019 Aug;20(8):1070-1082

ReDOS
Bolniki, ki niso vstopili v 3. cikel zdravljenja s Stivargo, a do dobili naslednjo terapijo

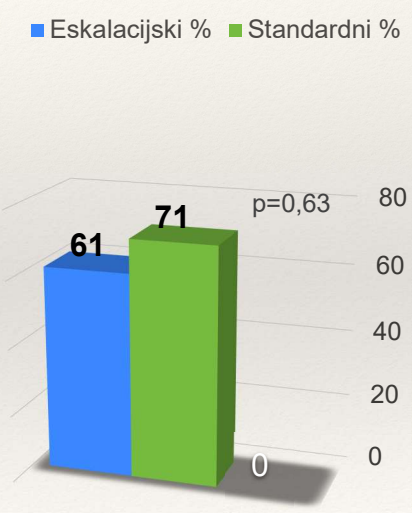
- V eskalacijski roki:
  18 bolnikov od 26 - **69%**
- V standardni roki:
  14 bolnikov od 42 - **33%**



Bekaii-Saab TS et al. Lancet Oncol. 2019 Aug;20(8):1070-1082

ReDOS
Bolniki, ki so vstopili v 3. cikel s Stivargo in so dobili nadaljno terapijo

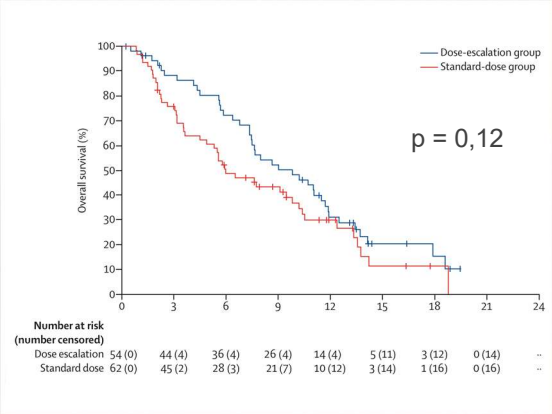
- V eskalacijski roki:
  11 od 18 bolnikov (61%)
- V standardni roki:
  5 od 7 bolnikov (71%)



Bekaii-Saab TS et al. Lancet Oncol. 2019 Aug;20(8):1070-1082

ReDOS - sekundarni cilj: mOS

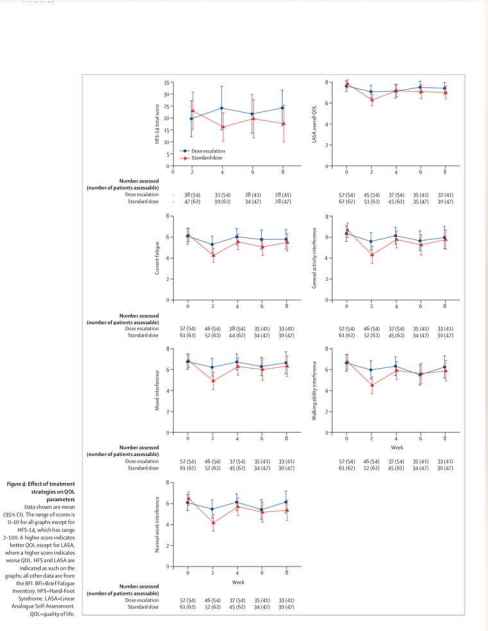
- **Preživetje v okviru pričakovanega (CORRECT)**
- **Eskalacijska roka: mOS 9,8 mes.**
- **Standardna roka: mOS 6,0 mes.**



Bekaii-Saab TS et al. Lancet Oncol. 2019 Aug;20(8):1070-1082

ReDOS: kvaliteta življenja

- Celokupno imajo bolniki v eskalacijski roki **boljšo kvaliteto življenja**, čeprav neznačilno.
- **Zlasti drugi teden** je v eskalacijski roki kvaliteta življenja boljša (manjša kumulacija metabolitov)



Bekaii-Saab TS et al. Lancet Oncol. 2019 Aug;20(8):1070-1082

ReDOS: varnost

- Varnost v obeh rokah je primerljiva
- V eskalacijski roki je manj utrudljivosti, SRN in hipertenzije gr. 3
- V eskalacijski roki je več abdominalne bolečine gr. 3.
- **Prva 2 ciklusa v eskalacijski roki je manj hipertenzije, utrudljivosti, SRN in driske.**

	Dose-escalation group (n=54)				Standard-dose group (n=62)			
	Grade 1-2	Grade 3	Grade 4	Grade 5	Grade 1-2	Grade 3	Grade 4	Grade 5
Fatigue	42 (78%)	7 (13%)	0	0	44 (71%)	11 (18%)	0	0
Hand-foot skin reaction	27 (50%)	8 (15%)	0	0	33 (53%)	10 (16%)	0	0
Hypertension	34 (63%)	4 (7%)	0	0	29 (47%)	9 (15%)	0	0
Nausea	23 (43%)	0	0	0	31 (50%)	0	0	0
Diarrhoea	23 (43%)	1 (2%)	0	0	25 (40%)	2 (3%)	0	0
Anorexia	14 (26%)	1 (2%)	0	0	16 (26%)	2 (3%)	0	0
Rash maculopapular	10 (19%)	0	0	0	16 (26%)	3 (5%)	0	0
Vomiting	13 (24%)	0	0	0	14 (23%)	1 (2%)	0	0
Blood bilirubin increased	7 (13%)	2 (4%)	0	0	13 (21%)	5 (8%)	0	0
Anaemia	12 (22%)	1 (2%)	0	0	12 (19%)	1 (2%)	0	0
Aspartate aminotransferase increased	8 (15%)	1 (2%)	0	0	12 (19%)	4 (6%)	0	0
Alkaline phosphatase increased	6 (11%)	3 (6%)	0	0	10 (16%)	1 (2%)	1 (2%)	0
Abdominal pain	1 (2%)	9 (17%)	0	0	5 (8%)	4 (6%)	0	0
Dysgeusia	5 (9%)	1 (2%)	1 (2%)	0	8 (13%)	4 (6%)	0	0
Alanine aminotransferase increased	8 (15%)	0	0	0	8 (13%)	1 (2%)	0	0
Hoarseness	8 (15%)	0	0	0	8 (13%)	0	0	0
Weight loss	4 (7%)	1 (2%)	0	0	10 (16%)	1 (2%)	0	0
Hyponatremia	0	2 (4%)	1 (2%)	0	7 (11%)	4 (6%)	1 (2%)	0
Platelet count decreased	7 (13%)	0	0	0	8 (13%)	0	0	0
Mucositis oral	4 (7%)	1 (2%)	0	0	8 (13%)	1 (2%)	0	0
Hypoalbuminemia	5 (9%)	1 (2%)	0	0	7 (11%)	0	0	0
Peripheral sensory neuropathy	6 (11%)	0	0	0	6 (10%)	0	0	0
Lymphocyte count decreased	1 (2%)	4 (7%)	0	0	6 (10%)	0	0	0
Hypocalcaemia	6 (11%)	0	0	0	3 (5%)	1 (2%)	0	0
Hypokalaemia	3 (6%)	1 (2%)	0	0	5 (8%)	0	1 (2%)	0
Generalised muscle weakness	5 (9%)	1 (2%)	0	0	2 (3%)	1 (2%)	0	0
Myalgia	0	1 (2%)	0	0	6 (10%)	2 (3%)	0	0
Pain	5 (9%)	0	0	0	3 (5%)	1 (2%)	0	0
Dehydration	1 (2%)	0	0	0	2 (3%)	5 (8%)	0	0
Investigations, other (specified)	3 (6%)	0	0	0	4 (6%)	1 (2%)	0	0
Back pain	1 (2%)	1 (2%)	0	0	5 (8%)	0	0	0
Dry skin	1 (2%)	1 (2%)	0	0	3 (5%)	0	0	0
Neoplasms: benign, malignant, unspecified, other (specified)	0	0	0	2 (4%)	0	0	0	2 (3%)
Colonic obstruction	0	3 (6%)	0	0	0	0	0	0
Hyperglycaemia	1 (2%)	1 (2%)	0	0	0	1 (2%)	0	0
Hyperkalaemia	1 (2%)	0	0	0	1 (2%)	1 (2%)	0	0
Sinus tachycardia	0	1 (2%)	0	0	1 (2%)	1 (2%)	0	0
Ascites	1 (2%)	1 (2%)	0	0	0	0	0	0
Chest wall pain	0	1 (2%)	0	0	1 (2%)	0	0	0
Death not otherwise specified	0	0	0	1 (2%)	0	0	0	1 (2%)
Encephalopathy	0	0	0	0	0	2 (3%)	0	0
Respiratory failure	0	0	1 (2%)	0	0	0	0	1 (2%)
Sepsis	0	0	1 (2%)	0	0	0	1 (2%)	0
Thromboembolic event	1 (2%)	1 (2%)	0	0	0	0	0	0
Abdominal infection	0	1 (2%)	0	0	0	0	0	0
Adult respiratory distress syndrome	0	0	1 (2%)	0	0	0	0	0
Atelectasis	0	0	0	0	0	1 (2%)	0	0
Colitis	0	1 (2%)	0	0	0	0	0	0
Confusion	0	0	0	0	0	1 (2%)	0	0
Hepatic failure	0	0	0	0	0	0	1 (2%)	0

(Table 2 continues on next page)

Bekaii-Saab TS et al. Lancet Oncol. 2019 Aug;20(8):1070-1082

1. alternativni način odmerjanja regorafeniba

- 80 mg odmerek varen in učinkovit alternativni način za uvedbo; večje število bolnikov na ta način dobi 3. cikel zdravljenja, ki ga bolje tolerirajo. V eskalacijski roki dobi več bolnikov nadaljno terapijo kot v standarni - višje mOS v eskalacijski skupini

Bekaii-Saab T et al. Clin Colorectal Cancer, Volume 18, Issue 1, e117 - e129

Konsenz ekpertov 2019

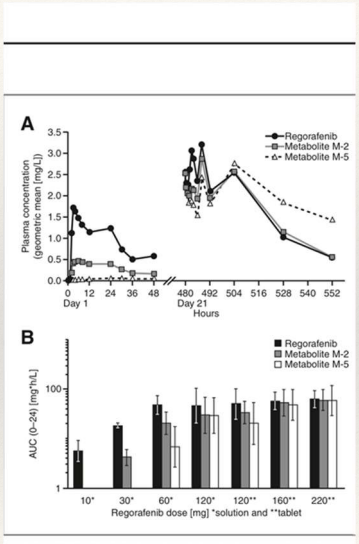
- Alternativne sheme odmerjanja niso odobrene[1]
- Prekiniti zdravljenje pri resnih ali življenje ogrožajočih NU gr ≥ 3, simptomatski hipertenziji gr ≥2, ali SRN gr 2, ki ne izzveni v 1 tednu po redukciji odmerka. Ponovna uvedba regorafeniba: odmerek zmanjšati za 40 mg[2]
- Prekiniti zdravljenje, če bolnik odmerka 80 mg ne tolerira ali v primeru življenje ogrožajoče hepatotoksičnosti[2]
- Kontrole: 1. in 2. ciklus– kontrola na 1 ali 2 tedna, nato na 4 tedne[1]

1. Bekaii-Saab T et al. Clin Colorectal Cancer, Volume 18, Issue 1, e117 - e129
2. Stivarga® SmPC

2. alternativni način odmerjanja regorafeniba pri starejših

Petrioli in sod:

- bolniki 75 > let (n= 23)
- Shema: 2 tedna na terapiji, 1t premora
- Zmanjšana izpostavljenost regorafenibu in metabolitom
- Začetna doza: fit bolniki 160 mg, 120 mg krhki bolniki z eno spremljajočo boleznijo in 80 mg bolniki z 2 spremljajočima boleznima in PS 2



Petrioli et al. Clinical Colorectal Cancer, Vol. 17, No. 4, 307-12, 2018

Mross K et al. Clin Cancer Res. 2012 May 1;18(9):2658-67

Učinkovitost in varnost

- DCR po 2 mesecih 52.2 % (31.6-72.6)
- PFS 4.8 meseca (3.8-6.3)
- OS 8.9 meseca (6.9-10.6)
- NU: večinoma gr ≤2, med gr. 3 najpogostejša SRN (9%) in utrujenost (9%)

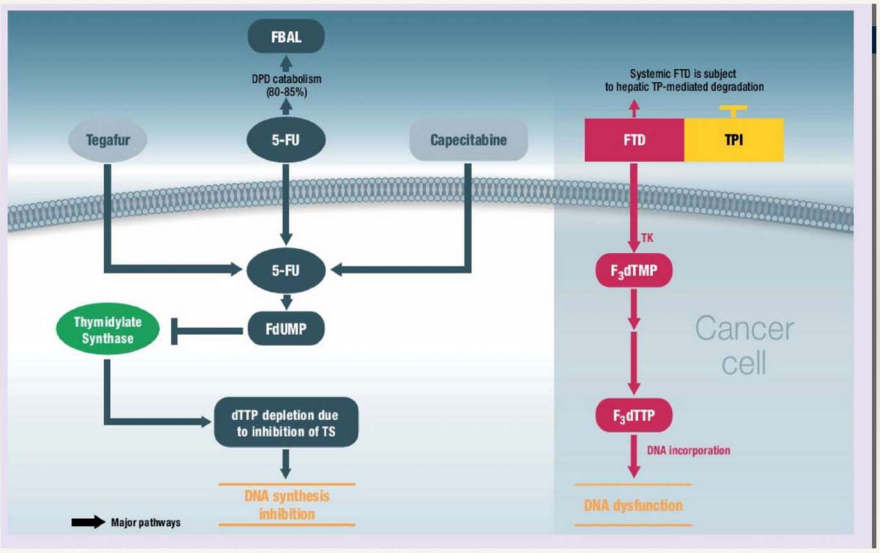
Petrioli et al. Clinical Colorectal Cancer, Vol. 17, No. 4, 307-12, 2018

Metaanaliza NU zdravljenja CRC, GIST z regorafenibom

- NU pogostejši pri starejših > 65 let
- >> pri odmerku 160 mg (p = 0,001), ni pa značilne korelacije pri 120 in 80 mg

Xie G. et al. Adv Ther (2019) 36: 1986-98

Trifluridin/tipiracil ≠ 5-FU



Trifluridin tipiracil

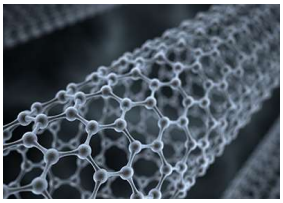
- Prednost: presnova ne gre prek DPD
- Manj kardiotoksičnosti (0,5%; vs 1,2-18% 5-FU)[1]
- Kriteriji za odmerjanje in prilagajanje[2]
- NUZ: ugodejši profil - razen hematološki NU (nevtropenija ≥ gr. 3 - 38 %, febrilna nevtropenija 4%), driska (32%, gr.≥ 3: 3%), navzea (48%; gr. ≥3: 2%), slabši apetit (39%; gr. ≥3: 4%), utrujenost (35% gr. ≥ 3: 4%)[3] …

1. Keramida K et al. J Gastrointest Oncol. 2019 Aug; 10(4): 797–80
2. Lonsurf SPC
3. Lee JJ, Chu E. Clin Colorectal Cancer. 2017 Jun; 16(2): 85–92

Konsenz ekpertov

- Kontrola hemograma 1. in 15. dan
- Kontrola med 1 in 2 ciklom na 1 ali 2 tedna, nato na 4 tedne
- Po nevtropeniji - rastni faktorji za granulocite

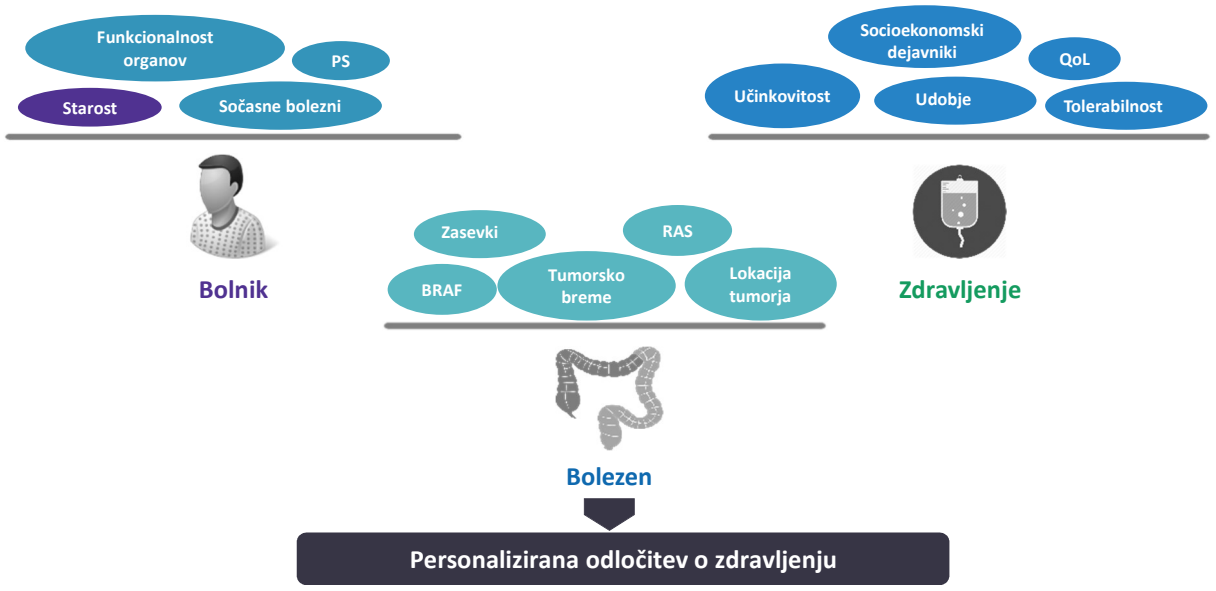
Bekaii-Saab T et al. Clin Colorectal Cancer, Volume 18, Issue 1, e117 - e129



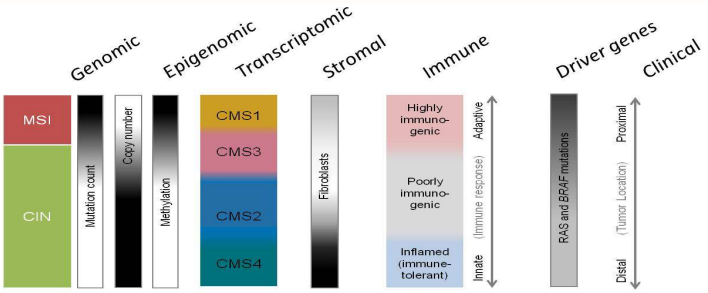
Novosti v personalizaciji zdravljenja bolnikov z rakom debelega črevesa in danke

9.šola tumorjev prebavil
22.11.2019

Doc.dr.Martina Reberšek, dr.med.
Sektor internistične onkologije
Onkološki inštitut Ljubljana



CRC subtypes multi-omics



Dienstmann et al, Nat Rev Cancer 2017

"Biomarkerji"

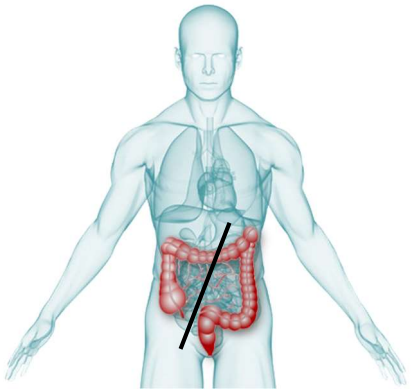
Molekularni biomarkerji:

- Somatske mutacije: *RAS*, *BRAF*, *PIKCA*, HER-2, EGFR, PTEN, AREG/EREG, VEGF
- MSI
- Farmakogenomski markerji: DPD, UGT1A1, ERCC1, TS

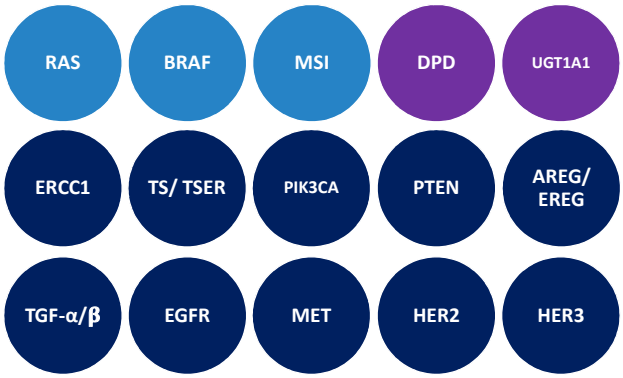
Lokacija tumorja

Mikrobiom

Lokalizacija tumorja



Molekularni biomarkerji



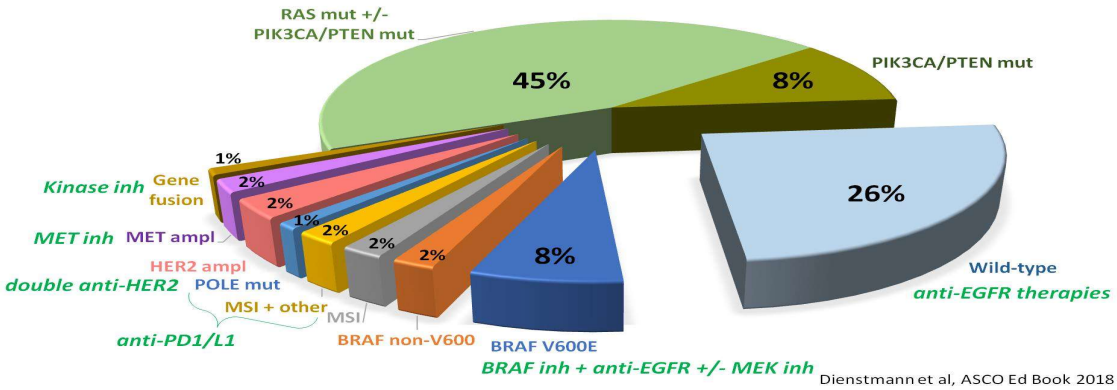
Priporočila kliničnih smernic[1,2]

- Priporočila za rutinsko obravnavo (ESMO and NCCN)
- Opcije za izbrano populacijo bolnikov (ESMO)
- Določanje ki ni priporočeno za rutinsko obravnavo (ESMO and NCCN)

AREG, amphiregulin; BRAF, rapidly accelerated fibrosarcoma B; DPD, dihydropyrimidine dehydrogenase; EGFR, epidermal growth factor receptor; ERCC1, excision repair cross-complementation group 1; EREG, epiregulin; HER, human epidermal growth factor receptor; MET, mesenchymal-epithelial transition factor receptor; MSI, microsatellite instability; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PTEN, phosphatase and tensin homolog; RAS, rat sarcoma; TGF, transforming growth factor; TS, thymidylate synthase; TSER, thymidylate synthase promoter; UGT1A1, UDP glucuronosyltransferase 1 family polypeptide A1.

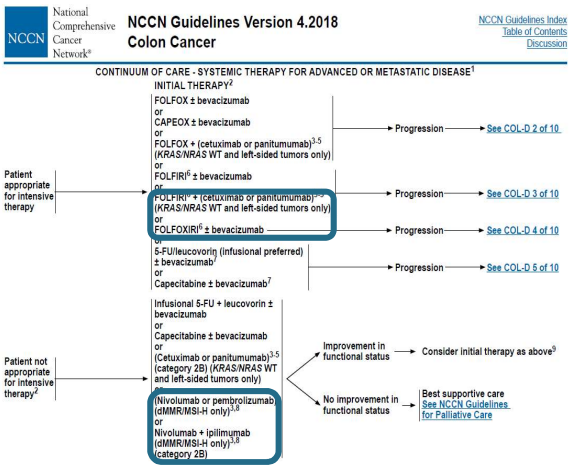
1. Van Cutsem E, et al. Ann Oncol 2016;27:1386–1422; 2. NCCN clinical practice guidelines; Colon Cancer, Version 2.2016. Available at www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Last accessed May 2016.

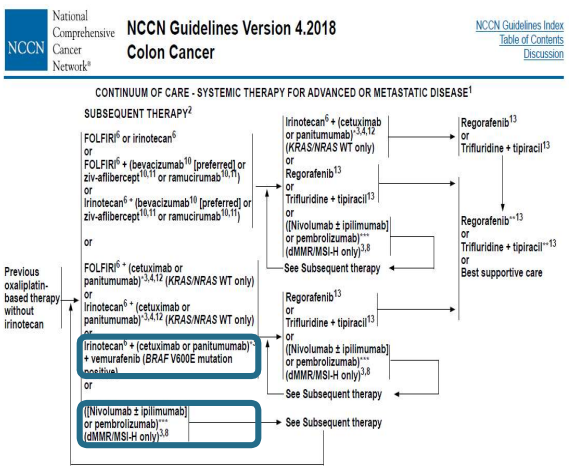
Genomic markers



Dienstmann et al, ASCO Ed Book 2018

NCCN 2018



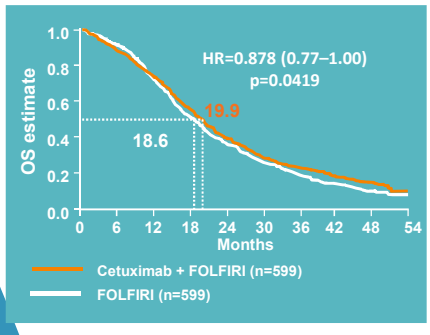


RAS

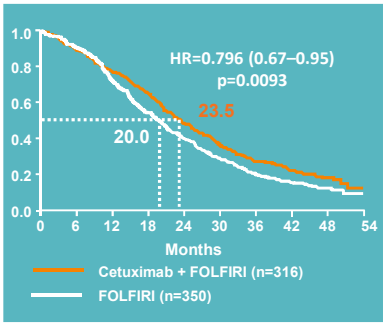
CRYSTAL raziskava III faze: izbira bolnikov na osnovi statusa biomarkerjev podaljša celokupno preživetje bolnikov

ITT (vsi)[1] → **KRAS exon 2 wt[1]** → **RAS wt[2]**

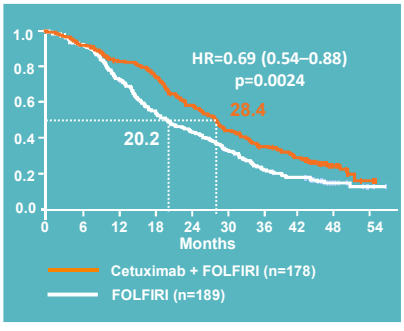
Δ = 1.3 mesecev



Δ = 3.5 mesecev



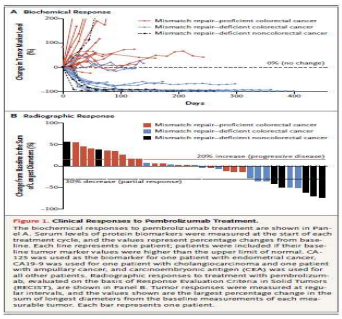
Δ = 8.2 mesecev



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

Vloga MSI

Imunoterapija z zaviralci imunskih kontrolnih točk- monoterapija



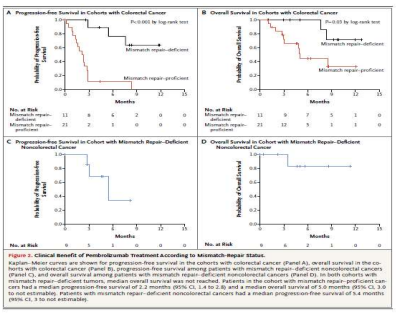


Table 2. Objective Responses According to RECIST Criteria.

Type of Response	Mismatch Repair–Deficient Colorectal Cancer (N = 10)	Mismatch Repair–Proficient Colorectal Cancer (N = 18)	Mismatch Repair–Deficient Noncolorectal Cancer (N = 7)
Complete response — no. (%)	0	0	1 (14)*
Partial response — no. (%)	4 (40)	0	4 (57)†
Stable disease at week 12 — no. (%)	5 (50)	2 (11)	0
Progressive disease — no. (%)	1 (10)	11 (61)	2 (29)
Could not be evaluated — no. (%)‡	0	5 (28)	0
Objective response rate (95% CI) — %	40 (12–74)	0 (0–19)	71 (29–96)
Disease control rate (95% CI) — %§	90 (55–100)	11 (1–35)	71 (29–96)
Median duration of response — wk	Not reached	NA¶	Not reached
Median time to response (range) — wk	28 (13–35)	NA¶	12 (10–13)

* The patient had a partial response at 12 weeks, which then became a complete response at 20 weeks.
† One patient had a partial response at 12 weeks.
‡ Patients could not be evaluated if they did not undergo a scan at 12 weeks because of clinical progression.
§ The rate of disease control was defined as the percentage of patients who had a complete response, partial response, or stable disease for 12 weeks or more.
¶ The median time to response was not applicable (NA) because no responses were observed among patients with mismatch repair–proficient colorectal cancer.

Le DT, et al.PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. N Engl J Med 2015;372:2509-20.

Vloga MSI

Imunoterapija z zaviralci imunskih kontrolnih točk-kombinacija

Table 2. ORR, Best Overall Response, and DCR per Investigator Assessment (N = 119)

Response	No. (%)	95% CI
ORR	65 (55)	45.2 to 63.8
Best overall response		
Complete response	4 (3)	
Partial response	61 (51)	
Stable disease	37 (31)	
Progressive disease	14 (12)	
Not determined	3 (3)	
Disease control for ≥ 12 weeks	95 (80)	71.5 to 86.6

Abbreviations: DCR, disease control rate; ORR, objective response rate.

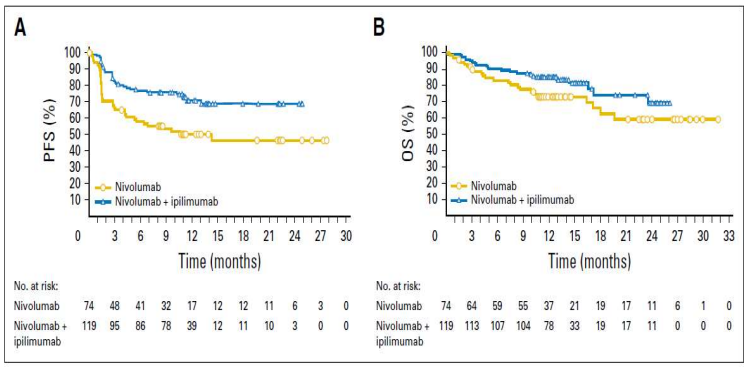


Fig 3. Kaplan-Meier plots of (A) progression-free survival (PFS) per investigator assessment and (B) overall survival (OS) in patients treated with nivolumab plus ipilimumab in the analyses presented herein or nivolumab in the monotherapy cohort of CheckMate-142 from an analysis that had a similar median follow-up (potential time on study from first dose to data cutoff: 13.4 months).[11]

Overman MJ, et al. Durable Clinical Benefit With Nivolumab Plus Ipilimumab in DNA Mismatch Repair–Deficient/Microsatellite Instability–High Metastatic Colorectal Cancer. J Clin Oncol 36:773-779.

HER 2+ status (1)

- trastuzumab+lapatinib

	Patients given trastuzumab and lapatinib (n=27)
Age (years)	62 (50–68)
Sex	
Men	23 (85%)
Women	4 (15%)
ECOG performance status 0–1	27 (100%)
HER2 expression by immunohistochemistry score	
3+	20 (74%)
2+	7 (26%)
Site of primary tumour	
Rectum	7 (26%)
Colon	20 (74%)
Proximal*	4 (20%)
Distal†	16 (80%)
Metastatic disease in multiple sites	26 (96%)
Number of previous lines of therapy	5 (4–6)
Patients with ≥4 previous lines of therapy	20 (74%)
Previous anti-angiogenesis treatment	20 (74%)
Previous therapy with panitumumab or cetuximab	27 (100%)
Patients eligible to be assessed for sensitivity to panitumumab or cetuximab‡	15 (56%)
Previous response to panitumumab or cetuximab	0
Time on previous treatment (total; months)§	20 (16–24)
By primary site	
Proximal	15 (13–19)
Distal	19 (15–24)
Rectum	23 (20–25)

Data are n (%) or median (IQR). ECOG=Eastern Cooperative Oncology Group. *Located in caecum, ascending colon, liver flexure, and transverse colon. †Located in splenic flexure, descending colon, and sigmoid colon. ‡Definition of eligibility reported in the appendix (p 16). §Information available for 135 of 136 total previous regimens (treatment holiday excluded).

Table 1: Baseline characteristics

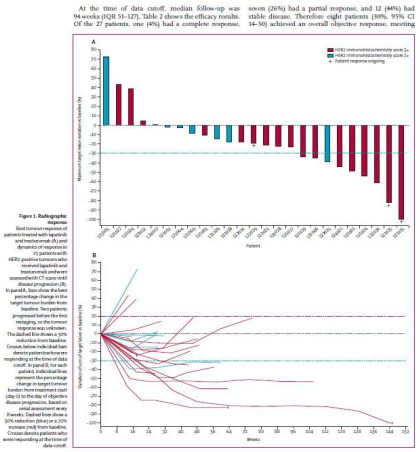


Figure 1: Radiographic response

	Patients given trastuzumab and lapatinib (n=27)
Complete response	1 (4%, −3 to 11)
Partial response	7 (26%, 9 to 43)
Stable disease ≥16 weeks*	8 (30%, 13 to 47)
Stable disease <16 weeks	4 (15%, 1 to 27)
Objective response	8 (30%, 14 to 50)
Disease control†	16 (59%, 39 to 78)
Duration of response (weeks)	38 (24 to 94+)
Time to response (weeks)	8 (3 to 16)

Data are n (%, 95% CI) or median (range). Response data are best response according to RECIST 1.1. RECIST=Response Criteria Evaluation in Solid Tumors. *Including one unconfirmed partial response according to RECIST 1.1. †Defined as complete plus partial responses plus stable disease >16 weeks.

Table 2: Responses to treatment

Sartore-Bianchi A, et al.. Dual-targeted therapy with trastuzumab and lapatinib in treatment-refractory, KRAS codon 12/13 wild-type, HER2-positive metastatic colorectal cancer (HERACLES): a proof-of-concept, multicentre, open-label, phase 2 trial. Lancet Oncol 2016; 17: 738–46

HER 2+ status (2)

- trastuzumab+pertuzumab

Table 2. Tumor Types and Molecular Alterations

Primary Site	HER2	BRAF	Hedgehog Pathway	EGFR	Total
Lung, non–small-cell	30	21	3	0	54
Colorectal	40	2	0	0	42
Biliary	11	3	0	1	15
Ovary	8	4	2	0	14
Bladder	13	0	0	0	13
Pancreas	9	4	0	0	13
Uterus	7	0	0	0	7
Breast	2†	0	2	2	6
Salivary gland	5	0	1	0	6
Small intestine	4	0	1	1	6
Prostate	1	3	1	0	5
Unknown primary	1	3	1	0	5
Other (21 tumor types)	20	9	10	5	44
Total	151 (66%)	49 (21%)	21 (9%)	9 (4%)	230

NOTE. N = 230.
Abbreviations: BRAF, murine sarcoma viral (v-raf) oncogene homolog B1; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor-2.
*One patient had a tumor with an RBMS-NRG1 fusion.
†Both had *HER2* mutations without amplification or overexpression.

Table 3. Efficacy of Treatment With Trastuzumab Plus Pertuzumab in Patients With HER2 Amplification/Overexpression

Primary Site	No. of Patients	Response, No. (%) CR	PR	SD > 120 Days	ORR, % (95% CI)
Colorectal	37	0	14 (38)	4 (11)	38 (23 to 55)
Lung, non–small-cell	16	0	2 (13)	2 (13)	13 (2 to 38)
Bladder	9	1 (11)	2 (22)	2 (22)	33 (8 to 70)
Pancreas	9	0	2 (22)	1 (11)	22 (3 to 60)
Biliary	7	0	2 (29)	3 (38)	29 (4 to 71)
Ovary	8	0	1 (13)	0	13 (0 to 53)
Uterus	7	0	0	0	0
Salivary gland	5	0	4 (80)	0	80 (28 to > 99)
Other (11 sites)*	16	1 (6)	1 (6)	3 (19)	13 (2 to 38)
Total	114	2 (2)	28 (25)	16 (14)	26 (19 to 35)

NOTE. N = 114. Includes 12 patients with amplification/overexpression plus mutation.
Abbreviations: CR, complete response; ORR, objective response rate; PR, partial response; SD, stable disease.
*Responses occurred in patients with adenocarcinomas of the prostate (one) and skin (apocrine; one).

Hainsworth JD, et al., Targeted Therapy for Advanced Solid Tumors on the Basis of Molecular Profiles: Results From MyPathway, an Open-Label, Phase IIa Multiple Basket Study. J Clin Oncol 36:536-542.

mt*BRAF*

- vemurafenib mono

Table 2. Tumor Types and Molecular Alterations

Primary Site	HER2	BRAF	Hedgehog Pathway	EGFR	Total
Lung, non–small-cell	30	21	3	0	54
Colorectal	40	2	0	0	42
Biliary	11*	3	0	1	15
Ovary	8	4	2	0	14
Bladder	13	0	0	0	13
Pancreas	9	4	0	0	13
Uterus	7	0	0	0	7
Breast	2†	0	2	2	6
Salivary gland	5	0	1	0	6
Small intestine	4	0	1	1	6
Prostate	1	3	1	0	5
Unknown primary	1	3	1	0	5
Other (21 tumor types)	20	9	10	5	44
Total	151 (66%)	49 (21%)	21 (9%)	9 (4%)	230

NOTE. N = 230.
Abbreviations: BRAF, murine sarcoma viral (v-raf) oncogene homolog B1; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor-2.
*One patient had a tumor with an RBMS-NRG1 fusion.
†Both had *HER2* mutations without amplification or overexpression.

Table 4. Efficacy of Treatment With Vemurafenib in Patients With *BRAF* V600E-Mutated Cancers

Primary Site	No. of Patients	Response, No. (%)			ORR, % (95% CI)
		CR	PR	SD > 120 Days	
Lung, non–small-cell	14	1 (7)	5 (36)	2 (14)	43 (18 to 71)
Ovary	4	0	2 (50)	1 (25)	50
Colorectal	2	0	1 (50)	0	50
Unknown primary	1	0	1 (100)	0	100
Thyroid (anaplastic)	1	1 (100)	0	0	100
Head/neck (larynx)	1	0	1 (100)	0	100
Other (3 sites)	3	0	0	0	0
Total	26	2 (8)	10 (38)	3 (12)	46 (27 to 67)

NOTE. N = 26.
Abbreviations: CR, complete response; ORR, objective response rate; PR, partial response; SD, stable disease.

Hainsworth JD, et al., Targeted Therapy for Advanced Solid Tumors on the Basis of Molecular Profiles: Results From MyPathway, an Open-Label, Phase IIa Multiple Basket Study. J Clin Oncol 36:536-542.

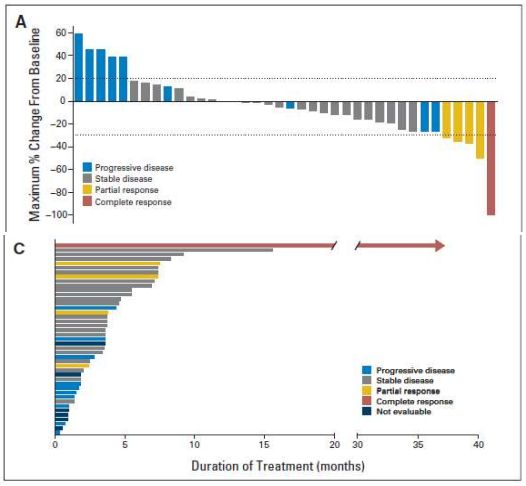
mt*BRAF*

- dabrafenib+trametinib

Table 1. Baseline Patient Demographic and Clinical Characteristics (N = 43)

Characteristic	No. (%)
Age, years	
Mean	55
SD	13
Female sex	34 (79)
ECOG performance status	
0	24 (56)
1	19 (44)
BRAF V600E mutation	43 (100)
No. of disease sites at screening	
< 3	22 (51)
≥ 3	21 (49)
No. of lines of prior systemic anticancer therapy*	
0	1 (2)
1	6 (14)
2	14 (33)
≥ 3	22 (51)
Prior EGFR inhibitor	20 (47)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; SD, standard deviation.
*Prior chemotherapy, immunotherapy, hormonal, biologic, or small-molecule targeted therapy regimens.



Ryan B, et al. Combined BRAF and MEK Inhibition With Dabrafenib and Trametinib in BRAF V600–Mutant Colorectal Cancer. J Clin Oncol 33:4023-4031.

mt*BRAF*

- dabrafenib+trametinib+ panitumumab

Investigator–assessed best response with confirmation (RECIST 1.1).

	D 150 mg BID+ P 6mg/kg Q2W N = 20	D 150 mg BID, T 1.5 mg QD, P 4.8 mg/kg Q2W N = 3	D 150 mg BID, T 2 mg QD, P 4.8 mg/kg Q2W N = 4	D 150 mg BID, T 1.5 mg QD, P 6 mg/kg Q2W N = 4	D 150 mg BID, T 2 mg QD, P 6 mg/kg Q2W N=24	D+T+P Total N = 35
Complete response, n (%)	1 (5)	0	1 (25)	0	0	1 (3)
Partial response, n (%)	1 (5)	2 (67)	1 (25)	0	5 (21)	8 (23)
Stable disease, n (%)	16 (80)	1 (33)	2 (50)	2 (50)	15 (63)	20 (57)
Progressive disease, n (%)	2 (10)	0	0	2 (50)	3 (13)	5 (14)
Not evaluable, n (%)	0	0	0	0	1 (4)	1 (3)
Response rate (CR+PR), n (%)	2 (10)	2 (67)	2 (50)	0	5 (21)	9 (26)
95% confidence interval, %	1.2–31.7	9.4–99.2	6.8–93.2	0.0–60.2	7.1–42.2	12.5 –43.3

JCO 2015: D+P vs T+P vs D+T+P

Atreya CE, et al. Updated efficacy of the MEK inhibitor trametinib (T), BRAF inhibitor dabrafenib (D), and anti-EGFR antibody panitumumab (P) in patients (pts) with BRAF V600E mutated (BRAFm) metastatic colorectal cancer (mCRC). J Clin Oncol 2015:33 (suppl; abstr 103).

mt*BRAF*

- BEACON: enkorafenib+binimetinib+cetuksimab

Characteristic	Patients* (N = 30)
BRAF V600E mutation†	29 (97)
Male	13 (43)
Race	
White	29 (97)
Black or African American	1 (3)
Median age, years (range)	59 (38-77)
ECOG PS of 0	17 (57)
Location of primary tumor	
Left side	9 (30)
Right side	18 (60)
Unknown	3 (10)
No. of organs with metastases ≥ 2	22 (73)
Metastatic site locations	
Liver	20 (67)
Lymph nodes	15 (50)
Peritoneum	11 (37)
Lung	9 (30)
Other	15 (50)
Resection of primary tumor	
Yes	21 (70)
No	9 (30)
No. of prior systemic therapies‡	
1	18 (60)
2	12 (40)
Received prior irinotecan	13 (43)
MSI-H§	1 (3)
Median CEA at baseline, μg/mL (range)	28 (1-3,434)

Abbreviations: CEA, carcinoembryonic antigen; ECOG PS, Eastern Cooperative Oncology Group performance status; MSI-H, microsatellite instability high.
*Values are numbers and percentages, unless otherwise noted.
†One patient treated had a non–*BRAF* V600E mutation.
‡Includes prior systemic therapies in the metastatic setting only.
§Based on immunohistochemical assessment of *MLH1* and *MSH6*.

Confirmed Best Overall Response	No. of Patients (N = 29)*
Local assessment†	
ORR (CR + PR)	14 (48)
95% CI (%)	29 to 68
CR	3 (10)
PR	11 (38)
SD	13 (45)
PD	0
Not evaluable for response	2 (7)
Central assessment†	
ORR (CR + PR)	12 (41)
95% CI (%)	24 to 61
CR	2 (7)
PR	10 (34)
SD	13 (45)
PD	0
Not evaluable for response	4 (14)

NOTE. Data in tables represent No. (%) unless otherwise indicated.
Abbreviations: CR, complete response; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.
*Patients with *BRAF* V600E mutations.
†Confirmed responses per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

Van Cutsem E, et al. Binimetinib, Encorafenib, and Cetuximab Triplet Therapy for Patients With BRAF V600E–Mutant Metastatic Colorectal Cancer: Safety Lead-In Results From the Phase III BEACON Colorectal Cancer Study. J Clin Oncol 37:1460-1469.

mt*BRAF*
-BEACON- PFS in OS

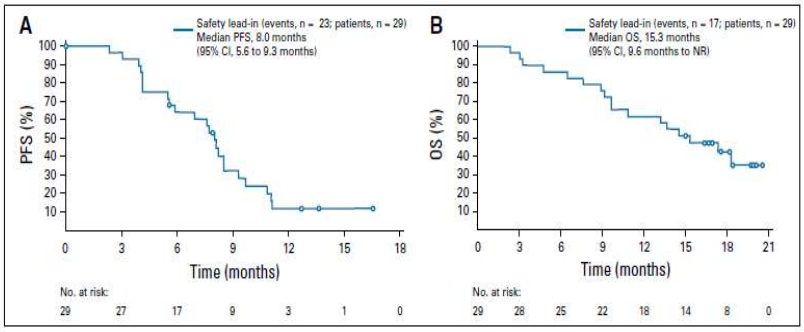


FIG 3. Kaplan-Meier plots of (A) progression-free survival (PFS; local assessment) and (B) overall survival (OS). NR, not reached.

Van Cutsem E, et al. Binimetinib, Encorafenib, and Cetuximab Triplet Therapy for Patients With BRAF V600E–Mutant Metastatic Colorectal Cancer: Safety Lead-In Results From the Phase III BEACON Colorectal Cancer Study. J Clin Oncol 37:1460-1469.

TRK genske fuzije
-larotrektinib

Table 1. Demographic and Clinical Characteristics of the 55 Patients.*

Characteristic	Value
Age	
Median (range) — yr	45.0 (0.3–76.0)
Distribution — no. (%)	
<2 yr	6 (11)
2–5 yr	5 (9)
6–14 yr	1 (2)
15–39 yr	12 (22)
≥40 yr	31 (56)
Sex — no. (%)	
Male	29 (53)
Female	26 (47)
ECOG performance-status score — no. (%)†	
0	24 (44)
1	27 (49)
2	4 (7)
No. of previous systemic chemotherapies — no. (%)	
0 or 1	27 (49)
2	9 (16)
≥3	19 (35)
Tumor type — no. (%)	
Salivary-gland tumor	12 (22)
Other soft-tissue sarcoma‡	11 (20)
Infantile fibrosarcoma	7 (13)
Thyroid tumor	5 (9)
Colon tumor	4 (7)
Lung tumor	4 (7)
Melanoma	4 (7)
GIST	3 (5)
Cholangiocarcinoma	2 (4)
Appendix tumor	1 (2)
Breast tumor	1 (2)
Pancreatic tumor	1 (2)
CNS metastases — no. (%)	
No	54 (98)
Yes	1 (2)
TRK gene — no. (%)	
NTRK1	25 (45)
NTRK2	1 (2)
NTRK3	29 (53)

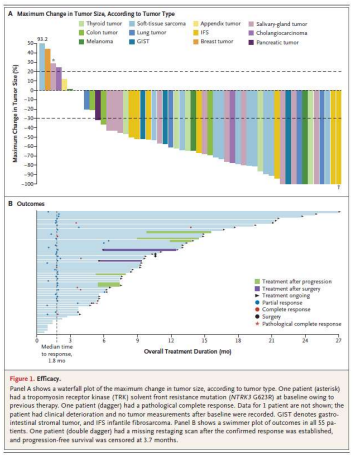
Table 2. Overall Response Rate, According to Investigator and Central Assessment.*

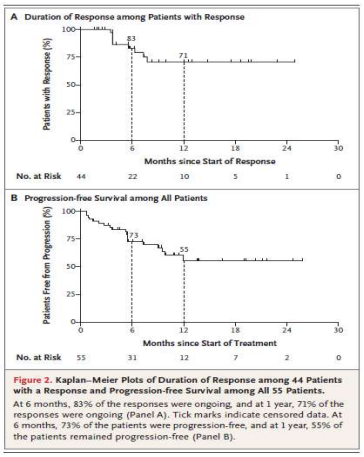
Response	Investigator Assessment (N=55)	Central Assessment (N=55)
	percent	
Overall response rate (95% CI)†	80 (67–90)	75 (61–85)
Best response		
Partial response	64‡	62
Complete response	16	13
Stable disease	9	13
Progressive disease	11	9
Could not be evaluated	0	4

Drilon A, et al Efficacy of Larotrectinib in TRK Fusion– Positive Cancers in Adults and Children. N Engl J Med 2018;378:731-9.

TRK genske fuzije

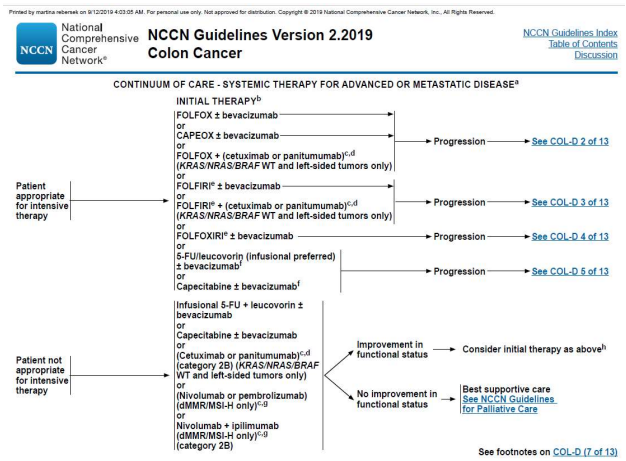
-larotrektinib- ORR+ PFS

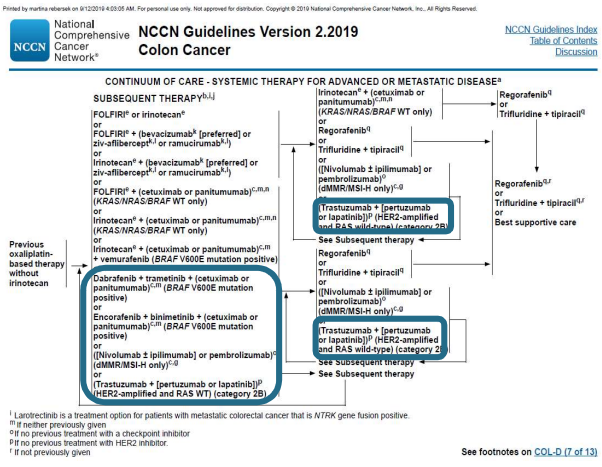




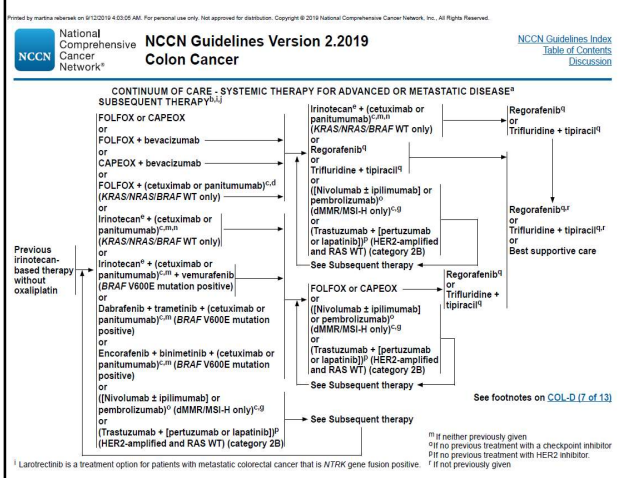
Drilon A, et al Efficacy of Larotrectinib in TRK Fusion– Positive Cancers in Adults and Children. N Engl J Med 2018;378:731-9.

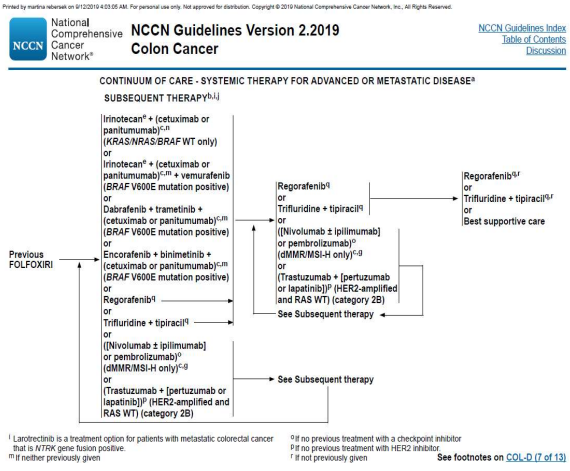
NCCN 2019- sistemsko zdravljenje mCRC (1)



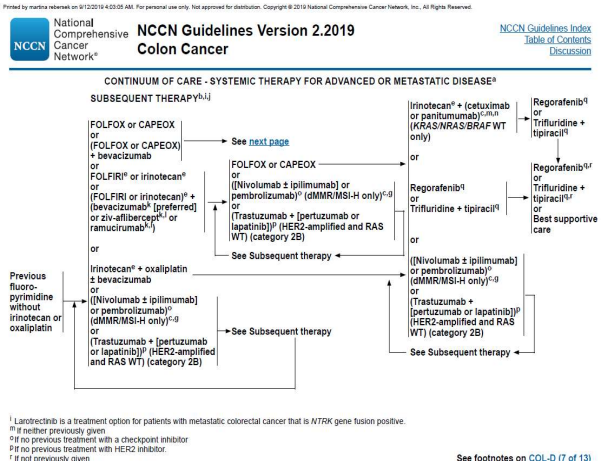


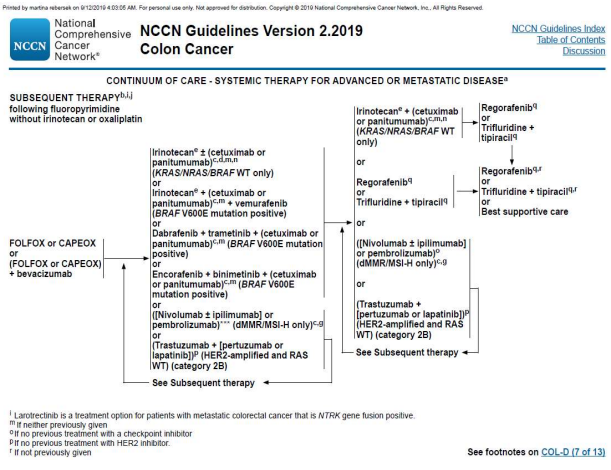
NCCN 2019 - sistemsko zdravljenje mCRC (2)





NCCN 2019 - sistemsko zdravljenje mCRC (3)





NCCN 2019 - sistemsko zdravljenje mCRC (4)

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Colon Cancer

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SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE - CHEMOTHERAPY REGIMENS

Capecitabine[8]
Capecitabine 850–1250 mg/m² PO twice daily, days 1–14
Repeat every 3 weeks

Capecitabine + bevacizumab[22,¶]
Bevacizumab 7.5 mg/kg IV, day 1
Repeat every 3 weeks

Irinotecan
Irinotecan 125 mg/m² IV over 30–90 minutes, days 1 and 8
Repeat every 3 weeks[23,24]
or Irinotecan 180 mg/m² IV over 30–90 minutes, day 1
Repeat every 2 weeks
or Irinotecan 300–350 mg/m² IV over 30–90 minutes, day 1
Repeat every 3 weeks

Irinotecan + cetuximab (*KRAS/NRAS/BRAF* WT only)
Cetuximab 400 mg/m² first infusion, then 250 mg/m² IV weekly[25]
or Cetuximab 500 mg/m² IV over 2 hours, day 1, every 2 weeks[13]

Irinotecan + panitumumab[14] (*KRAS/NRAS/BRAF* WT only)
Panitumumab 6 mg/kg IV over 60 minutes every 2 weeks

Irinotecan + ramucirumab[16]
Ramucirumab 8 mg/kg IV over 60 minutes every 2 weeks

Cetuximab (*KRAS/NRAS/BRAF* WT only)
Cetuximab 400 mg/m² first infusion, then 250 mg/m² IV weekly[25]
or Cetuximab 500 mg/m² IV over 2 hours, day 1, every 2 weeks[13]

Panitumumab[26] (*KRAS/NRAS/BRAF* WT only)
Panitumumab 6 mg/kg IV over 60 minutes every 2 weeks

Regorafenib
Regorafenib 160 mg PO daily on days 1–21[27]
or
First cycle: Regorafenib 80 mg PO daily on days 1–7, then 120 mg PO daily on days 8–14, then 160 mg PO daily on days 15–21[28]
Subsequent cycles: Regorafenib 160 mg PO daily on days 1–21
Repeat every 28 days

Trifluridine + tipiracil[29]
Trifluridine + tipiracil 35 mg/m² up to a maximum dose of 80 mg per dose (based on the trifluridine component)
PO twice daily days 1–5 and 8–12
Repeat every 28 days

Pembrolizumab[30] (dMMR/MSI-H only)
Pembrolizumab 2 mg/kg every 3 weeks
or Pembrolizumab 200 mg every 3 weeks

Nivolumab[31] (dMMR/MSI-H only)
Nivolumab 3 mg/kg every 2 weeks
or Nivolumab 240 mg IV every 2 weeks
or Nivolumab 480 mg IV every 4 weeks

Nivolumab + ipilimumab[32] (dMMR/MSI-H only)
Nivolumab 3 mg/kg (30-minute IV infusion) and ipilimumab 1 mg/kg (30-minute IV infusion) once every 3 weeks for four doses, then nivolumab 3 mg/kg IV or nivolumab 240 mg IV every 2 weeks

See References on COL-D (12 of 13)

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SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE - CHEMOTHERAPY REGIMENS

Trastuzumab + pertuzumab[33] (HER2-amplified and RAS WT)
Trastuzumab 8mg/kg IV loading dose on Day 1 of Cycle 1, then 6mg/kg IV every 21 days
Pertuzumab 840mg IV loading dose on Day 1 of Cycle 1, then 420mg IV every 21 days

Trastuzumab + lapatinib[34] (HER2-amplified and RAS WT)
Trastuzumab 4mg/kg IV loading dose on Day 1 of Cycle 1, then 2mg/kg IV weekly
Lapatinib 1000mg PO daily

Irinotecan + cetuximab + vemurafenib[35]
(*BRAF* V600E mutation positive)
Irinotecan 180 mg/m² IV every 2 weeks
Cetuximab 500 mg/m² IV every 2 weeks
Vemurafenib 960 mg PO twice daily

Irinotecan + panitumumab + vemurafenib[35]
(*BRAF* V600E mutation positive)
Irinotecan 180 mg/m² IV every 2 weeks
Panitumumab 6 mg/kg IV over 60 minutes every 2 weeks
Vemurafenib 960 mg PO twice daily

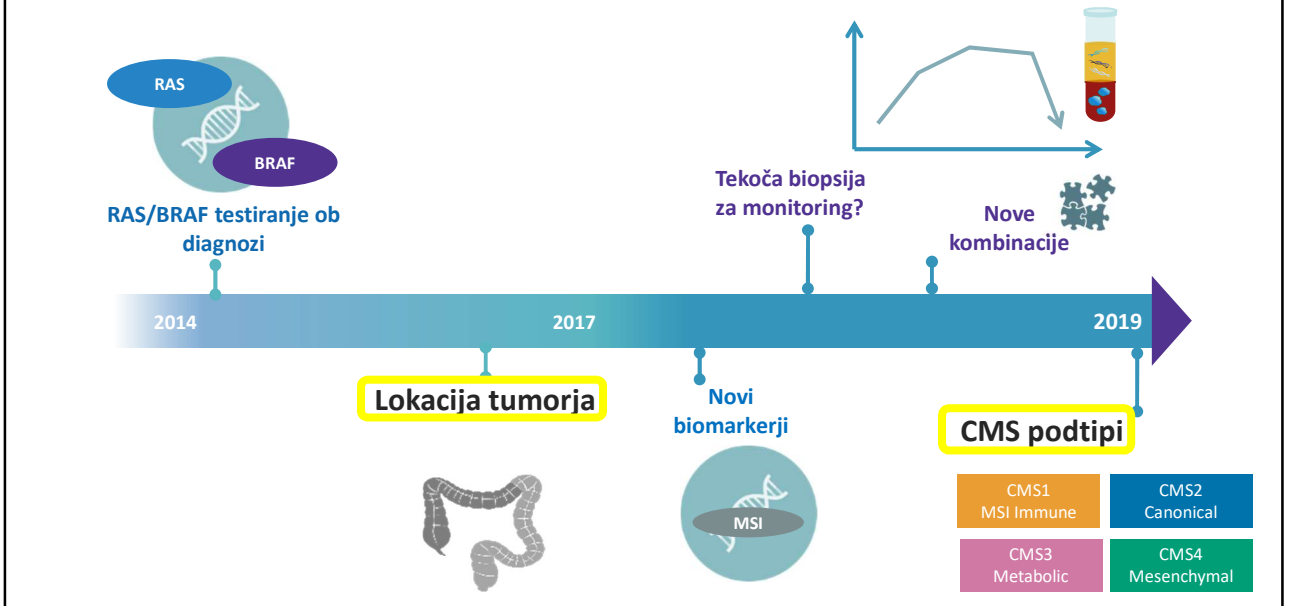
Dabrafenib + trametinib + cetuximab[36]
(*BRAF* V600E mutation positive)
Dabrafenib 150 mg PO twice daily
Trametinib 2 mg PO daily
Cetuximab 400 mg/m² followed by 250 mg/m² weekly

Dabrafenib + trametinib + panitumumab[36]
(*BRAF* V600E mutation positive)
Dabrafenib 150 mg PO twice daily
Trametinib 2 mg PO daily
Panitumumab 6 mg/kg IV every 14 days

Encorafenib + binimetinib + cetuximab[37,38]
(*BRAF* V600E mutation positive)
Encorafenib 300 mg PO daily
Binimetinib 45 mg PO twice daily
Cetuximab 400 mg/m² followed by 250 mg/m² weekly

Encorafenib + binimetinib + panitumumab[37,38]
(*BRAF* V600E mutation positive)
Encorafenib 300 mg PO daily
Binimetinib 45 mg PO twice daily
Panitumumab 6 mg/kg IV every 14 days

Larotrectinib[39]
(*NTRK* gene fusion positive)
100 mg PO twice daily

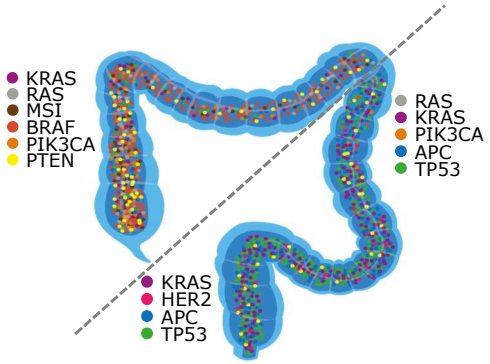


LOKACIJA TUMORJA[1–4]

Tumor location – a master prognostic factor

Right-sided (proximal) colon cancer[1]

- More common in women
- Microsatellite instability
- Derived from mid-gut



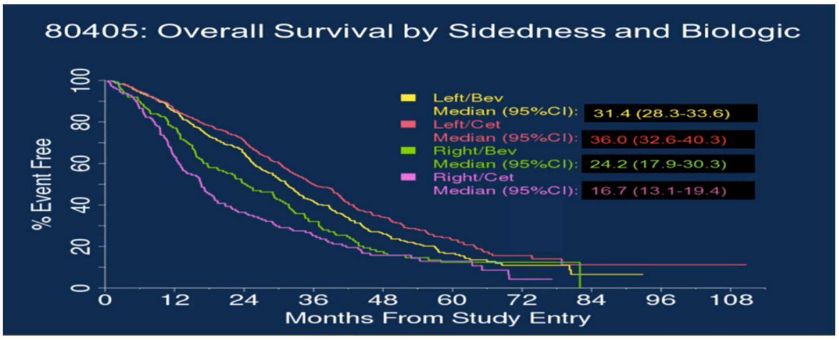
Left-sided (distal) colon cancer[1]

- More common in men
- Chromosomal instability
- Derived from hind-gut

Figure from Salem ME, et al. Oncotarget 2017;8:86356–86368.[5] mCRC, metastatic colorectal cancer.

1. Kim SE, et al. World J Gastroenterol 2015;21:5167–5175; 2. Venook A, et al. ESMO 2016 (Oral Presentation); 3. Dan Aderka. ESMO 2017 (Merck Satellite Symposium); 4. Venook A, et al. JAMA 2017;317:2392–2401; 5. Salem ME, et al. Oncotarget 2017;8:86356–86368.

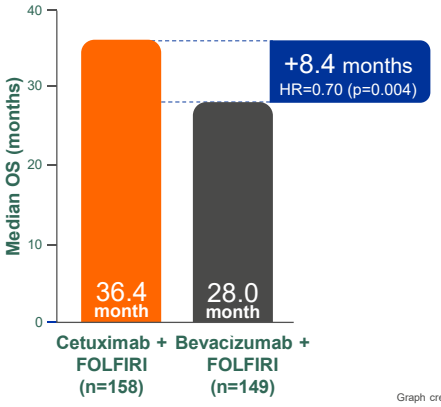
Why right versus left?



Venook A et al, ASCO 2016

TWO LARGE PHASE III 1ST-LINE TRIALS DEMONSTRATE UNPRECEDENTED OS BENEFIT OF CETUXIMAB + CT VS BEVACIZUMAB + CT IN LEFT-SIDED RAS WT MCRC*†‡1–4

Phase III FIRE-3*†1



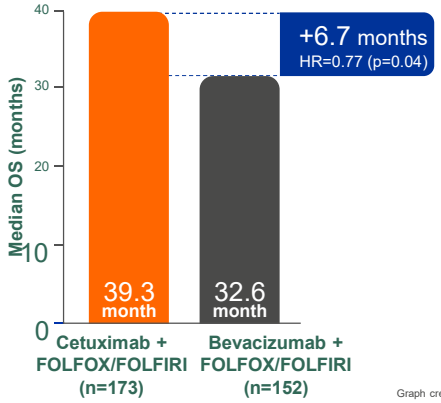
Graph created using data from Stintzing S, et al. ASCO 2018 (Abstract No. 3508).

*Retrospective analysis of patients with left-sided RAS wt mCRC. †FIRE-3 did not meet its primary endpoint of significantly improving overall response rate (ORR) based on investigators' read in patients with KRAS (exon 2) wt mCRC.[3] ‡The CALGB/SWOG 80405 study did not meet its primary endpoint of significantly improving overall survival in the cetuximab + CT arm vs bevacizumab + CT arm in patients with KRAS (exon 2) wt mCRC.[4]
CT, chemotherapy; HR, hazard ratio; OS, overall survival.

1. Stintzing S, et al. ASCO 2018 (Abstract No. 3508); 2. Venook A, et al. ESMO 2016 (Oral Presentation);
3. Heinemann V, et al. Lancet Oncol 2014;15:1065–1075; 4. Venook A, et al. JAMA 2017;317:2392–2401.

TWO LARGE PHASE III 1ST-LINE TRIALS DEMONSTRATE UNPRECEDENTED OS BENEFIT OF CETUXIMAB + CT VS BEVACIZUMAB + CT IN LEFT-SIDED RAS WT MCRC*†‡1–4

Phase III CALGB/SWOG 80405*‡2



Graph created using data from Venook A, et al. ESMO 2016 (Oral Presentation).

*Retrospective analysis of patients with left-sided RAS wt mCRC. †FIRE-3 did not meet its primary endpoint of significantly improving overall response rate (ORR) based on investigators' read in patients with KRAS (exon 2) wt mCRC.[3] ‡The CALGB/SWOG 80405 study did not meet its primary endpoint of significantly improving overall survival in the cetuximab + CT arm vs bevacizumab + CT arm in patients with KRAS (exon 2) wt mCRC.[4]

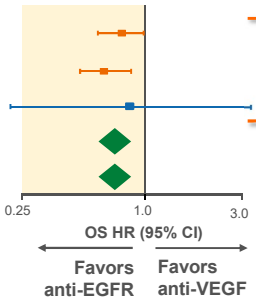
1. Stintzing S, et al. ASCO 2018 (Abstract No. 3508); 2. Venook A, et al. ESMO 2016 (Oral Presentation);
3. Heinemann V, et al. Lancet Oncol 2014;15:1065–1075; 4. Venook A, et al. JAMA 2017;317:2392–2401.

Benefit of 1st-line cetuximab + CT* is confirmed by independent pooled and meta-analyses[1,2]

Holch meta-analysis of 1st-line anti-EGFR vs anti-VEGF in left-sided RAS wt mCRC[1]

Trial	OS HR (95% CI)	p-value
CALGB/SWOG 80405† (n=325)	0.77 (0.59–0.99)	
FIRE-3‡ (n=306)	0.63 (0.48–0.85)	
PEAK (n=107)	0.84 (0.22–3.27)	
Summary (fixed effects)	**0.71 (0.58–0.85)**	**0.0003**
Summary (random effects)	**0.71 (0.58–0.85)**	**0.0003**

Heterogeneity: I^2=0% (95% CI: 0–95.1)
p=0.575 (chi-squared test)



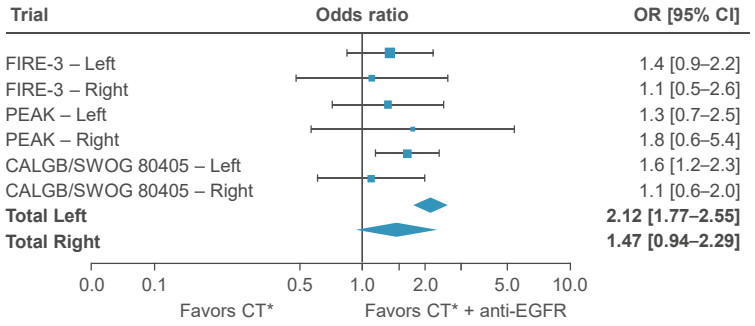
86% of patients treated with anti-EGFR agents received **cetuximab**

Supported by the Arnold pooled analysis: (OS HR 0.75 [0.67–0.84], p<0.001)[2]

*CT regimens were FOLFOX/FOLFIRI. †The CALGB/SWOG 80405 study did not meet its primary endpoint of significantly improving OS in the cetuximab + CT arm vs bevacizumab + CT arm in patients with KRAS (exon 2) wt mCRC.[3] ‡FIRE-3 did not meet its primary endpoint of significantly improving ORR based on investigators' read in patients with KRAS (exon 2) wt mCRC.[4] Cetuximab is indicated for the treatment of patients with EGFR-expressing, RAS wt mCRC in combination with irinotecan-based CT, in 1st line in combination with FOLFOX and as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan.[5]
CI, confidence interval.

- 1. Figure adapted from Holch JW, et al. Eur J Cancer 2017;70:87–98; 2. Arnold D, et al. Ann Oncol 2017;28:1713–1729; 3. Venook A, et al. JAMA 2017;317:2392–2401; 4. Heinemann V, et al. Lancet Oncol 2014;15:1065–1075; 5. Erbitux EU SmPC, May 2019.

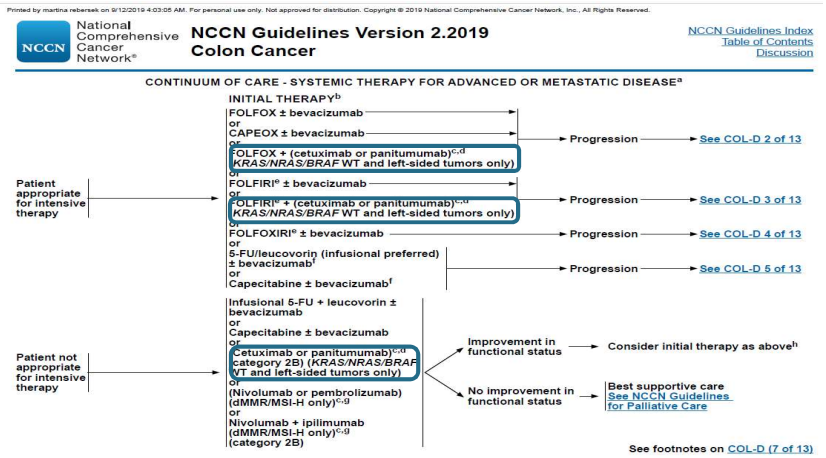
ORR FAVORS ANTI-EGFR + CT FOR LEFT- AND RIGHT-SIDED TUMORS



*CT regimens were FOLFOX/FOLFIRI. OR, odds ratio; ORR, overall response rate.

Arnold D, et al. Ann Oncol 2017;28:1713–1729.

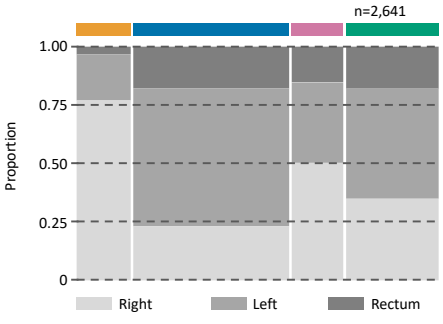
NCCN priporočila glede na lokacijo tumorja



CMS (Consensus Molecular Subtype) klasifikacijski sistem

- CMS (Consensus Molecular Subtype) klasifikacijski sistem vključuje številne molekularne markerje rKRR[1,2]
- Molekularne karakteristike rKRR se razlikujejo glede na lokalizacijo primarnega tumorja[2,3]

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



1. Van Cutsem E, et al. Ann Oncol 2016;27:1386–1422;
2. Guinney J, et al. NatMed 2015;21:1350–1356;
3. Lee GH, et al. Eur J Surg Oncol 2015;41:300–308.

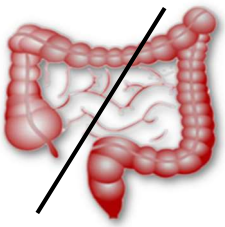
Deleži CMS skupin glede na lokacijo primarnega CRC[1,2]

Desnostranski tumorji so povezani z:

- BRAF mutacijami
- Hipermetilacijami
  - Močno regulirajo izražanje velikega števila genov, kot so EREG in AREG
- Izrazitimi vzorci izražanja genov
  - „Consensus molecular subtypes" (CMS) 1 & 3

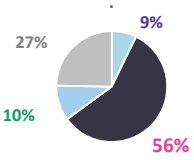
Desni kolon

↑ BRAF mt
= KRAS* mt
↓ ERCC1
↓ VEGFR2
↑ MSI-high
↑ CIMP high



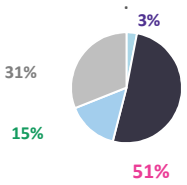
Levi kolon

↓ BRAF mt
= KRAS* mt
↓ ERCC1
↓ TS
↓ VEGFR2

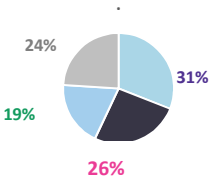


Rektum

↓ BRAF mt
= KRAS* mt
↑ ERCC1
↑ TS
↑ VEGFR2



CMS1
CMS2
CMS3
CMS4

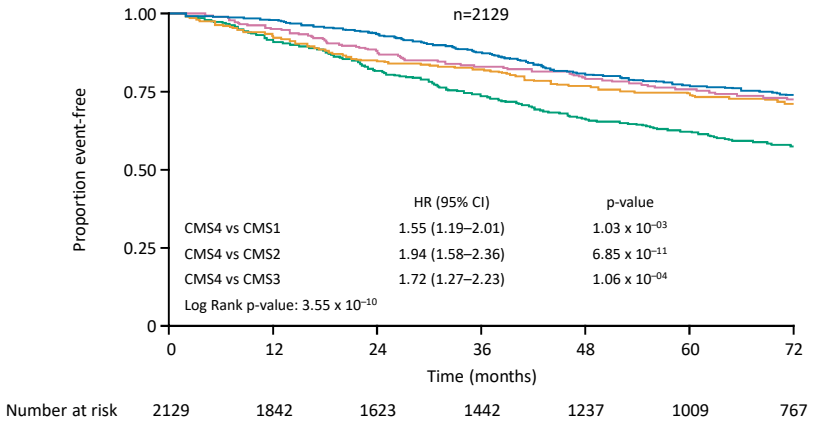


*No extended RAS mutation analysis was reported.
Analysis of FFPE tumor samples from 431 patients with advanced CC.
ERCC1, excision repair cross complement group 1 (low levels associated with sensitivity to platinum chemotherapy agents);
FFPE, formalin-fixed paraffin-embedded; TS, thymidylate synthase (low levels associated with sensitivity to fluoropyrimidines); VEGFR2, vascular endothelial growth factor receptor 2.

This figure has been created for illustrative purposes only using data from:
1. Maus MK, et al. Pharmacogenomics J 2015;15:354–362;
2. Guinney J, et al. Nat Med 2015;21:1350–1356.

Molekularni podtipi CRC - celokupno preživetje[1]

Celokupno preživetje glede na CMS skupine*

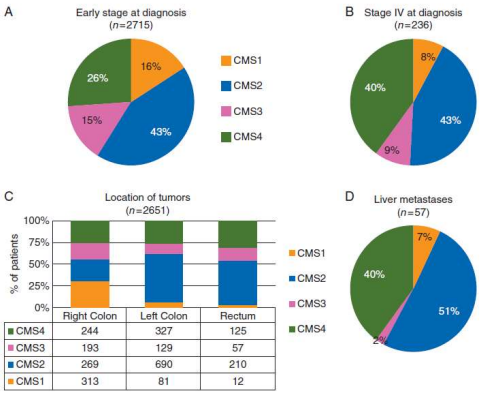


CMS1 MSI Immune
CMS2 Canonical
CMS3 Metabolic
CMS4 Mesenchymal

CMS, Consensus Molecular Subtype.
*Central repository of 18 data sets (n=4151). Cox Proportional Hazards modelling performed in the aggregated data sets after confirming proportionality of hazards across patient cohorts. OS models included all stage I–IV patients

1. Guinney J, et al. NatMed 2015;21:1350–1356.

Fontana E, et al. Context matters—consensus molecular subtypes of colorectal cancer as biomarkers for clinical trials. Annals of Oncology 30: 520–527, 2019



	Right Colon	Left Colon	Rectum
CMS4	244	327	125
CMS3	193	129	57
CMS2	269	690	210
CMS1	313	81	12

Figure 1. (A and B) The proportions of each consensus molecular subtypes (CMS) colorectal cancer (CRC) subtype in (A) early stage (I–III) at diagnosis, (B) stage IV at diagnosis, and (C) location of the tumors within the CRCSC dataset and (D) liver metastatic samples from the publicly available Khambata-Ford dataset [14].

Fontana E, et al. Context matters—consensus molecular subtypes of colorectal cancer as biomarkers for clinical trials. Annals of Oncology 30: 520–527, 2019

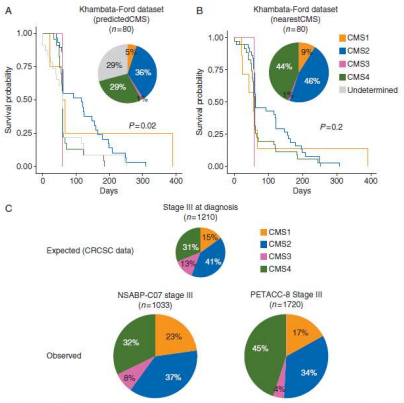


Figure 2. (A and B) Pie charts distribution and Kaplan–Meier survival analyses for cetuximab progression-free survival in the Khambata-Ford dataset [14] according to (A) predicted consensus molecular subtypes (CMS) subtype and (B) nearest CMS subtype. (C) The proportions of each CMS in stage III colorectal cancer samples from the CRCSC dataset (top), the NSABP-C07 ancillary study (left bottom, modified from previous publication [15]), and the PETACC-8 ancillary study (right bottom, modified from previous publication [8]).

Okita A, et al. Consensus molecular subtypes classification of colorectal cancer as a predictive factor for chemotherapeutic efficacy against metastatic colorectal cancer. Oncotarget, 2018, Vol. 9, (No. 27), pp: 18698-18711.

Table 4: Objective response of anti-EGFR treatment

	All		CMS1		CMS2		CMS3		CMS4		p value
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	
CR	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	
PR	33	(33.7)	1	(7.7)	18	(46.2)	7	(29.2)	7	(31.8)	
SD	39	(39.8)	3	(23.1)	18	(46.2)	7	(29.2)	11	(50)	
PD	26	(26.5)	9	(69.2)	3	(7.7)	10	(41.7)	4	(18.2)	
NE	5		1		0		3		1		
RR		(33.7)		(7.7)		(46.2)		(29.2)		(31.8)	0.07
DCR		(73.5)		(30.8)		(92.3)		(58.3)		(81.8)	<0.01

Abbreviations: CMS = consensus molecular subtype; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluated; RR = response rate; DCR = disease control rate.

Okita A, et al. Consensus molecular subtypes classification of colorectal cancer as a predictive factor for chemotherapeutic efficacy against metastatic colorectal cancer. Oncotarget, 2018, Vol. 9, (No. 27), pp: 18698-18711.

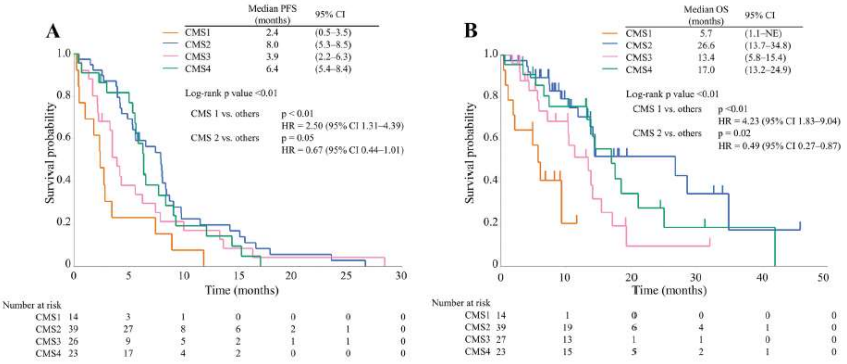


Figure 4: Kaplan–Meier survival curves of anti-EGFR therapy in CMS1 (orange line), CMS2 (blue line), CMS3 (pink line), and CMS4 (green line). **(A)** Progression-free survival time; **(B)** Overall survival time Abbreviations: PFS, progression-free survival; OS, overall survival; CI, confidence interval; HR, hazard ratio.

Lenz HJ.Impact of Consensus Molecular Subtype on Survival in Patients With Metastatic Colorectal Cancer: Results From CALGB/SWOG 80405 (Alliance). J Clin Oncol 2019,37;22:1876-1885.

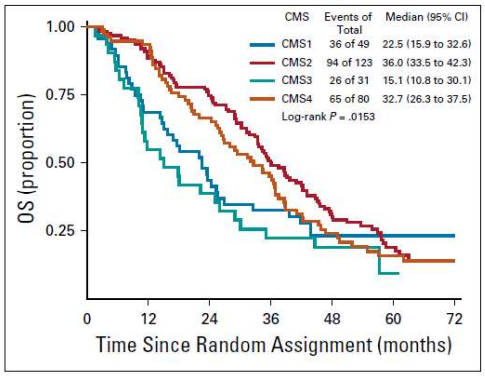


FIG 4. Overall survival (OS) among patients who received bevacizumab. CMS, consensus molecular subtype.

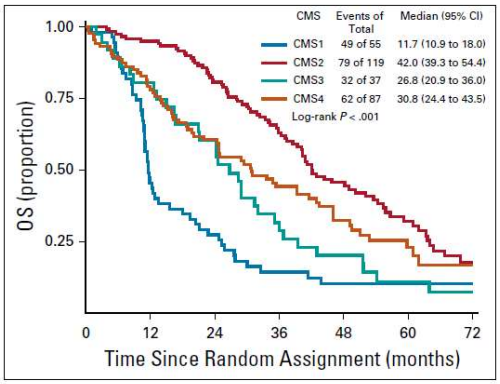


FIG 5. Overall survival (OS) among patients who received cetuximab. CMS, consensus molecular subtype.

Aderka D, et al. Explaining the unexplainable: discrepancies in results from the CALGB/SWOG 80405 and FIRE-3 studies. Lancet Oncol 2019; 20: e274–83.

	CALGB/SWOG 80405 Oxaliplatin (75% of patients) Median (95% CI) overall survival (months)		FIRE-3 Irinotecan (100% of patients) Median (95% CI) overall survival (months)		Most effective first-line combinations	Least effective first-line combinations
	Cetuximab	Bevacizumab	Cetuximab	Bevacizumab		
CMS1	11·7 (10·9–18·0)	22·5 (15·9–32·6)	17·9 (7·1–28·7)	13·1 (8·5–17·6)	Oxaliplatin-bevacizumab	Oxaliplatin-cetuximab
CMS2	42·0 (39·3–54·4)	36·0 (33·5–43·3)	38·3 (33·9–42·8)	29·1 (25·0–33·3)	Irinotecan/oxaliplatin-cetuximab	Irinotecan-bevacizumab
CMS3	26·8 (20·9–36·0)	15·1 (10·8–30·1)	16·6 (0·0–42·3)	18·6 (13·0–24·3)	Oxaliplatin-cetuximab	Oxaliplatin-bevacizumab
CMS4	30·8 (24·4–43·5)	32·7 (26·3–37·5)	40·1 (20·3–59·9)	21·1 (14·8–27·3)	Irinotecan-cetuximab	Irinotecan-bevacizumab

Figure 4: **Overall survival by first-line biological therapy and chemotherapy combinations and CMS classification**
Most effective combinations for each CMS subtype are highlighted in red. Least effective combinations for each CMS subtype are highlighted in blue. 80% of the left-sided tumours (CMS2 and CMS4) could benefit from irinotecan with cetuximab. Cetuximab is part of the most effective combination for 86% of tumours (CMS2, CMS3, and CMS4). Data are reproduced from the FIRE-3 study[2] and the CALGB study.[3] CMS=Consensus Molecular Subtypes.

1. The CMS classification seems to be predictive of the most effective **1st-line** chemotherapy + biological combination that achieves the longest survival for each CMS tumor subtype[1]

2. Each CMS tumor has a ***different*** 'best 1st-line combination' further demonstrating that the era of 'one treatment fits all' – is over!

3. Choosing the best 1st-line combination for a CMS tumor subtype can **double the survival** of the patient or **increase the median survival by almost a year**[1]

4. It seems that the CMS classification is a unique and most comprehensive **'personalized approach' which may** guide the CRC treatment[1]

5. The dramatic life prolongation is obtained not by a 'new drug' but by simple **optimization** of the combinations of established drugs to obtain benefit according to the CMS prediction[1]

Most effective 1st-line combination[1]

- FOLFOX + Bevacizumab
- FOLFIRI/FOLFOX + Cetuximab
- FOLFOX + Cetuximab
- FOLFIRI + Cetuximab

86%

Median Overall Survival[1]

	CALGB/SWOG 80405* Oxaliplatin (75%)		FIRE-3† Irinotecan (100%)	
	Cetuximab	Bevacizumab	Cetuximab	Bevacizumab
CMS1	11.7	22.5	17.9	13.1
CMS2	42.0	36.0	38.3	29.1
CMS3	26.8	15.1	16.6	18.6
CMS4	30.8	32.7	40.1	21.1

6. **FINAL CONCLUSION: cetuximab is part of the 1st-line 'best' combination in 86% of the CRC tumors while bevacizumab is in 14%[1]**

1. Aderka D, et al. Lancet Oncol 2019;20:e274–283; 2. Venook AP, et al. JAMA 2017;317:2392–2401; 3. Heinemann V, et al. Lancet Oncol 2014;15:1065–1075.

Zaključki (1)….2019

- wt*RAS* ⟹ anti-EGFR
- mt*BRAF* ⟹ BRAF+ MEK+ anti- EGFR, BRAF + KT(irinotekan) + anti- EGFR
- MSI- H ⟹ anti- PD-1 mono, anti- PD- 1 + anti- CTLA-4
- HER- 2 ⟹ anti- HER 2 kombinacija
- TRK genske fuzija ⟹ NTRK inhibitorji

Zaključki (2)….2019…..

- Lokacija primarnega tumorja- sistemska terapija:
  - wtRAS/wtBRAF levi kolon: KT+anti-EGFR
  - wtRAS/wtBRAF desni kolon: ?

- CMS podtipi → sistemska terapija?

"CMS klasifikacija trenutno predstavlja najboljši opis tumorske heterogenosti raka debelega črevesa in danke na ravni izražanja genov in predstavlja napredek v personalizirani medicini."

ONKOLOŠKI INŠTITUT
INSTITUTE OF ONCOLOGY
LJUBLJANA

Naslov

ADJUVANTNO SISTEMSKO ZDRAVLJENJE RAKA DEBELEGA ČREVESA IN DANKE

9. Šola tumorjev prebavil
22. 11. 2019, Ljubljana, Slovenija

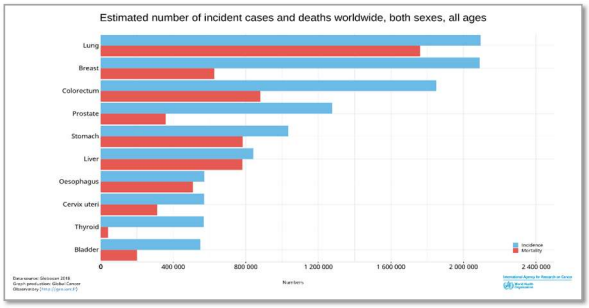
Marija Ignjatović, dr. med

AGENDA

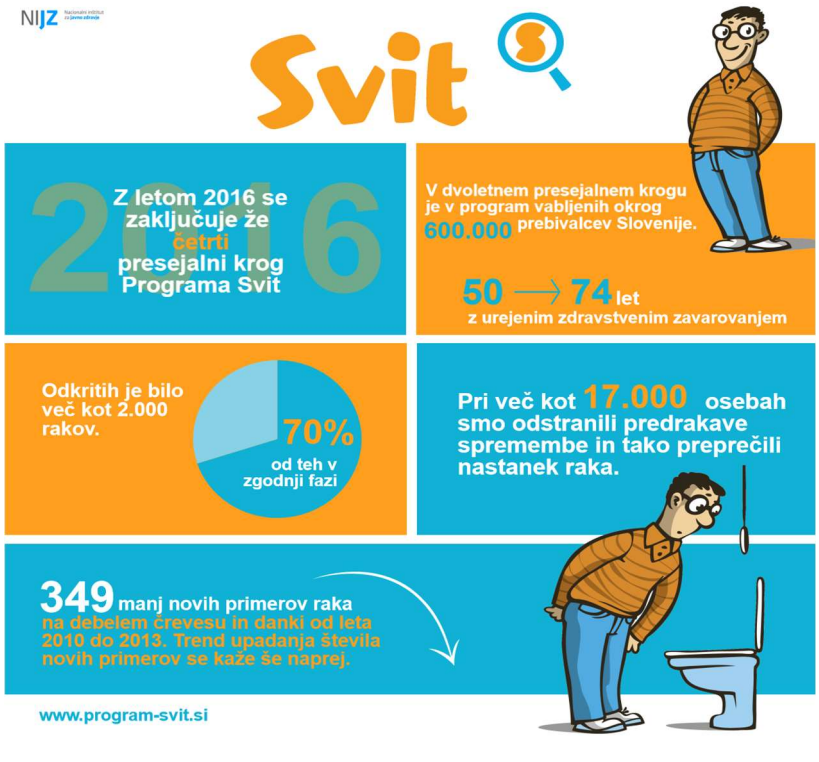
- ✓ **Splošne informacije**
- ❑ Stadij II
- ❑ Stadij III
- ❑ Pravi čas za adjuvantno kemoterapijo (adj. KT)
- ❑ Kaj ne smemo narediti?

RAK DEBELGA ČREVESA IN DANKE (RDČD)

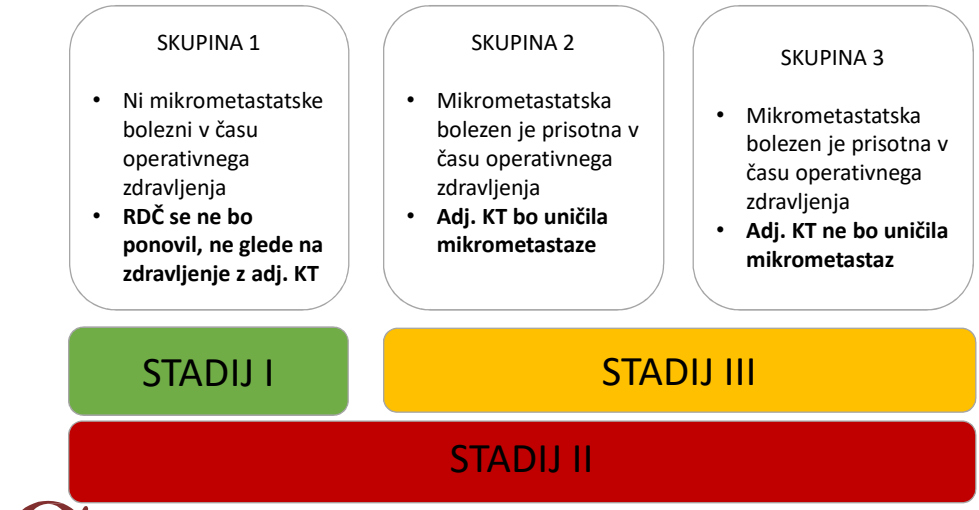
- **Incidenca: 3.** najpogostejši malignom
- **Mortaliteta: 2.** najpogostejši malignom zaradi katerega umrejo bolniki
  - upada v bolj razvitih državah! (presejalni program, boljše zdravljenje raka debelega črevesa in danke)
- **Presejalni program**



Bray F, Ferlay J, Soerjomataram I et al. CA Cancer J Clin. 2018 Nov;68(6):394-424; Arnold M, Sierra MS, Laversanne M, et al. Gut. 2017;66:683-691



BOLNIKI Z ZGODNJIM RDČ



Varghese A. Clin Colon Rectal Surgery 2015;28:256-261

AGENDA

- ❑ Splošne informacije
- ✓ **Stadij II**
- ❑ Stadij III
- ❑ Pravi čas za adjuvantno kemoterapijo (adj. KT)
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″the role of adjuvant therapy in stage II CRC remains an area of great controversy despite multiple clinical trials and meta-analyses. Questions remain not only about ***which patients will benefit from treatment*** but also ***what chemotherapy to use*** if adjuvant chemotherapy is recommended″.

Varghese A. Clin Colon Rectal Surgery 2015;28:256-261

KAKO IZBRATI PRAVEGA BOLNIKA ZA adj. KT

- ❑ Fizična zmogljivost
- ❑ Pridružene bolezni
- ❑ **Kliničnopatološki rizični dejavniki**
- ❑ **Molekularne lastnosti tumorja**

RIZIČNI DEJAVNIKI (RD)

- Klinični RD
  - Perforacija
  - Obstrukcija
- Kirurški RD
  - < 12 odstranjenih limfnih bezgavk (LN)
- Patološki RD
  - G3
  - Limfovaskularna invazija (LVI)
  - Perinevralna invazija (PNI)

NIZKO rizična skupina	***VISOKO rizična skupina***
T3	T4
Brez perforacije	Perforacija
Brez obstrukcije	Obstrukcija
≥ 12 LN	< 12 LN
G1, G2	G3
Brez LVI	LVI
Brez PNI	PNI
BREZ adj. KT	***ZA adj. KT***

MMR KOT MOLEKULARNI FAKTOR

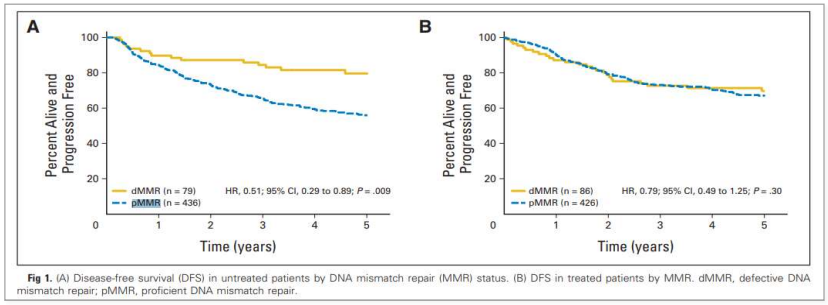


Fig 1. (A) Disease-free survival (DFS) in untreated patients by DNA mismatch repair (MMR) status. (B) DFS in treated patients by MMR. dMMR, defective DNA mismatch repair; pMMR, proficient DNA mismatch repair.

	dMMR	**pMMR**
PROGNOZA	boljša	slabša
OBČUTLJIVOST NA FLUOROPIRIMIDINE (FP)	ne	da
IZID ZDRAVLJENJA S FLUOROPIRIMIDINI	slabši	boljši

Sargent et al. J Clin Oncol. 2010;3219-3226

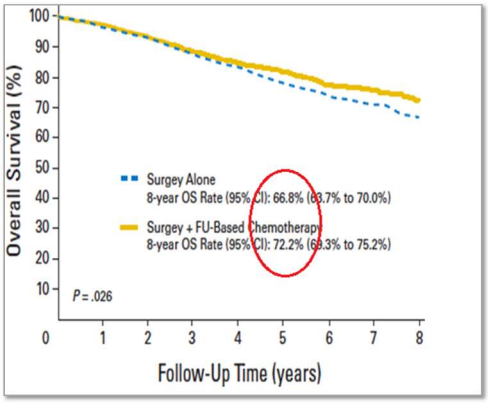
Kaj, če ima bolnik z dMMR tumorjem dva ali več RD (T4b, perforacija)?

NIZKO RIZIČNI	SPREMLJANJE	
*VISOKO RIZIČNI, **dMMR***	*SPREMLJANJE ZA VEČINO BOLNIKOV*	*ADJ. KT SAMO ZA IZBRANE BOLNIKE*
VISOKO RIZIČNI, **pMMR**	ADJ. KT	

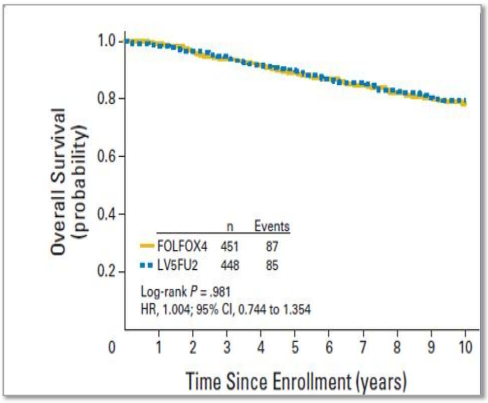
″the role of adjuvant therapy in stage II CRC remains an area of great controversy despite multiple clinical trials and meta-analyses. Questions remain not only about which patients will benefit from treatment but also ***what chemotherapy to use*** if adjuvant chemotherapy is recommended″.

Varghese A. Clin Colon Rectal Surgery 2015;28:256-261

FP ZADOSTUJEJO (pMMR)



8-letna absolutna dobrobit
5.4%



MOSAIC klinična študija

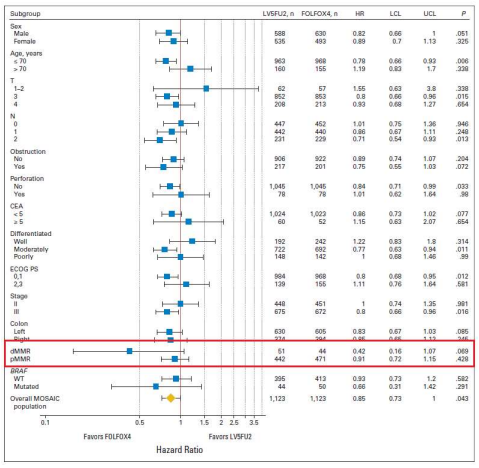
Sargent D. et al. J Clin Oncol. 2009; 29:872-877; Tournigand C. et al. J Clin Oncol 2015;33:4176-4187

NIZKO RIZIČNI	SPREMLJANJE	
VISOKO RIZIČNI, dMMR	*SPREMLJANJE ZA VEČINO BOLNIKOV*	*KATERA KT? REZISTENTNI NA FP!*
VISOKO RIZIČEN, pMMR	ADJ. KT	Samo FP 6 mesecev

HR, dMMR in OKSALIPLATIN

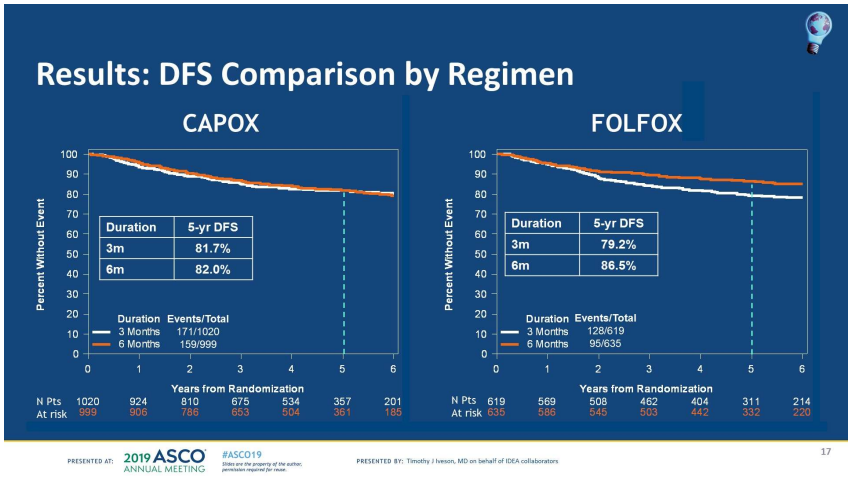
˝for patients who have dMMR tumors and HR features, we suggest the use of an oxaliplatin-based regiment rather than fluoropyrimidines alone˝

- ❑ *Ni prospektivnih randomiziranih raziskav,* ***samo retrospektivne analize***
- ❑ MOSAIC (posodobljeni podatki po 10-letnem spremljanju)



André T et al. J Clin Oncol 2015;

IDEA:*International* ***D****urations* ***E****valuation of* ***A****djuvant Cht. In* ***HR stage II CRC***



NIZKO RIZIČNI | **SPREMLJANJE**

VISOKO RIZIČNI, dMMR | ***ADJ. KT SAMO ZA IZBRANE BOLNIKE*** *ZA OSTALE SPREMLJANJE* | ***XELOX 3 mesece FOLFOX 6 mesecev***

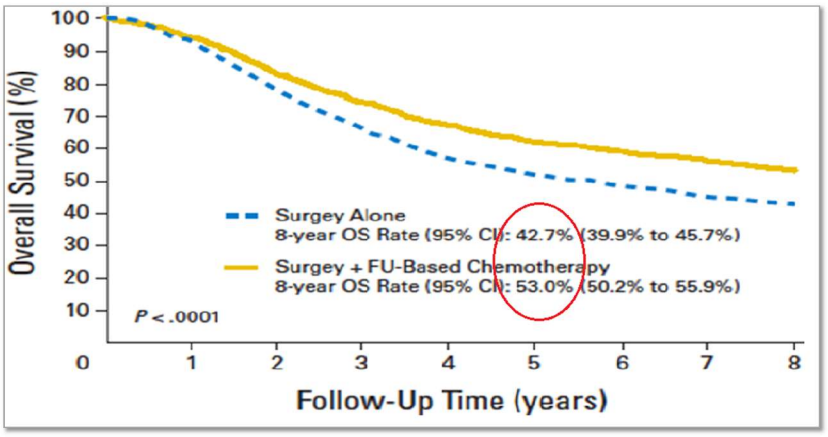
HIGH RISK, pMMR | **ADJ.ChT** | **Samo FP 6 mesecev**

AGENDA

- ❑ Splošne informacije
- ❑ Stadij II
- ✓ **Stadij III – ni tako kompliciran**
- ❑ Pravi čas za adjuvantno kemoterapijo (adj. KT)
- ❑ Kaj ne smemo narediti?

Adj. KT je standarno zdravljenje vseh bolnikov z RDCD stadija III

ADJ. KT NA BAZI FP



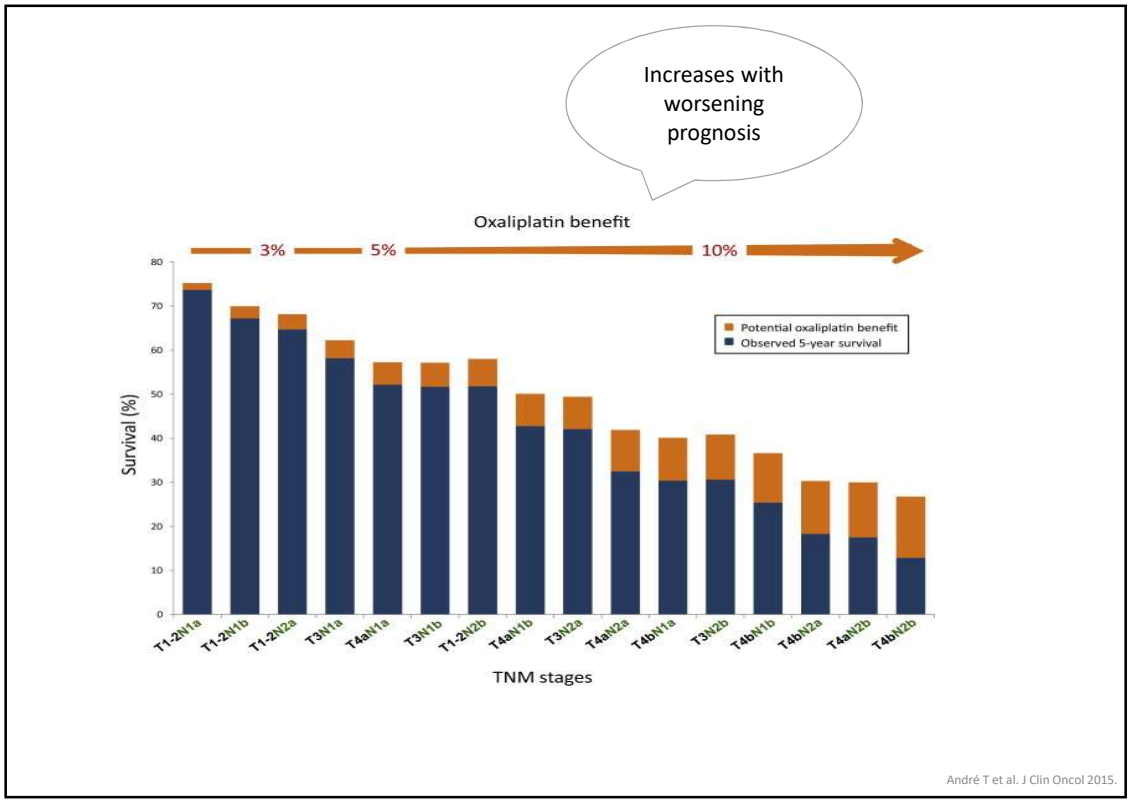
8-letna absolutna dobrobit
10.3%

Sargent D. et al. J Clin Oncol. 2009; 29:872-877

FOLFOX ali XELOX 6 mesecev

KL. ŠTUDIJA	ŠT. BOL.	STADIJ	EKSPERIMENTALNA VS KONTROLNA skupina	FOLLOW UP	REZULTATI	HR (p)	OS (abs.ben.)
MOSAIC	2246	**III**/II	FOLFOX vs bFU 6 months	10 DFS **10 OS**	62% vs 54% 67.1% vs 59%	0.79 (0.007) 0.80 (0.016)	**8.1 %**
NSABP-C07	2407	**III**/II	FLOX vs bFU 6 months	5-DFS **5 OS**	69% vs 65% 80% vs 78%	0.80 (0.0038) 0.82 (0.002)	**2%**
XELOXA	1886	**III**	CAPOX vs bFU 6 months	7 DFS **7 OS**	63% vs 56% 73% vs 67%	0.80 (0.004) 0.83 (0.04)	**6%**

André T et al. J Clin Oncol 2015; Yothers G et al. J Clin Oncol 2011; Schmoll HJ et al. J Clin Oncol 2015.



André T et al. J Clin Oncol 2015.

POLINEVROPATIJA IN OKSALIPLATIN

Grade	NCI-CTC 3.0	Oxaliplatin-specific scale
I	loss of deep tendon reflexes or paresthesia, including tingling, but not interfering with function	sensory symptoms of **short duration**
II	objective sensory alteration or paresthesia, including tingling, interfering with function, but not interfering with activities of daily living	sensory symptoms **persisting** between cycles
III	sensory alteration or paresthesia interfering with activities of daily living	sensory symptoms causing **functional impairment**
IV	Permanent sensory losses that are disabling	-

KL. ŠTUDIJA	PNP G3
MOSAIC	12%
NSABP-C07	8.2%
XELOXA	11%

André T et al. J Clin Oncol 2015; Yothers G et al. J Clin Oncol 2011; Schmoll HJ et al. J Clin Oncol 2015.

Lahko zdravljenje z ADJ. KT (FP + oksaliplatin) traja manj kot 6 mesecev???

*IDEA:International Durations Evaluation of Adjuvant Cht. In **stage III CRC***

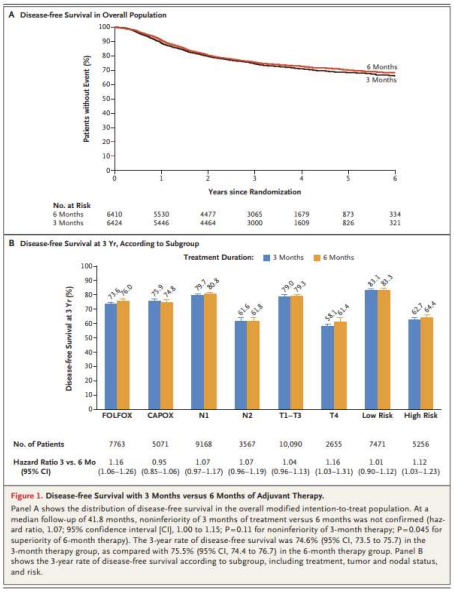
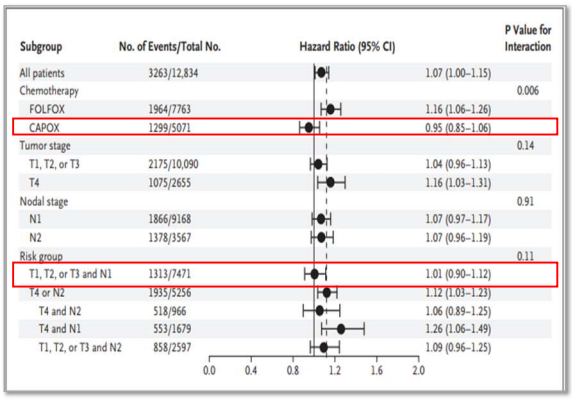


Figure 1. Disease-free Survival with 3 Months versus 6 Months of Adjuvant Therapy.
Panel A shows the distribution of disease-free survival in the overall modified intention-to-treat population. At a median follow-up of 41.8 months, noninferiority of 3 months of treatment versus 6 months was not confirmed (hazard ratio, 1.07; 95% confidence interval [CI], 1.00 to 1.15; P=0.11 for noninferiority of 3-month therapy; P=0.045 for superiority of 6-month therapy). The 3-year rate of disease-free survival was 74.6% (95% CI, 73.5 to 75.7) in the 3-month therapy group, as compared with 75.5% (95% CI, 74.4 to 76.7) in the 6-month therapy group. Panel B shows the 3-year rate of disease-free survival according to subgroup, including treatment, tumor and nodal status, and risk.



Grothey A et al. N Engl J Med 2018.

	XELOX	FOLFOX
NIZKO RIZIČNI	3 MESECE	*3 do **6** mesecev*
VISOKO RIZIČNI	*3 do **6** mesecev*	6 MESECEV

Table 3. Selected Adverse Events, According to Treatment and Duration of Therapy.*

Adverse Event	FOLFOX				CAPOX			
	Grade 1	Grade 2	Grade 3 or 4	P Value	Grade 1	Grade 2	Grade 3 or 4	P Value
	number (percent)				*number (percent)*			
Any adverse event				<0.001				<0.001
3 mo	1008 (30.7)	1039 (31.6)	1236 (37.6)		496 (35.0)	578 (40.8)	342 (24.2)	
6 mo	363 (11.0)	1056 (32.1)	1874 (56.9)		203 (14.6)	674 (48.5)	512 (36.9)	
Peripheral sensory neurotoxicity†				<0.001				<0.001
3 mo	2661 (83.4)	450 (14.1)	80 (2.5)		1211 (85.8)	164 (11.6)	37 (2.6)	
6 mo	1700 (52.2)	1036 (31.8)	519 (15.9)		763 (55.0)	500 (36.0)	124 (8.9)	
Diarrhea				<0.001				0.01
3 mo	2611 (83.8)	356 (11.4)	147 (4.7)		1171 (82.8)	139 (9.8)	104 (7.4)	
6 mo	2525 (79.8)	411 (13.0)	227 (7.2)		1090 (78.5)	176 (12.7)	122 (8.8)	
Febrile neutropenia				0.33				0.04
3 mo	2897 (97.7)	7 (0.2)	62 (2.1)		1407 (99.4)	6 (0.4)	2 (0.1)	
6 mo	2933 (97.1)	20 (0.7)	68 (2.3)		1373 (98.8)	9 (0.6)	8 (0.6)	
Neutropenia				<0.001				<0.001
3 mo	1310 (66.4)	264 (13.4)	400 (20.3)		898 (73.4)	231 (18.9)	94 (7.7)	
6 mo	1087 (54.1)	389 (19.4)	534 (26.6)		733 (61.2)	321 (26.8)	143 (11.9)	
Thrombocytopenia				<0.001				<0.001
3 mo	1812 (92.0)	139 (7.1)	19 (1.0)		1104 (90.3)	93 (7.6)	26 (2.1)	
6 mo	1703 (85.0)	264 (13.2)	37 (1.8)		966 (80.7)	181 (15.1)	50 (4.2)	
Nausea				<0.001				0.02
3 mo	1729 (87.6)	213 (10.8)	31 (1.6)		1070 (87.4)	117 (9.6)	37 (3.0)	
6 mo	1636 (81.5)	327 (16.3)	45 (2.2		997 (83.3)	163 (13.6)	37 (3.1)	
Vomiting				0.29				0.91
3 mo	1863 (94.6)	82 (4.2)	25 (1.3)		1151 (94.0)	48 (3.9)	25 (2.0)	
6 mo	1878 (93.6)	101 (5.0)	27 (1.3)		1119 (93.5)	62 (5.2)	16 (1.3)	
Mucositis				<0.001				0.007
3 mo	1029 (95.2)	44 (4.1)	8 (0.7)		1085 (97.1)	29 (2.6)	3 (0.3)	
6 mo	1005 (91.4)	76 (6.9)	18 (1.6)		1050 (95.1)	44 (4.0)	10 (0.9)	
Fatigue				<0.001				<0.001
3 mo	1722 (87.4)	215 (10.9)	34 (1.7)		1130 (92.3)	82 (6.7)	12 (1.0)	
6 mo	1594 (79.6)	327 (16.3)	82 (4.1)		1034 (86.4)	129 (10.8)	34 (2.8)	
Hand–foot syndrome				0.03				<0.001
3 mo	307 (98.7)	4 (1.3)	0		654 (94.4)	34 (4.9)	5 (0.7)	
6 mo	294 (96.1)	11 (3.6)	1 (0.3)		593 (86.2)	77 (11.2)	18 (2.6)	

Grothey A et al. N Engl J Med 2018.

AGENDA

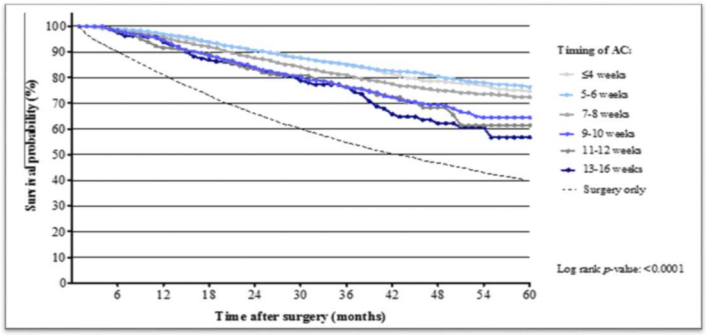
- ❑ Splošne informacije
- ❑ Stadij II
- ❑ Stadij III – ni tako kompliciran
- ✓ **Pravi čas za adjuvantno kemoterapijo (adj. KT)**
- ❑ Kaj ne smemo narediti?

KDAJ JE NAJBOLJŠE ZAČETI Z ADJ. KT?

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
European Society for Medical Oncology
Guidelines

Adjuvant chemotherapy should be started as early as possible starting from the fourth week up to a maximum of 8–12 weeks after surgery [IV, B] (refer to colon cancer chapter 7.3.2.5). Adjuvant treatment should not be started in the presence of inadequate postoperative recovery or pelvic septic complications.

ing of chemotherapy after surgery. In this report, our systematic review and meta-analysis indicates that relative OS decreases by 14% for every 4-week delay to initiation of AC. Our results are also consistent across DFS and cancer-specific survival analyses.



Biagi JJ et al. JAMA 2011; Acrk et al, Eur J Cancer 2015

KDAJ JE NAJBOLJŠE ZAČETI Z ADJ. KT?

- ***4 do 8 tednov po operativnem zdravljenju!***
- Daljši čas do začetka adj. KT, slabše preživetje

- ***Bolnik: pooperativni zapleti, pridružene bolezni***
- Problem zdravstvenega sistema: čakalne dobe,…

AGENDA

- ❑ Splošne informacije
- ❑ Stadij II
- ❑ Stadij III – ni tako kompliciran
- ❑ Pravi čas za adjuvantno kemoterapijo (adj. KT)
- ✓ **Kaj ne smemo narediti?**

NE ZDRAVITE VAŠE BOLNIKE

- ***Z adj. KT, ki je na osnovi irinotekana***
- ***Adj. KT + zaviralec angiogeneze/EGFR inhibitor***

ADJ. KT pri RDČD

- **Začeti 4 do 8 tednov po operaciji**
- **Stadij II**
  - **ADJ. KT NI standard zdravljenja za vse bolnike**
  - **Visoko rizični, pMMR: kapecitabin** ali 5FU, 6 mesecev
  - **Visoko rizični, dMMR: samo za izbrane bolnike, XELOX 3 mesece ali FOLFOX 6 mesecev**
- **Stadij III**
  - **Je standard zdravljenja za vse bolnike**
  - **Nizko rizični, XELOX 3 mesece**
  - **Visoko rizični, XELOX ali FOLFOX 6 mesecev**
  - Kapecitabin 6 mesecev (če niso primerni za zdravljenje v kombinaciji z oksaliplatinom)

Totalno neoadjuvantno zdravljenje raka danke

Vaneja Velenik

Standardna KRT

- Standardna KRT
  - 45-54 Gy
  - 5-FU/kapecitabin
  - Interval do operacije

Izid zdravljenja zelo različen

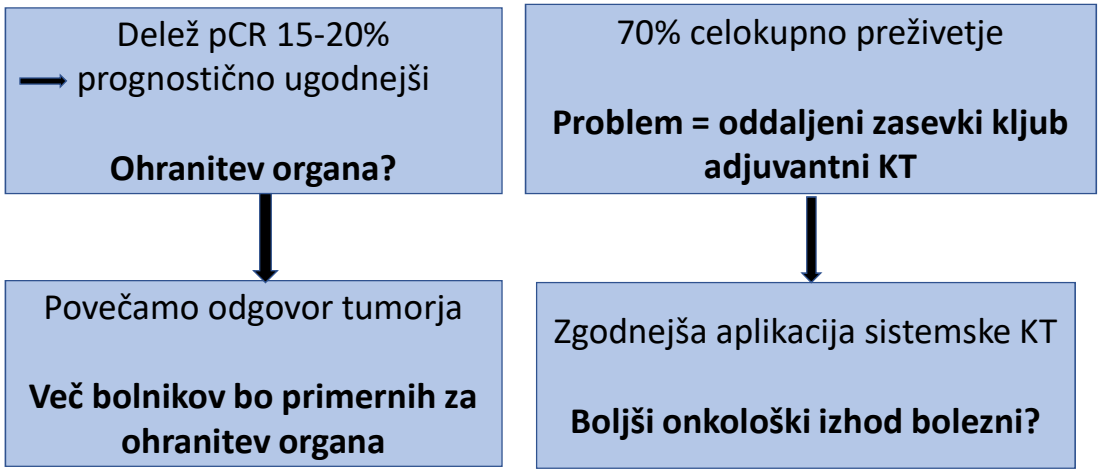
Delež pCR 15-20%
⟶ prognostično ugodnejši

Ohranitev organa

70% celokupno preživetje

Problem = oddaljeni zasevki kljub adjuvantni KT

Standardna KRT



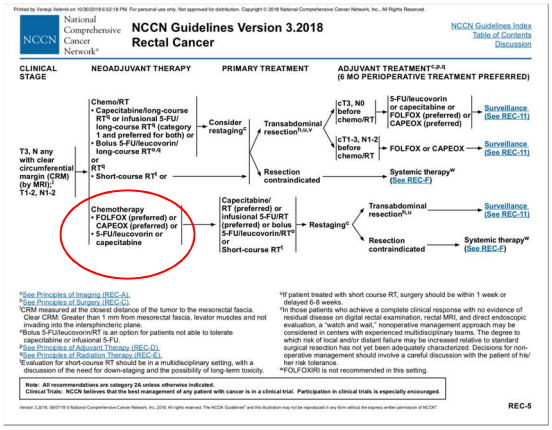
Totalno neoadjuvantno zdravljenje

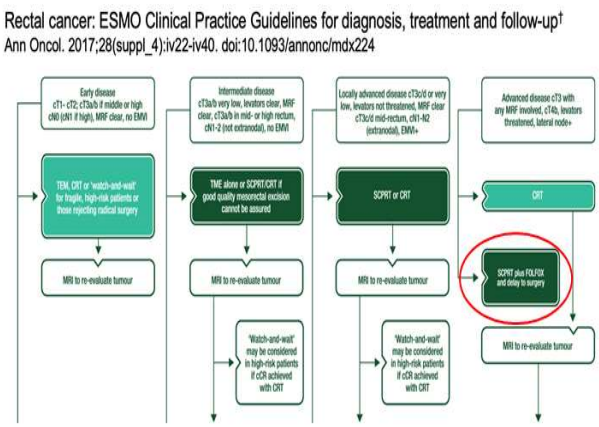
- Kombinacija predoperativne (K)RT s predoperativno KT namesto pooperativne

Katero zaporedje terapij?
Najprej KT ali najprej RT?

Dvojni cilj:
1. Komplianca na zdravljenje
2. Izhod bolezni (ohranitev organa, DFS)

KT + KRT **ali** **RT + KT**



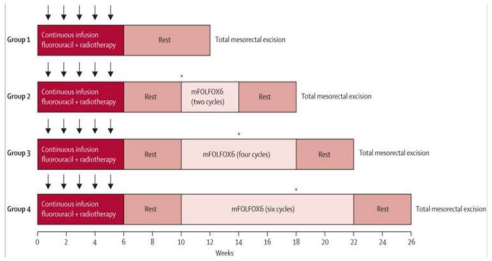


Najprej KT

- Španska GCR-3 raziskava (n=108)
  - 4x CAPOX + CRT (CAPOX)
  - CRT (CAPOX) + adj. 4x CAPOX
- EXPERT raziskava (n=105)
  - 4x CAPOX + CRT (cape) + adj cape
- EXPERT-C raziskava (n=165)
  - 4x CAPOX+cet + CRT (cape+cet) + adj. CAPOX+cet
  - 4xCAPOX + CRT (cape) + adj.4xCAPOX

Najprej RT

- Garcia-Aguilar (n=259)



- Poljska II raziskava (n=515)
  - Kratek RT + 3xFOLFOX4
  - KRT (5-FU/Oxali)

Najprej KT

ZA

- Zgodnje zdravljenje mikrometastaz
- Večja komplianca na zdravljenje s KT
  - [1]Španska GCR-3: 94%
  - [2]EXPERT: 87%
  - [3]EXPERT-C: 94%

PROTI

- Možnost slabše compliance na kasnejšo KRT
- Možna indukcija pospešene repopulacije in zato slabša učinkovitost KRT[4]

[1]Fernandez-Martos et al. Ann Oncol 2015
[2]Chua et al. Lancet Oncol 2010
[3]Dewdney et al. JCO 2012

[4]Glynne-Jones et al. Br J Cancer 2006

Najprej RT

ZA

- Ni indukcije pospešene repopulacije z uvodno KT
- Večja komplianca na KRT
- Še vedno zgodnja uvedba sistemskega zdravljenja mikrometastaz

PROTI

- Možnost slabše compliance na kasnejšo KT
  - [1]Garcia-Aguilar: 77%-81%-82%
  - [2]Poljska: 72%

[1]Garcia-Aguilar et al. et al. Lancet Oncol 2015
[2]Bujko et al. Ann Oncol 2016

Kaj pa izhod bolezni?

Preživetje

Najprej KT

5-L OS

Španska GCR-3: 75% vs 78% (standardna roka)

EXPERT (3L): 83%

EXPERT-C: ↑ OS v roki s cet

5-L DFS

Španska GCR-3: 62% vs 64% (standardna roka)

EXPERT: 62%

EXPERT-C: :↑ DFS v roki s cet

Najprej RT

5-L OS

~~Garcia-Aguilar: NR~~

~~Poljska (3L): 73% vs 65% (standardna~~ roka)

5-L DFS

- Garcia Aguilar: NR
- Poljska (3L): 53% vs 52% (standardna roka)

Preživetje

Najprej KT

5-L OS

Španska GCR-3: 62% vs 64% (standardna roka)

EXPERT: 62%

EXPERT-C: : ↑DFS v roki s cet

Najprej RT

5-L OS

- Garcia Aguilar: NR
- Poljska: 53% vs 52% (standardna roka)

Ni direktne primerjave
Raziskave so se osredotočale na patološki izid
Ni sklepa, katera strategija je boljša

Popolni patološki odgovor

Najprej KT

Španska GCR-3: 13% vs 14% (standardna roka)

EXPERT: 20%

EXPERT-C: 11% vs 9% (standardna roka)

Najprej RT

Garcia-Aguilar:
stand.roka 18%
2x mFOLFOX6 25%
4x mFOLFOX6 30%
6x mFOLFOX6 38%

Poljska: 3xFOLFOX 16% vs 12% (standardna roka)

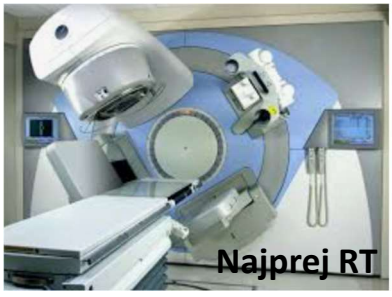
Popolni patološki odgovor

Najprej KT | **Najprej RT**

Različne stopnje pCR:
- heterogenost kohort bolnikov
- heterogenost zdravljenja
- različen časovni interval do operacije
- ni randomizacije

→ **Nemogoče narediti zaključek**

VS

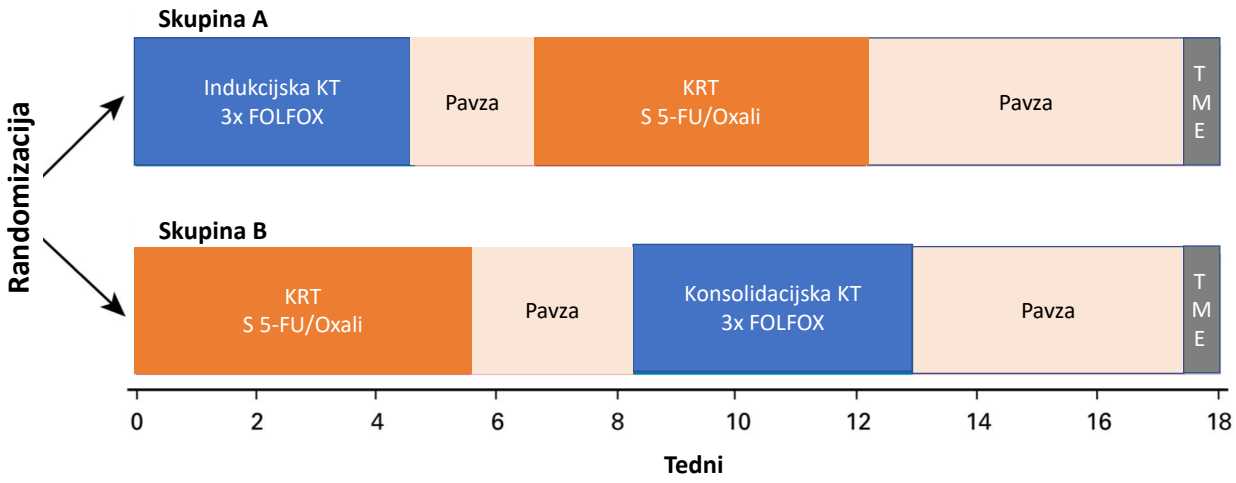


original report

Randomized Phase II Trial of Chemoradiotherapy Plus Induction or Consolidation Chemotherapy as Total Neoadjuvant Therapy for Locally Advanced Rectal Cancer: CAO/ARO/AIO-12

Emmanouil Fokas, MD, DPhil[1,2,3,4]; Michael Allgäuer, MD[5]; Bülent Polat, MD[6]; Gunther Klautke, MD[7]; Gerhard G. Grabenbauer, MD[8]; Rainer Fietkau, MD[9]; Thomas Kuhnt, MD[10]; Ludger Staib, MD[11]; Thomas Brunner, MD[12,13]; Anca-Ligia Grosu, MD[12]; Wolff Schmiegel, PhD, MD[14]; Lutz Jacobasch, MD[15]; Jürgen Weitz, MD[2,16,17]; Gunnar Folprecht, MD[2,16,17]; Anke Schlenska-Lange, MD[2]; Michael Flentje, MD[6]; Christoph-Thomas Germer, PhD[6]; Robert Grützmann, MD[5]; Matthias Schwarzbach, MD[18]; Vittorio Paolucci, MD[19]; Wolf O. Bechstein, MD[1]; Tim Friede, PhD[20]; Michael Ghadimi, MD[20]; Ralf-Dieter Hofheinz, MD[21]; and Claus Rödel, MD[1,2,3,4]; on behalf of the German Rectal Cancer Study Group

Fokas et al. JCO 2019 (ahead of print)



Faza II raziskave z zasnovo “pick the winner”

Hipoteza = porast deleža pCR na 25% po TNT v primerjavi s standardom, ki je 15%

Najprej KT (N=156)	Najprej RT (N=150)
S KRT povezana G3 in 4 toksičnost 37%	**S KRT povezana G3 in 4 toksičnost** 27%
• **Komplianca** Polna doza RT: 91% Konkomitantni 5-FU: 78% Konkomitantni oxali: 76% Indukcijska KT: 92%	• **Komplianca** Polna doza RT: 97% Konkomitantni 5-FU: 87% Konkomitantni oxali: 93% Konsolidacijska KT: 85%
• **Delež pCR** 17% (p = 0.210)	• **Delež pCR** 25% (p < 0.001)

Glavne ugotovitve:

- **Nižja toksičnost in višja komplianca, če je najprej RT**
  - Sočasen 5-FU/oxali lahko prispeva k večji toksičnosti KRT in nižji kompliance (posebno po indukcijski KT)
- **Večja komplianca na indukcijsko KT, če je najprej KT v primerjavi s konsolidacijsko KT, če je najprej RT**
- **Višji delež pCR, če je najprej RT**
  - Vendar: interval, če je najprej RT = 90 dni vs 45 dni, če je najprej KT
  - Pretvorba višjega pCR v boljši onkološki izid?
    - Ni še podatkov
    - Slabša komplianca na konsolidacijo lahko vpliva na DFS

Imamo zmagovalca!

…….?????

- Različni TNT pristopi za različne cilje zdravljenja ali skupine bolnikov?

➡ Najprej RT, če želimo zmanjšanje tumorja

➡ Najprej KT, če obstoja visoko tveganje za mikrometastatsko bolezen

- Potrebujemo dolgoročne rezultate!

BJS

Systematic review

Systematic review of outcomes after total neoadjuvant therapy for locally advanced rectal cancer

A. Zaborowski ✉, A. Stakelum, D. C. Winter

- 10 raziskav z indukcijsko KT, 612 bolnikov
- Vsaj 50% raziskav je vključevalo KRT z oxaliplatinom
- pCR 21.8% (10-40%), R0 94.9%
- lokalna ponovitev: 3.5%

  sistemska ponovitev: 20.6%

  5L OS 74.4%

  5L DFS 65.4%

ANNALS OF SURGERY

Total Neoadjuvant Therapy in Rectal Cancer

A Systematic Review and Meta-analysis of Treatment Outcomes

Petrelli, Fausto MD*; Trevisan, Francesca MD†; Cabiddu, Mary MD*; Sgroi, Giovanni MD‡; Bruschieri, Lorenza MD†; Rausa, Emanuele MD‡; Ghidini, Michele MD§; Turati, Luca MD‡

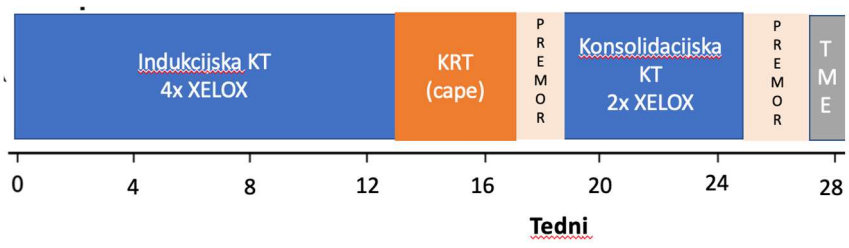
- 28 raziskav z indukcijsko ali konsolid. KT, 3579 bolnikov
- pCR 22.4.8% (10-40%), R0 95%
- lokalna ponovitev: 6%

  sistemska ponovitev: 21.5%

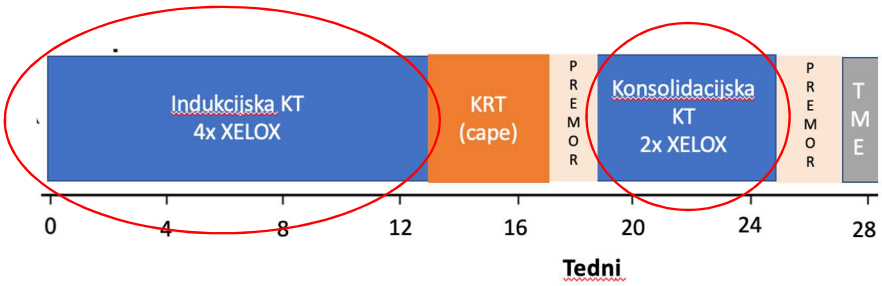
  5L OS 74 %

  5L DFS 65%

TNT v Sloveniji – od 2016

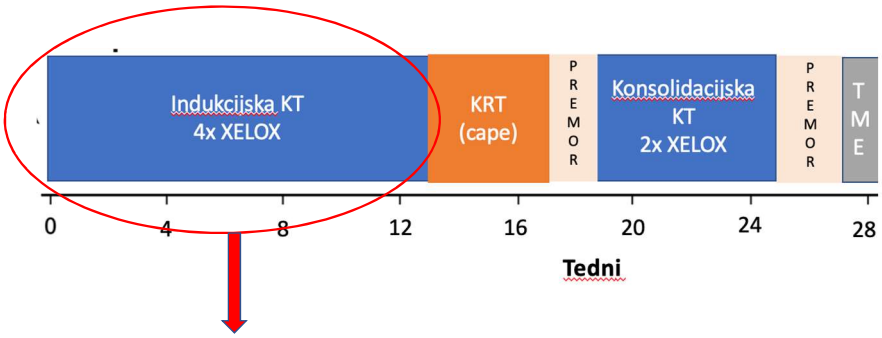


TNT v Sloveniji – od 2016



Kombinacija indukcijske in konsolidacijske KT
Skupaj 6 krogov KT (namesto 3-4 kot pri drugih)

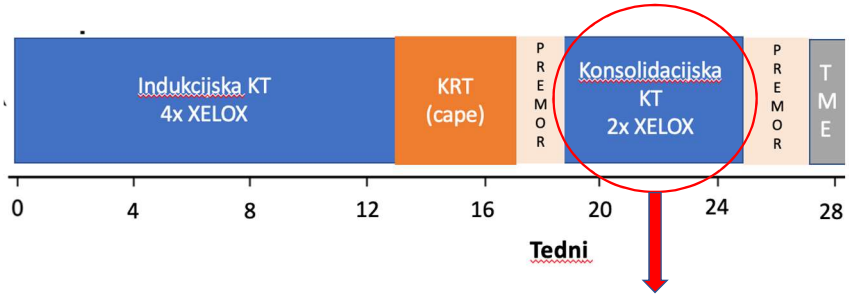
TNT v Sloveniji – od 2016



T4
EMVI +
Elstramezorektalne lgl +
N2 (2019)
MRF+ (2019)

Visoko tveganje za sistemsko ponovitev

TNT v Sloveniji – od 2016



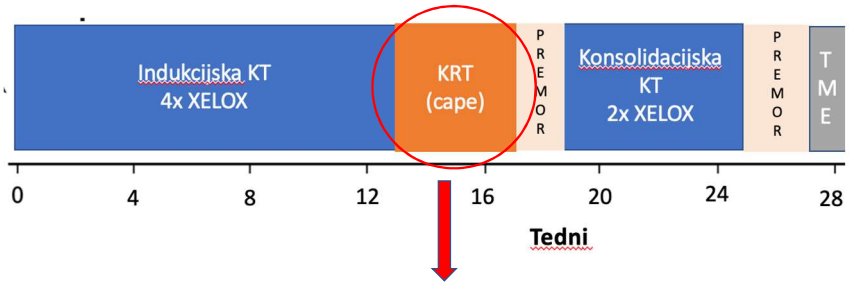
pCR 17.5% (klasična th < 10%)
Znižanje stadija N 77.7%
Znižanje stadija bolezni 79.3%

Radiol Oncol. 2018 Sep 11;52(3):267-274. doi: 10.2478/raon-2018-0028.

Induction chemotherapy, chemoradiotherapy and consolidation chemotherapy in preoperative treatment of rectal cancer - long-term results of phase II OlGIT-01 Trial.

Golo D[1], But-Hadzic J[1], Anderluh F[1], Brecelj E[2], Edhemovic I[2], Jeromen A[1], Omejc M[3], Oblak I[1], Secerov-Ermenc A[1], Velenik V[1].

TNT v Sloveniji – od 2016



IMRT tehnika (ostali 3D konformno-box)
Hipofrakcionacija (22 x 1.9 Gy + SIB 22 x 2.1/2.2 Gy) (ostali 28-30x 1.8 Gy)

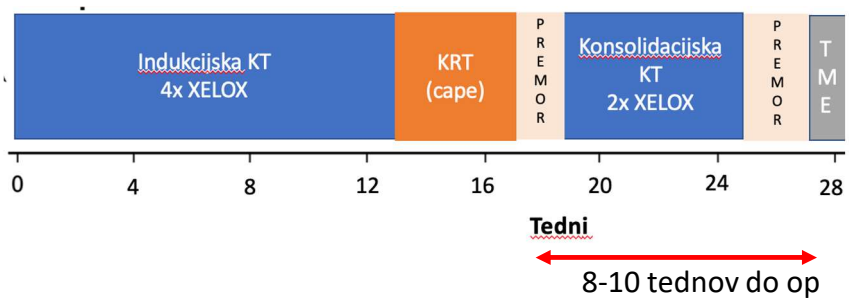
pCR 25.5%
Znižanje stadija T 68%
Znižanje stadija N 83%
Znižanje stadija bolezni 87%

Int J Radiat Oncol Biol Phys. 2016 Dec 1;96(5):1003-1010. doi: 10.1016/j.ijrobp.2016.08.031. Epub 2016 Aug 31.

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.

But-Hadzic J[1], Anderluh F[2], Brecelj E[3], Edhemovic I[3], Secerov-Ermenc A[2], Hudej R[2], Jeromen A[2], Kozelj M[4], Krebs B[4], Oblak I[2], Omejc M[5], Vogrin A[6], Velenik V[2].

TNT v Sloveniji – od 2016



8-10 tednov do op

CAO/ARO/AIO-12: najprej KT: 6.5 tednov
najprej RT: 13 tednov

TNT v Sloveniji – od 2016

Spodnja in srednja tretjina: 81.7%
Zgornja tretjina: 18.3%

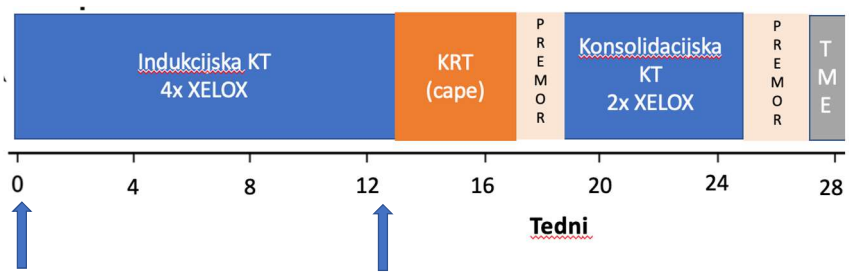
Stadij	N (%)
T2N2	1 (1.2)
T3N1	24 (29.3)
T3N2	27 (32.9)
T4N0	1 (1.2)
T4N1	6 (7.3)
T4N2	23 (28)

82 pts

- 53 M, 29 Ž
- 59 let (33-74)
- Na 0-15 cm od anorektalne zveze

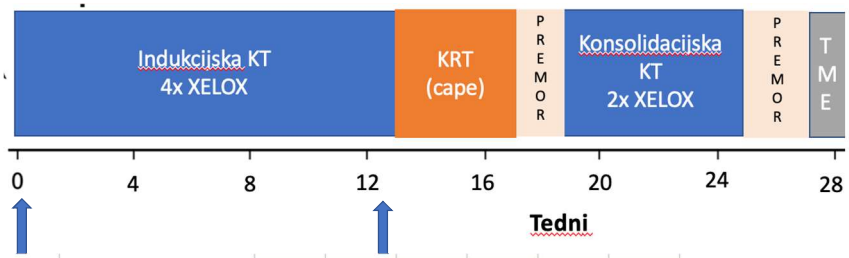
Dejavniki visokega tveganja za ponovitev bolezni	cT4	30	36,6%
	cN2	52	63,4%
	EMVI+	52	63,4%
	ekstramezor.lgl	6	7,3%
	MRF+	48	58,5%

Indukcijska KT



59 (71.9%) prejelo polni odmerek

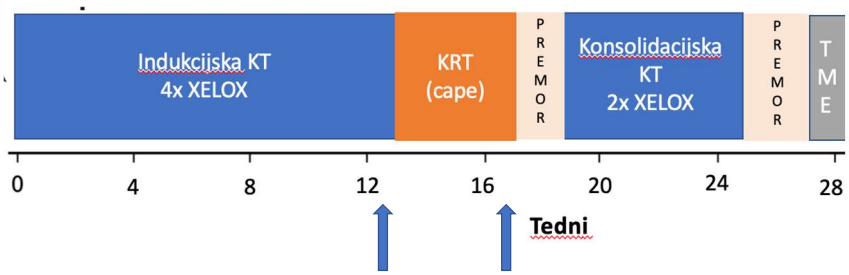
Indukcijska KT



		G1		G2		G3	
		N	%	N	%	N	%
Med indukcijsko KT	trombocitopenija	2	2,4	3	3,7		
	anemija	5	6,1	2	2,4		
	nevtropenija	1	1,2	5	6,1		
	febrilna nevtropenija					1	1,2
	patološki jetrni testi	1	1,2	2	2,4		
	okužba			2	2,4	1	1,2
	driska	4	4,9	3	3,7	1	1,2
	slabost	22	26,8	4	4,9		
	bruhanje	4	4,9	2	2,4		
	sindrom roka noga	6	7,3			2	2,4
	nevrotosičnost	38	46,3	4	4,9		

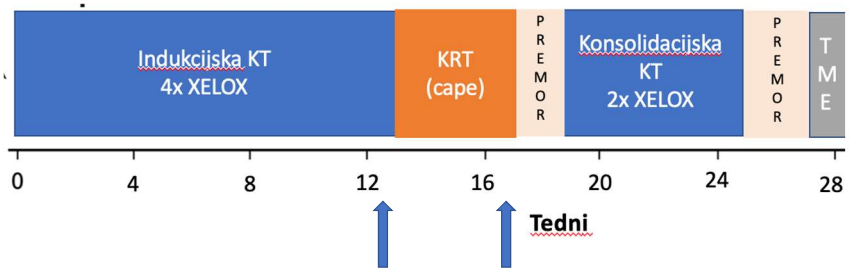
17/82 (21%) brez toksičnosti
5/82 (6%) G3

Radiokemoterapija



82 (100%) prejelo celotno TD
65 (79.3%) prejelo polni odmerek KT

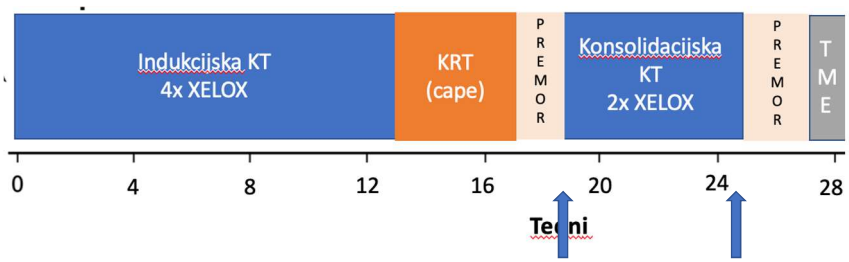
Radiokemoterapija



		G1		G2		G3	
		N	%	N	%	N	%
Med RTKT	trombocitopenija	11	13,4	2	2,4		
	anemija	5	6,1	4	4,9		
	nevtropenija	2	2,4	6	7,3		
	driska	25	30,5	4	4,9	3	3,7
	slabost	8	9,8				
	bruhanje	1	1,2				
	cistitis	22	26,8	4	4,9		
	proktitis	12	14,6	4	4,9		
	radiodermatitis	5	6,1	5	6,1	2	2,4
	sindrom roka noga	6	7,3	3	3,7	1	1,2

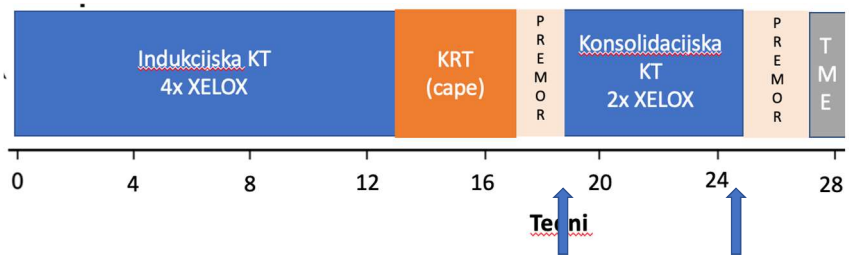
20/82 (24%) brez toksičnosti
6/82 (7.3%) G3

Konsolidacijska KT



76 (92.7%) prejelo oba kroga
59 (71.9%) prejelo polni odmerek KT

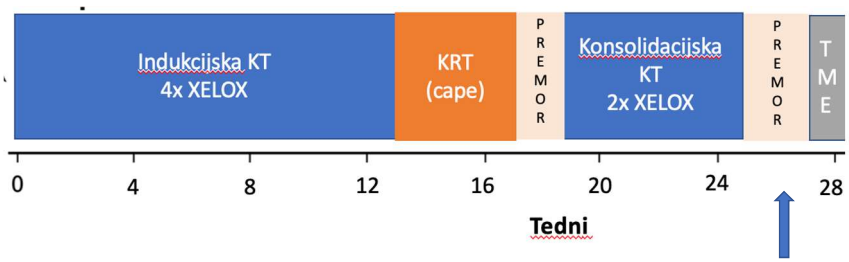
Konsolidacijska KT



48/82 (58.5%) brez toksičnosti
0/82 (0%) G3

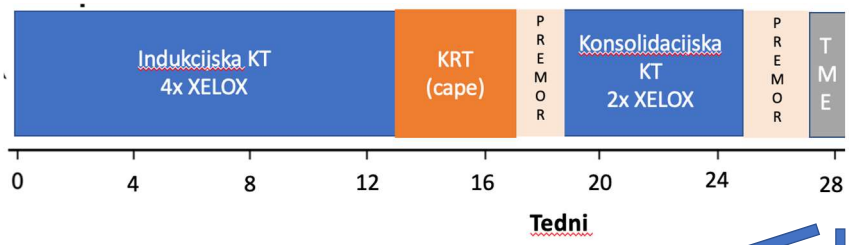
		G1		G2		G3	
		N	%	N	%	N	%
Med konsolidacijsko KT	trombocitopenija	2	2,4	3	3,7		
	anemija	7	8,5	1	1,2		
	nevtropenija			3	3,7		
	enterokolitis			1	1,2		
	driska			1	1,2		
	slabost	2	1,2				
	sindrom roka noga	3	3,7	1	1,2		
	nevrotoksičnost	13	15,9	2	2,4		

Predoperativna zamejitev lokalnega stadija



Kontrolni MRI ???
41%?? (88% na OI)

Operacija



- 5 bolnikov cCR -odklonijo op
- 1 bolnik cT2N0 – odkloni op, čez 1 leto zaradi ostanka op (pT1N0)
- 1 smrt pred definitivno op

75/82 (91.5%) bolnikov

Operacija

75

T
M
E

- Srednji čas do op (od konca RTKT): 11 tednov
- 28 kirurgov v 9 centrih (52% na OI)
- Ohranitev sfinktra pri 83% (62/75)
- Delež APE pri tumorjih spodnje tretjine: 43% (12/28)
- Brez perioperativnih zapletov 72% (54/75)

Učinkovitost

- pCR 22.7% (17/75)
- Znižanje stadija T 68% (51/75)
- Znižanje stadija N 90.7% (68/75)
- Znižanje stadija TN 93.3% (70/75)
- R0 94.7% (71/75)
- Srednji čas do zapore stome 18 tednov (7-61 tednov)

Pred zdravljenjem

Dejavniki visokega tveganja za ponovitev bolezni	cT4	30	36,6%
	cN2	52	63,4%
	EMVI+	52	63,4%
	ekstramezor.lgl	6	7,3%
	MRF+	48	58,5%

Kompletni odgovor

- cCR 6%
- pCR 22.7%

= 28.7%

Tehnika RT	N (%)	pCR	P
3D konformno	34 (45.3)	4 (11.8)	
IMRT /VMAT SIB	41 (54.6)	13 (31.7)	P= 0.04

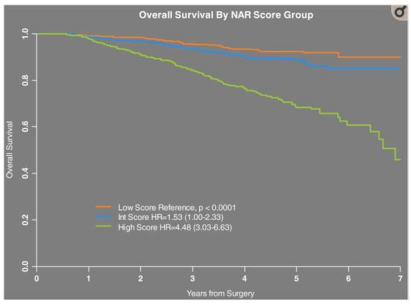
- skoraj pCR 8.5%

58.5% MRF+ ⟶ 5.3% R1

Kaj to pomeni za preživetje?

- Neoadjuvant rectal (NAR) score
  - Na osnovi pN in downstaging T (cT v pT)
  - Regres bolezni je boljši napovednik OS kot pCR

$$NAR = \frac{[5\,pN - 3(cT - pT) + 12]^2}{9.61}$$



NAR	N (%)
<8	31 (37.8)
8-16	30 (36.6)
>16	14 (17.1)

Srednja vrednost: 8.4

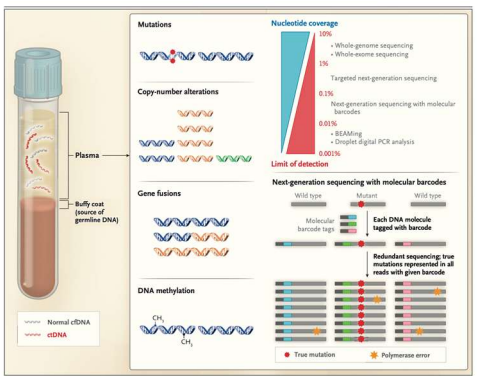
George TJ et al. Curr Colorectal Cancer Report 2015

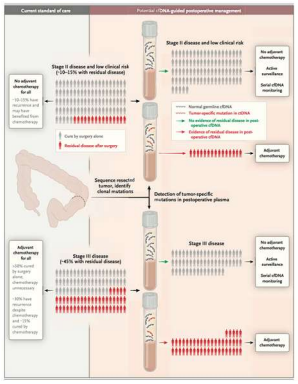
Ali bi izhodiščno klinično prognostično ugodnejše skupine imele dobrobit od TNT?

Katero bi bilo pravo zaporedje modalitet?

Tekočinska biopsija

- cirkulirajoča tumorska DNA lahko usmerja sistemsko zdravljenje

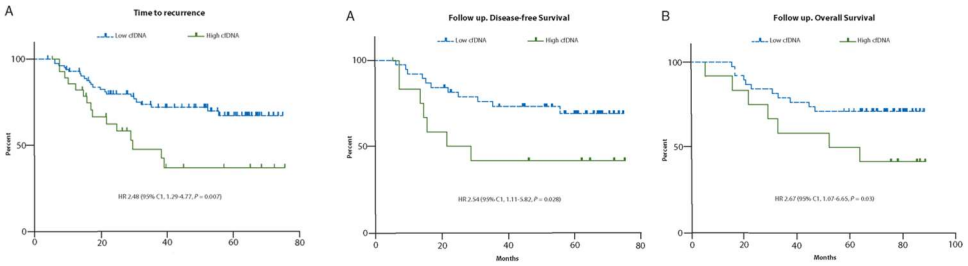




Corcoran et al. NEJM 2018

Kandidati za uvodno KT?

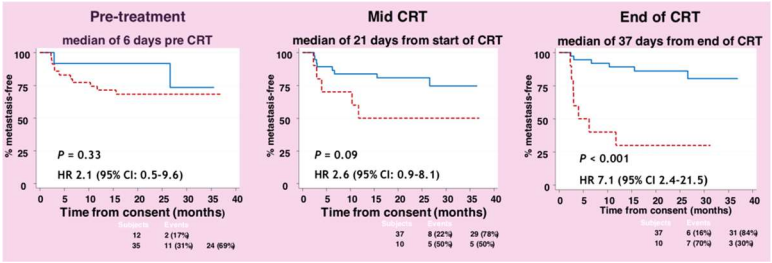
- Visok nivo ctDNA v plazmi pred pričetkom zdravljenja (nad 75-im percentilom) pomeni višje tveganje za lokalno ali sistemsko ponovitev, krajši čas do ponovitve in slabše preživetje



Schou et al. Ann Oncol 2018

Kandidati za konsolidacijsko KT?

- ctDNA med neoadjuvantno KRT lahko potencialno identificira bolnike, pri katerih bo verjetno prišlo do razsoja
- Pri precejšnjem deležu teh bolnikov pride do razsoja kmalu po zaključeni KRT



Khakoo et al. Predstavitev na EACR-ESMO Joint Conderence on Liquid biopsies 2019

PREHABILITACIJA

Erik Brecelj
Onkološki inštitut
ŠOLA TUMORJEV PREBAVIL 22.11.2019

PREHABILITACIJA

PREHABILITACIJA

UKREPI, KI V ČASU DO OPERACIJE OPTIMIZIRAJO BOLNIKOVO FIZIČNO STANJE Z NAMENOM POSPEŠENEGA POOPERATIVNEGA OKREVANJA

PREHABILITACIJA

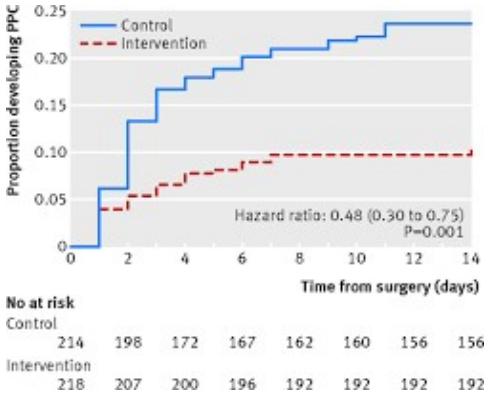
- ni rehabiliatcija
- ni samo fizična aktivnost pred operacijo

- Standardne definicije prehabilitacije ni
  - fizična aktivnost
  - fizična aktivnost in prehranska podpora
  - trimodalno; prehranska priprava, fizične vaje in relaksacijske vaje za zmanjšanje strahu pred operacijo
- obdobje trajanja prerehabilitacije; do 4 tedne naj bi zadostovalo za izvedbo prehabilitacije pri kolorektalnem raku

PREHABILITACIJA

VPLIV PREOPERATIVNE FIZIOTERAPIJE NA POSTOPERATIVNE ZAPLETE

- **incidenca resp.zapletov je prepolovljena s fizioterapijo**



Preoperative physiotherapy for the **prevention** of **respiratory complications after upper abdominal surgery**: **pragmatic, double blinded, multicentre randomised controlled trial**.
Boden I, Skinner EH, Browning L, Reeve J, Anderson L, Hill C, Robertson IK, Story D, Denehy L.
BMJ. 2018 Jan 24

PREHABILITACIJA

Bolniki redno dnevno izvajajo

- **fizično aktivnost (hoja, tek, kolesarjenje..) dvakrat dnevno po vsaj 30 min.**
- **prenehati morajo s kajenjem**
- **zmanjšati dnevno dozo zaužitega alkohola.**

POMEMBNA JE PREHRANSKA PODPORA

PREHABILITACIJA

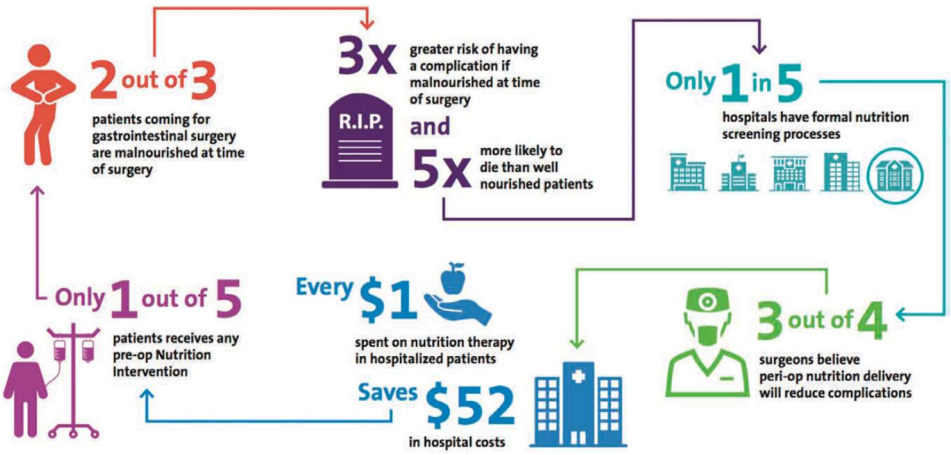
SUBOPTIMALNI PREHRANSKI STATUS → **SLABŠI POSTOPERATIVNI POTEK**

PODHRANJENI KIRURŠKI BOLNIKI IMAJO SIGNIFIKANTNO VIŠJO:

- **postoperativno morbiditeto**
- **mortaliteto**
- **ležalno dobo**

- **večji delež ponovnih hospitalizacij**
- **višje stroške zdravljenja**

PREHABILITACIJA

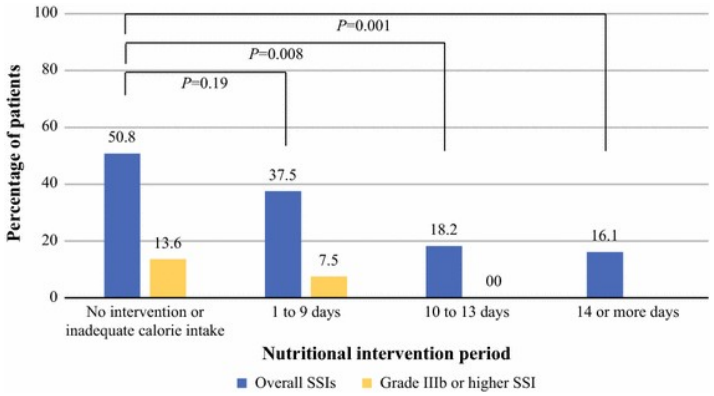


Facts and data for perioperative nutrition screening and therapy

American Society for Enhanced Recovery and Perioperative Quality Initiative Joint Consensus Statement on Nutrition Screening and Therapy Within a Surgical Enhanced Recovery Pathway.
Anesth Analg. 2018 Jun;126(6):1883-1895

PREHABILITACIJA

Prevalenca kirurških infekcij pri podhranjenih bolnikih



PRAVILNA PREDOPERATIVNA PREHRANSKA PODPORA ZNIŽA INCIDENCO POSTOPERATIVNIH KIRURŠKIH INFEKCIJ PRI PODHRANJENIH BOLNIKIH

Ann Surg Oncol. 2015 Dec;22 Suppl 3:S778-85. doi: 10.1245/s10434-015-4820-9. Epub 2015 Aug 19.
Prevalence of Malnutrition Among Gastric Cancer Patients Undergoing Gastrectomy and Optimal Preoperative Nutritional Support for Preventing Surgical Site Infections.
Fukuda Y[1], Yamamoto K[2],

PREHABILITACIJA

PREHABILITACIJA

Lahko izvjamo prehabilitacijo pri urgentnih bolnikih ?

PREHABILITACIJA

	Elective		Emergency		p-value*
	n	%	n	%	
Major resection					
Mortality (in hospital)	27	(3.5)	16	(10)	<0.01
Overall complications	182	(24)	62	(38)	<0.01

Short term outcome after emergency and elective surgery for colon cancer.
Sjo OH, Larsen S, Lunde OC, Nesbakken A.
Colorectal Dis. 2009 Sep;11(7):733-9.

PREHABILITACIJA

PREHABILITACIJA

MULTIMODALEN PROTOKOL PRI BOLNIKIH Z OBSTRUKCIJO KOLOREKTUMA

- **zmanjšanje simptomov zaradi obstrukcije**
- **zmanjšanje distenzije črevesja**
- **zmanjšanjem bolečine**

PREHABILITACIJA

Bolniki z obstruktivnim tumorjem;

- **stadij 1: abdominalna bolečina, pretakanje vsebine črevesja, brez razširjenih vijug črevesja**
- **stadij 2: abdominalna bolečina, izrazito pretakanje črevesne vsebine, segmentno razširjene vijuge črevesja**
- **stadij 3: abdominalna bolečina, razširjen celoten ali večji del kolona**
- **stadij 4: grozeča perforacija, sepsa ali perforacija**

Fahim M et al., Promising results of a new treatment in patients with bowel obstruction in colorectal surgery, EuropeanJournal of Surgical Oncology, https://doi.org/10.1016/j.ejso.2019.10.011

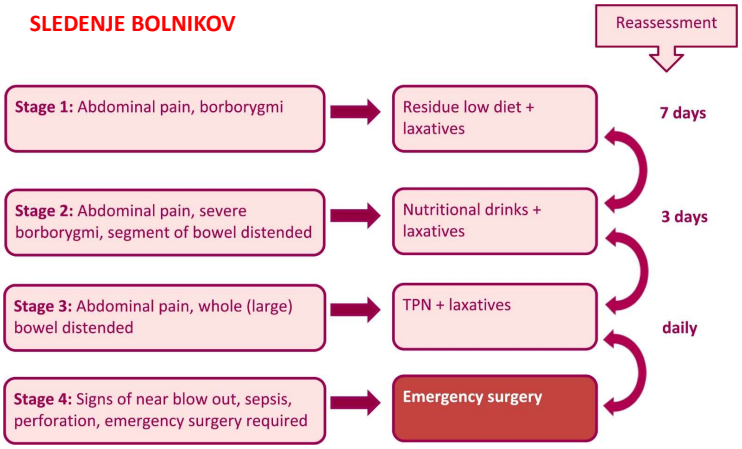
PREHABILITACIJA

Bolniki z obstruktivnim tumorjem;

- **stadij 1: brezcelulozna dieta glede na ocenjeno prehransko potrebo, laksativi**
- **stadij 2: kompletna dieta s prehranskimi napitki, laksativi**
- **stadij 3: totalna parenteralna prehrana z napitki, laksativi**
-
- **<u>stadij 4; operacija !!!</u>**

PREHABILITACIJA

SLEDENJE BOLNIKOV



Fahim M et al., Promising results of a new treatment in patients with bowel obstruction in colorectal surgery, EuropeanJournal of Surgical Oncology, https://doi.org/10.1016/j.ejso.2019.10.011

PREHABILITACIJA

Bolniki z obstruktivnim tumorjem;

- **stadij 1: abdominalna bolečina, pretakanje vsebine črevesja, brez razširjenih vijug črevesja**
- **stadij 2: abdominalna bolečina, izrazito pretakanje črevesne vsebine, segmentno razširjene vijuge črevesja**

PRIPRAVE TRAJAJO 3 DO 4 TEDNE

PREHABILITACIJA

Bolniki z obstruktivnim tumorjem;

BOLNIKI NA TOTALNI PARENTERALNI PREHRANI (STADIJ 3)

- **čas od 7-14 dni je primeren za pripravo**
- **koristnost predoperativne priprave s PN 7-14 dni je dokazan le pri izrazito podhranjenih bolnikih**

PREHABILITACIJA

	n=61
URGENTNA OPERACIAJ	4 (7%)
Laparoskopsa op.	42 (69%)
Konverzija	2/42 (5%)
Anastomoza	51 (84%)

Fahim M et al., Promising results of a new treatment in patients with bowel obstruction in colorectal surgery, EuropeanJournal of Surgical Oncology, https://doi.org/10.1016/j.ejso.2019.10.011

PREHABILITACIJA

	n = 61
30-DNEVNA SMRTNOST	**0 (0)**
Postoperativni zapleti	**23 (38)**
Clavien Dindo klasifikacija	
Grade I	10 (16)
Grade II	9 (15)
Grade IIIA	1 (2)
Grade IIIB	3 (5)
Dehiscenca anastomoze	**0 (0)**
Postoperativa hospitaizacija	9 (6–15)[a]

Fahim M et al., Promising results of a new treatment in patients with bowel obstruction in colorectal surgery, EuropeanJournal of Surgical Oncology, https://doi.org/10.1016/j.ejso.2019.10.011

PREHABILITACIJA

ZAKLJUČKI

PREHABILITACIJA

- **zmanjša postoperativne zaplete in smrtnost**
- **omogoča odlog in pripravo bolnikov na operacijo**
- **zmanjša potrebo po urgentnih operacijah**
- **najpomembnejša je prehranka priprava**

- **natančen protokol prehabilitacije ni izdelan**

Kemoterapija pri jetrnih zasevkih raka debelega črevesa in danke

Janja Ocvirk

Ljubljana, 22.11.19

Role of neoadjuvant therapy in clearly R0 resectable CRLM

- However, the majority of retrospective studies failed to demonstrate any overall survival (OS) benefits from neoadjuvant therapy – five-year OS rates ranged from 38.9% to 74% in patients who had pre-operative chemotherapy before liver resection, compared with 20.7 to 56% in patients who underwent upfront surgery

Nigri G, Petrucciani N, Ferla F, La Torre M, Aurello P, Ramacciato G. Neoadjuvant chemotherapy for resectable colorectal liver metastases: what is the evidence? Results of a systematic review of comparative studies. Surgeon. 2015;13:83–90. [

EORTC intergroup trial 40983

- perioperative FOLFOX (folinic acid, fluorouracil, and oxaliplatin; 6 cycles before and 6 cycles after surgery) improved 3-year progression-free survival (PFS) modestly – 42.4% compared with 33.2% in surgery-only patients, an absolute 9.2% increase – at the cost of higher peri-operative morbidity (25% *vs* 16%). This did not translate into any overall survival benefit at a median follow-up of 8.5 years

Nordlinger B, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, Bechstein WO, Primrose JN, Walpole ET, Finch-Jones M, Jaeck D, Mirza D, Parks RW, Collette L, Praet M, Bethe U, Van Cutsem E, Scheithauer W, Gruenberger T EORTC Gastro-Intestinal Tract Cancer Group; Cancer Research UK; Arbeitsgruppe Lebermetastasen und-tumoren in der Chirurgischen Arbeitsgemeinschaft Onkologie (ALM-CAO); Australasian Gastro-Intestinal Trials Group (AGITG); Fédération Francophone de Cancérologie Digestive (FFCD) Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. Lancet. 2008;371:1007–1016. [PMC free article] [PubMed] [Google Scholar]
Nordlinger B, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, Bechstein WO, Primrose JN, Walpole ET, Finch-Jones M, Jaeck D, Mirza D, Parks RW, Mauer M, Tanis E, Van Cutsem E, Scheithauer W, Gruenberger T EORTC Gastro-Intestinal Tract Cancer Group; Cancer Research UK; Arbeitsgruppe Lebermetastasen und–tumoren in der Chirurgischen Arbeitsgemeinschaft Onkologie (ALM-CAO); Australasian Gastro-Intestinal Trials Group (AGITG); Fédération Francophone de Cancérologie Digestive (FFCD) Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. Lancet Oncol. 2013;14:1208–1215. [PubMed] [Google Scholar]

- A meta-analysis including 18 studies concurred neoadjuvant treatment, in general, did not offer PFS or OS advantage; however, it could improve survival in patients considered high risk of recurrence (pooled hazard ratio for 5-year OS = 0.69)

Liu W, Zhou JG, Sun Y, Zhang L, Xing BC. The role of neoadjuvant chemotherapy for resectable colorectal liver metastases: a systematic review and meta-analysis. Oncotarget. 2016;7:37277–37287. [PMC free article] [PubMed] [Google Scholar]

CONVERSION CHEMOTHERAPY

- A subset of patients with initially unresectable CRLM (around 15%-30% depending on the definition of unresectability) may be rendered resectable after conversion chemo-therapy. In a systematic review of 10 studies using different downsizing regimens, an objective radiological response was achieved in 64% (range 43%-79%) patients; 22.6% underwent macroscopically curative liver resection (most studies reported a range of 12.5%-45%) and R0 resection rate was 87%. The median OS and DFS after liver metastasectomy were 45 and 14 months respectively

Lam VW, Spiro C, Laurence JM, Johnston E, Hollands MJ, Pleass HC, Richardson AJ. A systematic review of clinical response and survival outcomes of downsizing systemic chemotherapy and rescue liver surgery in patients with initially unresectable colorectal liver metastases. Ann Surg Oncol. 2012;19:1292–1301. [PubMed] [Google Scholar]

- The optimal regimen for conversion to operable disease remains unclear.
- Standard doublet chemotherapy FOLFOX or FOLFIRI had conversion rates between 9% to 33%
- FOLFOXIRI improved the secondary R0 resection rate from 12% to 36%, median PFS from 6.9 to 9.8 mo, and median OS from 16.7 to 22.6 mo; albeit at the cost of greater but manageable toxicity *e.g.*, peripheral neuropathy and neutropenia

Kanat O. Current treatment options for patients with initially unresectable isolated colorectal liver metastases. World J Clin Oncol. 2016;7:9–14. [PMC free article] [PubMed] [Google Scholar]
Falcone A, Ricci S, Brunetti I, Pfanner E, Allegrini G, Barbara C, Crinò L, Benedetti G, Evangelista W, Fanchini L, Cortesi E, Picone V, Vitello S, Chiara S, Granetto C, Porcile G, Fioretto L, Orlandini C, Andreuccetti M, Masi G Gruppo Oncologico Nord Ovest. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. J Clin Oncol. 2007;25:1670–1676. [PubMed] [Google Scholar]

Targeted therapy + ChT

- Addition of targeted agents is recommended by guidelines, but there is no concrete supporting evidence.
- In a large RCT, giving bevacizumab together with XELOX/ FOLFOX only moderately improved resectability (from 6.1% to 8.4%) and PFS (from 8 to 9.4 mo), but did not prolong OS.
- According to a recent meta-analysis, the combination of bevacizumab and FOLFOXIRI offers more promising results – the R0 surgery conversion rate was 28.1%, and the median OS and PFS were 30.2 and 12.4 mo respectively

Saltz LB, Clarke S, Díaz-Rubio E, Scheithauer W, Figer A, Wong R, Koski S, Lichinitser M, Yang TS, Rivera F, Couture F, Sirzén F, Cassidy J. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol. 2008;26:2013–2019. [PubMed] [Google Scholar]
Tomasello G, Petrelli F, Ghidini M, Russo A, Passalacqua R, Barni S. FOLFOXIRI Plus Bevacizumab as Conversion Therapy for Patients With Initially Unresectable Metastatic Colorectal Cancer: A Systematic Review and Pooled Analysis. JAMA Oncol. 2017;3:e170278. [PMC free article] [PubMed] [Google Scholar]

Targeted therapy + ChT

- Multiple randomized trials have shown the addition of cetuximab to chemotherapy in *RAS* wild-type (WT) unresectable disease improved the R0 resection rate by 2-3 folds.
- An increase in complete resection rate from 11 to 18%, however, did not translate into survival benefit in a meta-analysis.

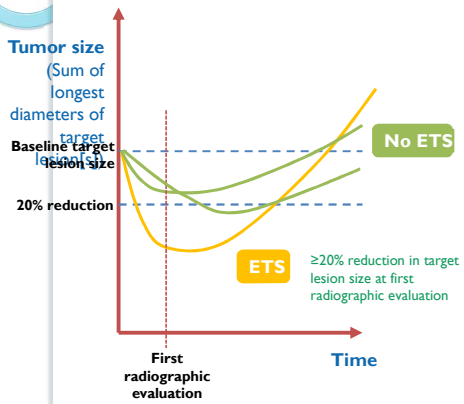
Kanat O. Current treatment options for patients with initially unresectable isolated colorectal liver metastases. World J Clin Oncol. 2016;7:9–14. [PMC free article] [PubMed] [Google Scholar]
Ye LC, Liu TS, Ren L, Wei Y, Zhu DX, Zai SY, Ye QH, Yu Y, Xu B, Qin XY, Xu J. Randomized controlled trial of cetuximab plus chemotherapy for patients with KRAS wild-type unresectable colorectal liver-limited metastases. J Clin Oncol. 2013;31:1931–1938. [PubMed] [Google Scholar]
Petrelli F, Barni S Anti-EGFR agents for liver metastases. Resectability and outcome with anti-EGFR agents in patients with KRAS wild-type colorectal liver-limited metastases: a meta-analysis. Int J Colorectal Dis. 2012;27:997–1004. [PubMed] [Google Scholar]

Targeted therapy + ChT

- Panitumumab, another anti-EGFR agent, has also been linked with greater likelihood of curative resection when added to FOLFOX (29% *vs* 17%) in *KRAS*-WT unresectable CRLM.

Peeters M, Tabernero J, Douillard JY, Siena S, Davison C, Braun S, Sidhu R, Öhrling K. Resection rates and survival in patients with wild-type KRAS/NRAS metastatic colorectal cancer and liver metastases: data from the PRIME study. In: Eggermont AMM, editors. Abstract book for Markers in cancer: a joint meeting by ASCO, EORTC and NCI; 2013 Nov 7-9. Brussels, Belgium. Eur J Cancer. 2013;49 suppl 4:517–18. [Google Scholar]

What is early tumor shrinkage?



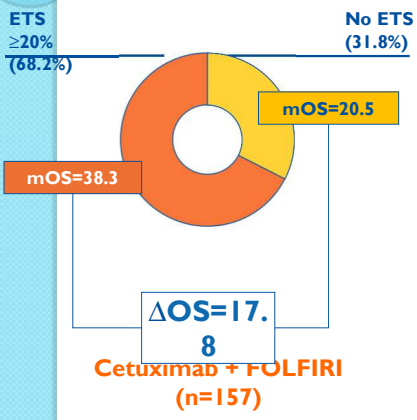
ETS Early Tumour Shrinkage

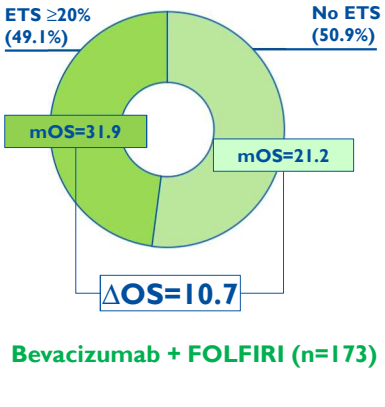
- On-treatment marker of response to treatment[1]
- First suggested in 2009, on basis of rapid tumor shrinkage with cetuximab in a subset of patients in the BOND study[1]
- Hallmark of tumor EGFR dependency and cetuximab sensitivity

1. Piessevaux H, et al. Ann Oncol. 2009;20:1375–82.

FIRE-3 analysis demonstrated significant correlation between ETS and OS in patients with RAS wt mCRC

Randomized Phase III FIRE-3* trial (RAS wt)[1,2]





*FIRE-3 did not meet its primary endpoint of significantly improving ORR in patients with KRAS (exon 2) wt mCRC based on investigators' read.[3]

1. Heinemann V, et al. Eur J Cancer 2015;51:1927–1936;
2. Stintzing S, et al. ESMO 2014 (Abstract No. LBA11);
3. Heinemann V, et al. Lancet Oncol 2014;15:1065–1075.

Correlation between ETS and increased OS has been consistently observed in 1st line Phase III clinical trials

Trial	Biomarker status	Treatment regimen (n)	OS, months		ΔOS, months
			ETS <20%	ETS ≥20%	
CRYSTAL[1]	KRAS exon 2 wt*	FOLFIRI + cetuximab (n=299)	18.6	30.0	**11.4**
		FOLFIRI (n=332)	18.6	24.1	5.5
FIRE-3[**2]	RAS wt	FOLFIRI + cetuximab (n=157)	20.5	38.3	**17.8**
		FOLFIRI + bevacizumab (n=173)	21.2	31.9	10.7
PRIME[3]	RAS wt	FOLFOX4 + panitumumab (n=219)	12.6	32.5	**19.9**
		FOLFOX4 (n=221)	15.2	26.0	10.8
TRIBE[4]	Unselected	FOLFOXIRI + bevacizumab/ FOLFIRI + bevacizumab (n=407)	21.9†	31.9†	**10.0**

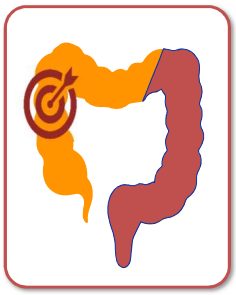
*KRAS exon 2 wt population; Cetuximab is approved in patients with RAS wt mCRC.[6] Cetuximab is not indicated for the treatment of patients with mCRC whose tumors have RAS mutations or for whom RAS tumor status is unknown.[5]
**FIRE-3 did not meet its primary endpoint of significantly improving ORR in patients with KRAS (exon 2) wt mCRC based on investigators' read.[6]
†Not including the first four months after randomization.

1. Piessevaux H, et al. J Clin Oncol 2013;31:3764–3775;
2. Stintzing S, et al. ESMO 2014 (Abstract No. LBA11);
3. Douillard JY, et al. Eur J Cancer 2015;51:1231–1242;
4. Cremolini C, et al. Ann Oncol 2015;26:1188–1194;
5. Erbitux SmPC June/2014;
6. Heinemann V, et al. Lancet Oncol 2014;15:1065–1075.

Cytoreduction is a primary goal for patients with RS mCRC[1,2]

ESMO guidelines recommend cytoreduction (tumor shrinkage) as the primary goal for patients in need of:[2]

- Conversion to resectable disease
- Avoidance of impending clinical threat
- Prevention of impending organ dysfunction
- Alleviation of severe symptoms



1. Yoshino T, et al. Ann Oncol 2018;29:44–70; 2. Van Cutsem E, et al. Ann Oncol 2016;27:1386–1422.

When cytoreduction is the goal, cetuximab + FOLFOX or FOLFIRI is an efficacious 1st-line treatment for right-sided RAS wt mCRC[1,2]

Phase III FIRE-3 trial[*†‡1]

RS RAS wt mCRC treated with cetuximab + CT (n=30)

56.7% attained ETS*

27.9 months† mOS in patients with ETS ≥20%

RS RAS wt mCRC treated with bevacizumab + CT (n=38)

42.1% attained ETS*

23.2 months† mOS in patients with ETS ≥20%

Numerically higher OS with cetuximab + CT (p=0.90)‡

Retrospective analysis of patients with right-sided RAS wt mCRC. FIRE-3 did not meet its primary endpoint of significantly improving ORR based on investigators' read in patients with KRAS (exon 2) wt mCRC.[3] *OR for ETS=1.80; p=0.33.[1] †In patients with ETS, HR for OS=1.05; p=0.903.[1] ‡ETS defined as ≥20% reduction in sum of longest tumor diameters of target lesions followed according to RECIST 1.1 at Week 6.[4] ETS, early tumor shrinkage; mOS, median overall survival.

1. Holch JW, et al. J Clin Oncol 2017;35:3586; 2. Arnold D, et al. Ann Oncol 2017;28:1713–1729; 3. Heinemann V, et al. Lancet Oncol 2014;15:1065–1075; 4. Stintzing S, et al. Lancet Oncol 2016;17:1426–1434.

- The role of neoadjuvant therapy in operable disease is still controversial, while the use of adjuvant chemotherapy has gained generalized acceptance.
- Chemotherapy dublets or triplets± biological drugs are currently recommended as first-line treatment in unresectable CRLM.

- In the absence of standardized evidence-based protocols, the optimal management of CRLM should be determined by a multi-disciplinary team.

Kirurško zdravljenje jetrnih zasevkov KRR

Doc. dr. Blaž Trotovšek
KOZAK
UKC Ljubljana

SOME STATISTICS:

100% of men didn't notice King Kong is on picture

Malo statistike!

- 2012, KRR **2** najpogostejši rak Europe[1]
  - 447,000 novih primerov in 215,000 smrti
- **~ 50%** bolnikov s KRR razvije jetrne zasevke[2]
  - Jetrni zasevki so vzrok smrti pri **2/3** bolnikov s KRK[2]
- **0-6%** 5 letno preživetje bolnikov s KRR z nezdravljenimi jetrnimi zasevki[3]

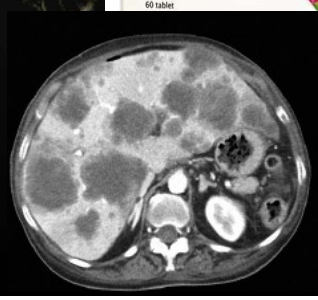
1. Ferlay J et al. Eur J Cancer. 2013;49(6):1374–403;
2. Van den Eynde M, and Hendlisz A. Rev Recent Clin Trials. 2009;4(1):56–62;
3. Simmonds PC et al. Br J Cancer. 2006;94(7):982–99.

Malo statistike!!

- ≈1530 novih primerov KRR v RS 2013
  - 180 maligniziranih polipov – R0 reseciranih endo
- ≈ 1350 novih primerov KRR
- 50 % jih bo razvilo JZ KRR – vzrok za 2/3 smrti
  - 25% - sinhrone ≈ 340 bolnikov
  - 15% - resektabilnih ≈ 51 bolnikov
  - 85% - neresektabilnih ≈ 290 bolnikov

PEGASTI BADELJ

- Flavonid SILIMARIN



Osnovni vprašanji

- Kaj želimo doseči?

- Kakšne so naše možnosti?

NO GO!!

Vrste zasevkov

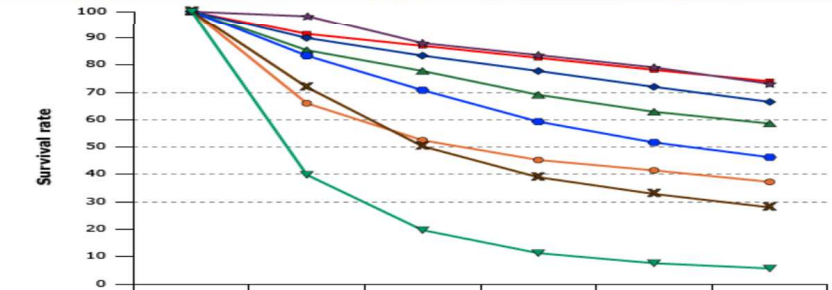
- Sinhrone
- Metahrone

Table 2 Treatment Sequences Examined in the Decision-Making Models

Sequence Number	Description
1	Chemotherapy/colectomy/hepatectomy
2	Chemotherapy/colectomy/chemotherapy/hepatectomy
3	Chemotherapy/hepatectomy/colectomy
4	Chemotherapy/hepatectomy/chemotherapy/colectomy
5	Colectomy/chemotherapy/hepatectomy
6	Colectomy/hepatectomy/chemotherapy
7	Colectomy/chemotherapy/hepatectomy/chemotherapy
8	Hepatectomy/colectomy/chemotherapy
9	Hepatectomy/chemotherapy/colectomy
10	Hepatectomy/chemotherapy/colectomy/chemotherapy
11	Colohepatectomy/chemotherapy
12	Chemotherapy/colohepatectomy
13	Chemotherapy/colohepatectomy/chemotherapy

Kirurško zdravljenje jetrnih zasevkov KRR je zlati standard!?!

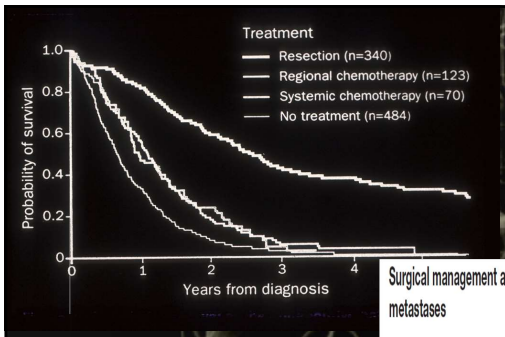
Preživetje 28491 bolnikov s KRR



	0	1	2	3	4	5
I	100.0	91.4	87.0	82.6	78.2	74.0
IIA	100.0	89.9	83.4	77.8	72.0	66.5
IIB	100.0	85.4	77.8	69.1	62.9	58.6
IIC	100.0	66.0	52.5	45.3	41.5	37.3
IIIA	100.0	98.3	88.0	83.6	79.1	73.1
IIIB	100.0	83.4	70.8	59.3	51.7	46.3
IIIC	100.0	71.9	50.3	39.0	32.9	28.0
IV	100.0	39.9	19.7	11.3	7.6	5.7

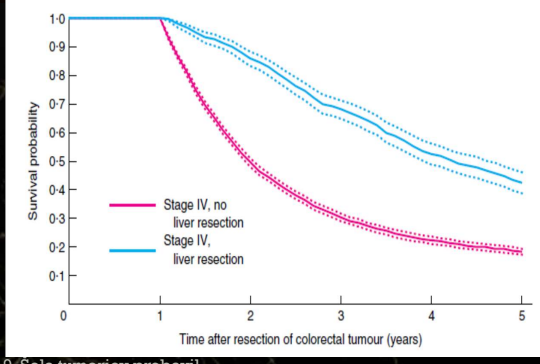
Years from diagnosis

Data from the SEER 1973-2005 Public Use File diagnosed in years 1998-2000. Stage I includes 7417; Stage IIA, 9956; Stage IIB, 997; Stage IIC, 725; Stage IIIA, 868; Stage IIIB, 1492; Stage IIIC, 2000; and Stage IV,



Surgical management and outcomes of colorectal cancer liver metastases

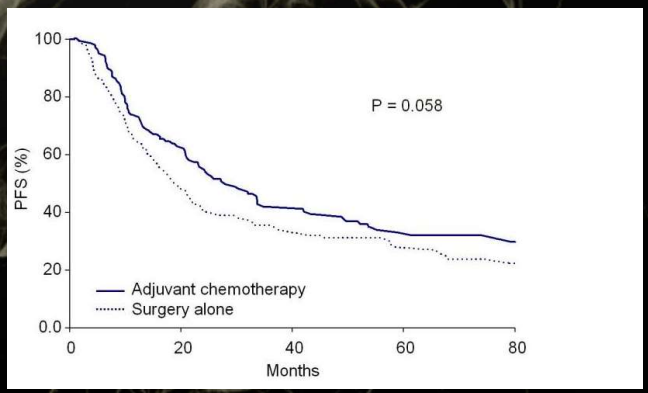
British Journal of Surgery 2010; 97: 1110–1118



TODA!

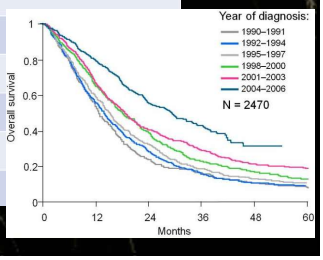
Adjuvantna KT po resekciji

- Mitry E. et all, J Clin Oncol 2008



Jetrna resekcija za mKRR

Author and year (case series)	Number of patients	5 Year OS (percent)	Median Survival in months
Hughes, KS ; 1986	607	33	Not reported (NR)
Scheele,J;1995	434	33	40
Nordlinger,B ;1996	1568	28	NR
Jamison,RL :1997	280	27	33
Fong,Y ;1999	1001	37	42
Iwatsuki,S;1999	305	32	NR
Choti,M;2002	133	58	NR
Abdalla,E ;2004	190	58	NR
Fernandez,FG;2004	100	58	NR
Wei,AC;2006	423	47	NR
Rees,M;2008	929	36	42.5
De Jong ,M;2009	1669	47	36
Morris,EJ ;2010	3116	44	NR



MULTIDISCIPLINARNI PRISTOP

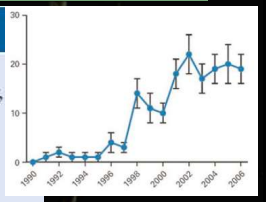
DIAGNOSTIKA

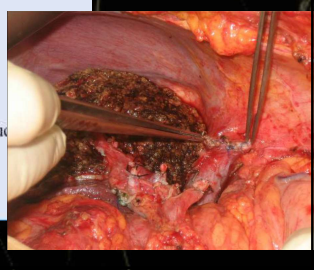
- UZ
- CT
- MRI
- Tu markerji (CEA, Ca19-9, Ca125…)

- Biopsija – le po sklepu multidisciplinarnega HPB konzilija!!!

Spremembe pogleda na resektabilnost v 4D tehniki

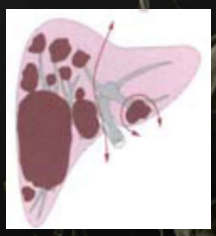
Conventional indications	Aggressive modern indications
≤ 3 liver metastases, unilobar	No limits for number or distribution (neoadjuvant chemotherapy, two-stage hepatectomy, radiofrequency ablation)
Size ≤ 5 cm	No size limits
No extrahepatic metastases	Resection of the extrahepatic disease (hepatic pedicle lymph-node metastases, local recurrence of the colorectal cancer, lung metastases)
Resection margin >1 cm	Negative resection margin
Adequate FRL	PVE or PVL in case of inadequate FLR
Metachronous metastases	Synchronous and metachronous metastases
No infiltration of IVC, hepatic veins, and hilar structures	No limits. Possible resection and/or reconstru of vascular structures
Radical resection	

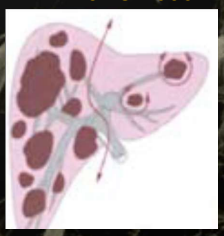


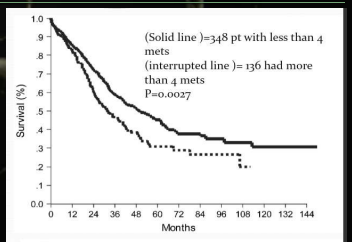


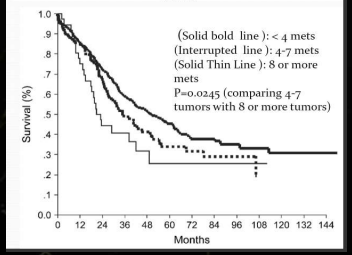
Število zasevkov

MalikHZ. EJSO 2006 – R0 67%







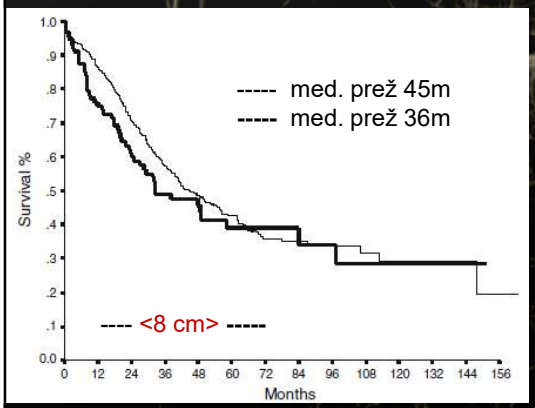


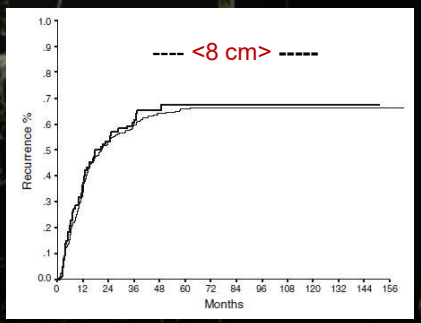
22.11.2019, OI, 9. Šola tumorjev prebavil

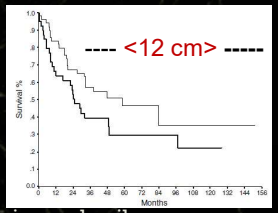
Hepatic Resection for Colorectal Metastasis: Impact of Tumour Size

Zaed Z. R. Hamady, MRCS, Hassan Z. Malik, MD, FRCS, Robert Finch, FRACS, Robert Adair, MBChB, Ahmad Al-Mukhtar, FRCS, K. Rajendra Prasad, FRCS, Giles J. Toogood, DM, FRCS, and J. Peter A. Lodge, MD, FRCS

Velikost zasevkov

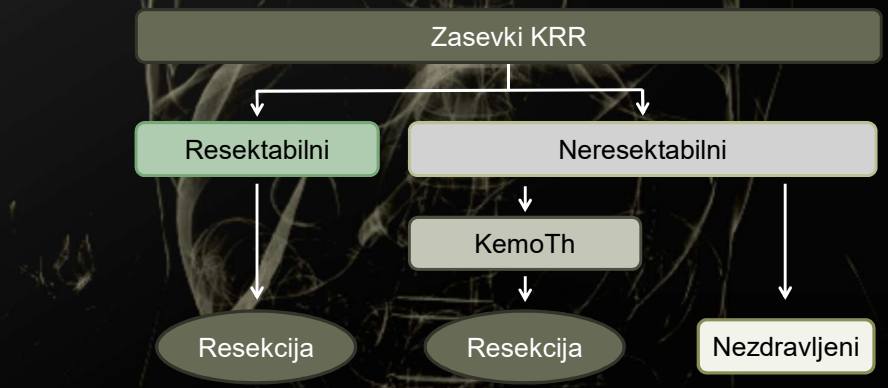






22.11.2019, OI, 9. Šola tumorjev prebavil

Zmanjšanje (↓size) primarno neresektabilnih zasevkov KRR



5-l preživetje (interval)	**38%** (30-68%)[2]	**37%** (8-79%)[2]	**0%** (0-6%)[3]

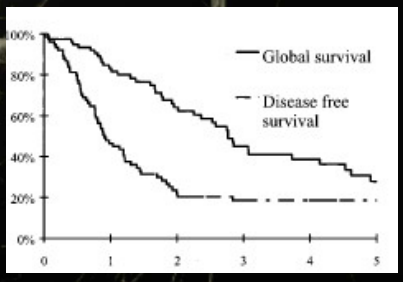
Van den Eynde M, and Hendlisz A. Rev Recent Clin Trials. 2009;4(1):56–62;
Kanas GP, et al. Clin Epidemiol. 2012;4:283–301;
Simmonds PC et al. Br J Cancer. 2006;94(7):982–99.

Results of R0 Resection for Colorectal Liver Metastases Associated With Extrahepatic Disease

Dominique Elias, MD, PhD, Lucas Sideris, MD, FRCSC, Marc Pocard, MD, PhD, Jean-Francois Ouellet, MD, FRCSC, Valérie Boige, MD, Philippe Lasser, MD, Jean-Pierre Pignon, MD, PhD, and Michel Ducreux, MD

Zunajjetrni zasevki

- 3- in 5-letno preživetje bolnikov z JZ je 56% in 33%
- 3- in 5-letno preživetje bolnikov z JZ in ekstrahepatičnimi zasevki po R0 resekciji pa je bilo 45% in 28% (p =0.15)



Pomen zunajjetrnih zasevkov

Review

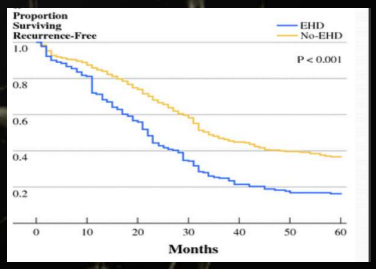
Hepatectomy and resection of concomitant extrahepatic disease for colorectal liver metastases – A systematic review

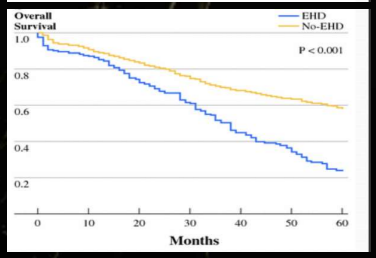
Terence C. Chua [a,c], Akshat Saxena [a], Winston Liauw [b], Francis Chu [a], David L. Morris [a,c,]*

EUROPEAN JOURNAL OF CANCER 48 (2012) 1757–1765

- 1629 bolnikov z JZ od 1996-2007.
- 10,4% R0 resekcija ZJZ

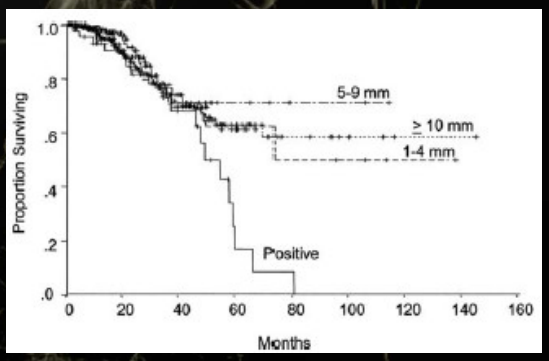
Site	*n* (%)	Median survival (mo)	3-Year survival (%)	5-Year survival (%)
Lung	62 (36.2)	46	60	33
Peritoneum	25 (14.6)	32	32	26
Hepatic pedicle lymph nodes	41 (23.9)	29	43	27
Aortocaval lymph nodes	14 (8.1)	13	22	7
Other	11 (6.5)	–[a]	–[a]	–[a]
Multiple sites	18 (10.5)	15	26	14





Resekcijski rob

- Pomemben dejavnik preživetja bolnikov z JZ KRR.

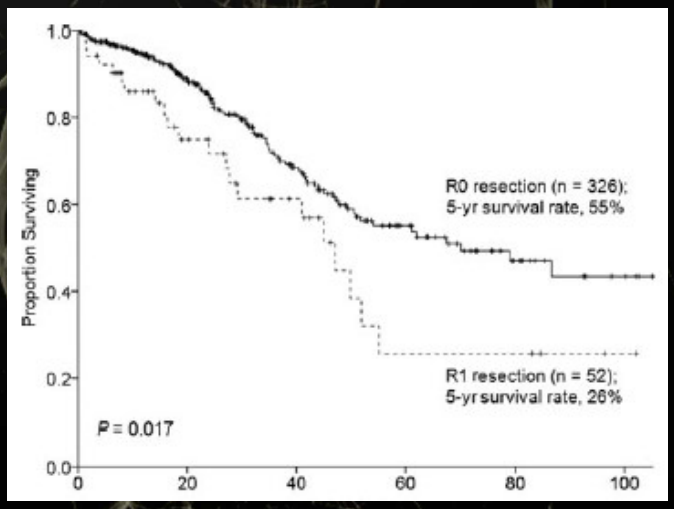


Margin Status Remains an Important Determinant of Survival After Surgical Resection of Colorectal Liver Metastases in the Era of Modern Chemotherapy

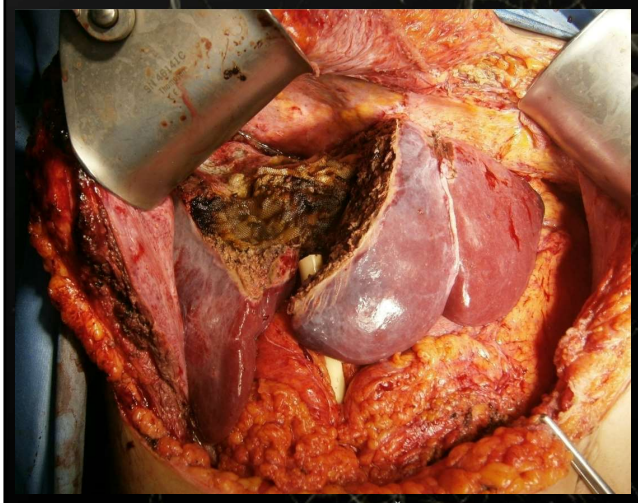
Andreas Andreou, MD, Thomas A. Aloia, MD, FACS,* Antoine Brouquet, MD,* Paxton V. Dickson, MD,* Giuseppe Zimmitti, MD,* Dipen M. Maru, MD,† Scott Kopetz, MD, PhD,‡ Evelyne M. Loyer, MD,§ Steven A. Curley, MD, FACS,* Eddie K. Abdalla, MD, FACS,* and Jean-Nicolas Vauthey, MD, FACS**

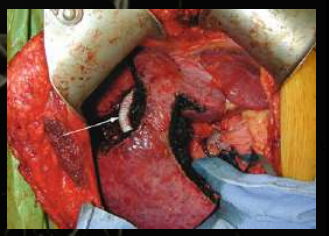
Annals of Surgery • Volume 257, Number 6, June 2013

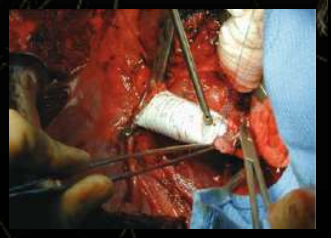
Resekcijski rob



Žilne strukture







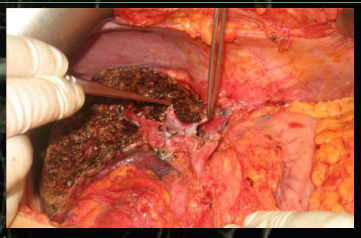
Napovedovanje

- Različni sistemi
  - Fong
  - CRS
  - .....

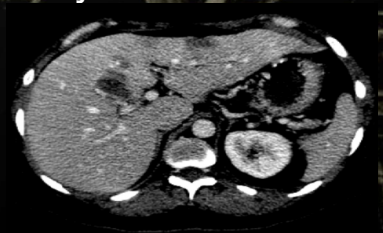
Factor				Points[a]
Node metastases in primary tumor				1
Disease free interval <12 months				1
More than one liver metastasis				1
Preoperative CEA >200 ng/mL				1
Largest tumor >5 cm				1
Score	**One year**	**Three years**	**Five years**	**Median (months)**
0	93%	72%	60%	74
1	91%	66%	44%	51
2	89%	60%	40%	47
3	86%	42%	20%	33
4	70%	38%	25%	20
5	71%	27%	14%	22

Resektabilnost

- **PRETEKLOST**
- Kaj odstranimo?
  - Število JZ
  - Velikost JZ
  - ZJZ



- **DANES**
- Kaj ostane?
  - R0 resekcija
  - FRV



Neresektabilnost JZ

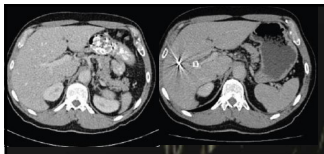
- Sodobni kriteriji neresektabilnosti JZ so:
  - R0 resekcija ni mogoča:
    - Histološko + rob (?),
    - Neodstranljivost katerekoli **zaznane** razširjenosti bolezni ,
    - Progres bolezni ob KT.

Resektabilnost

- JZ so resektabilni, ko lahko dosežemo R0 resekcijo, tako da:
  - Ohranimo dva skupaj ležeča segmenta (od 8) z ohranjeno jetrno veno in portalno triado,
  - Ohranimo funkcijsko zadosten del jeter.

Delovanje ostanka

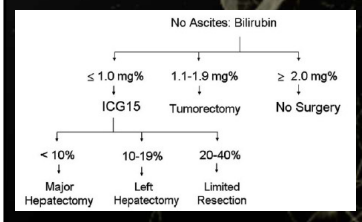
- Prostornina FRV napove delovanje ostanka jeter po resekciji in pooperativni potek.
- Pri bolnikih z resekcijo jeter
  - FRV = 20% zapleti v 50%,
  - FRV > 20% zapleti v 13%.
- FRV_{min} je odvisen od:
  - Zapletenosti posega na jetrih,
  - Sočasnih posegov,
  - Komorbiditete,
  - Stanja jetrnega parenhima.



Delovanje ostanka

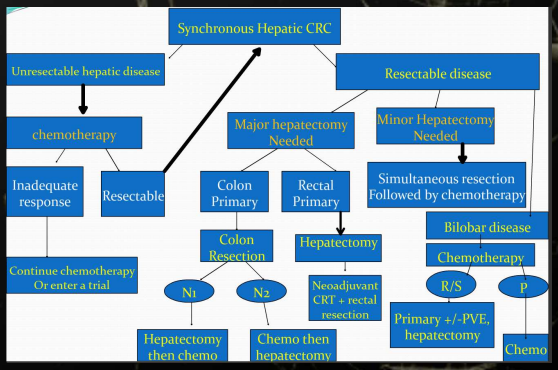
- Pri bolnikih z resekcijo jeter
  - Neprizadet jetrni parenhim
  - KT, steatoza, hepatitis
  - Ciroza

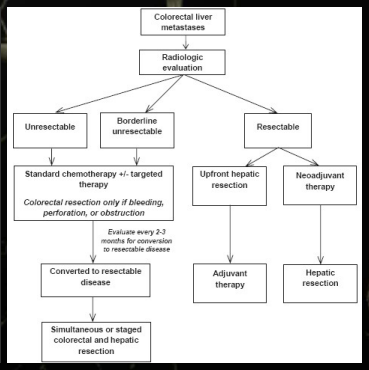
FRV_{min} > 20%,
FRV_{min} > 30%,
FRV_{min} > 40%.



- LIMON – očistek indocyanine zelene (ICG)
  - Japonski algoritem – MR 0%

KIRURŠKO ZDRAVLJENJE





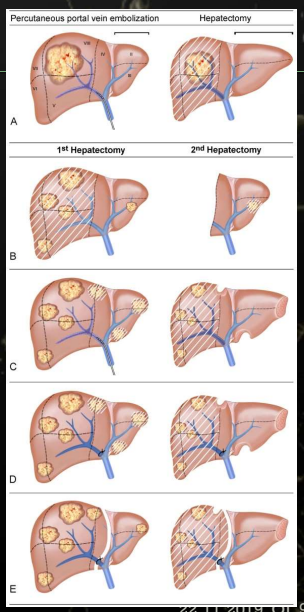
KIRURŠKO ZDRAVLJENJE

- SINHRONI JZ
  - Dvostopenjska hepatektomija
    - Ligatura PV
    - Resekcija ali LR terapija kontralateralnih JZ
    - ALPPS
  - Sinhrona resekcija
  - "Colon V Liver " FIRST

Dvostopenjska hepatektomija

- Omogoči hipertrofijo ostanka jeter.
  - Kadar ni možno odstraniti vseh zasevkov med enim posegom (bilobarni JZ),
  - To uspešno kombiniramo z sinhrono resekcijo primarnega tumorja ob prvem posegu, ali z EPV.
- 5- letno preživetje 42% pri izbranih bolnikih.

Dvostopenjska hepatektomija ALPPS

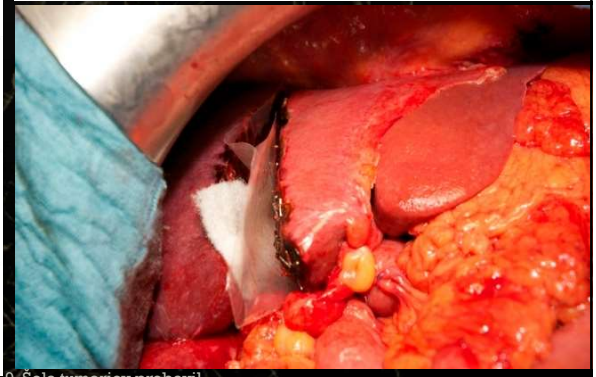


J Gastrointest Surg
DOI 10.1007/s11605-012-2132-y

ORIGINAL ARTICLE

ALPPS in Right Trisectionectomy: a Safe Procedure to Avoid Postoperative Liver Failure?

Jun Li · Paolo Girotti · Ingmar Königsrainer · Ruth Ladurner · Alfred Königsrainer · Silvio Nadalin



22.11.2019, OI, 9. Šola tumorjev prebavil

Sinhrona resekcija

- Izvedljiva pri ¼ bolnikov z JZ.
- Omogoča hkratno odstranitev celotnega tumorskega bremena.
  - Skrajša hospitalizacijo
  - Zniža stroške ob sprejemljivi obolevnosti.
- Odločitev za tehniko temelji na:
  - Obsegu obeh posegov
  - Oceni sinergističnih učinkov na zaplete
  - Tveganje je nižje pri posegih < od 4 segmentov in pri posegih na desnem DČ

Sinhrona resekcija

- Priporoča se pri:
  - 4 ali < segmentov pri posegih na desnem DČ.
  - 2 ali < oz. atipične resekcije pri posegih na levem DČ.

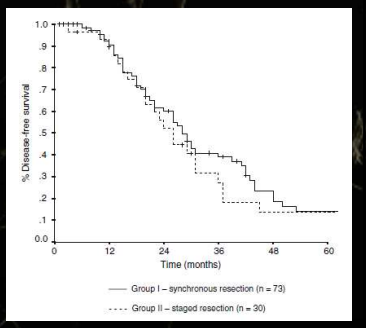
Synchronous Colorectal Liver Metastases: Is It Time to Reconsider Traditional Paradigms of Management?

Srinevas K. Reddy, MD, Andrew S. Barbas, MD, and Bryan M. Clary, MD

Department of Surgery, Duke University Medical Center, Box 3247, Durham, NC

PREŽIVETJE PO RESEKCIJI

recent studies have demonstrated long-term survival after resection of synchronous CLM. Bockhorn et al. show no difference in overall (5-year 47% vs. 39%; $P = .78$) or disease-free (5-year 33% vs. 13%, $P = .28$) survival between 63 patients with synchronous disease and 63 patients with metachronous disease who underwent margin-negative resection of CLM.[60] Similarly, Minagawa et al. show no difference in overall survival between 187 synchronous and 182 metachronous patients after hepatic extirpation (3-year, 5-year, 10-year 49%, 35%, 25% vs. 55%, 41%, 28%,



Tradicionalni / sinhroni - zapleti

Synchronous Resection of Colorectal Primary Cancer and Liver Metastases

World J Surg (2007) 31:1496–1501
DOI 10.1007/s00268-007-9085-4

Tristan D. Yan · Francis Chu · Deborah Black · Denis W. King · David L. Morris

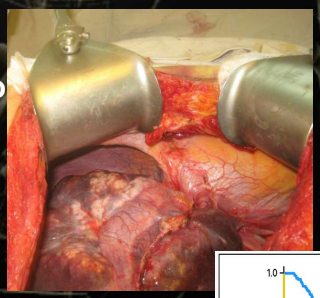
Perioperative adverse events-	Total (no.)	Group I (no.)	Group II (no.)	*p*
Total	103 (100%)	73 (100%)	30 (100)	—
Wound infection	21 (20%)	14 (19%)	7 (23%)	0.788
Perihepatic collection	13 (13%)	10 (14%)	3 (10%)	0.751
Bile leak	2 (2%)	1 (1%)	1 (3%)	0.500
Other intraabdominal collection	14 (14%)	9 (12%)	5 (17%)	0.543
Respiratory complication	8 (8%)	5 (7%)	3 (10%)	0.689
Cardiac complication	1 (1%)	1 (1%)	0	1.000
Septicemia	2 (2%)	1 (1%)	1 (3%)	0.500

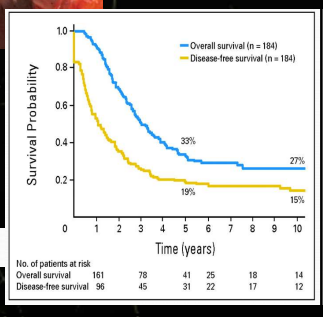
"Colon V Liver " FIRST

- 'liver-first'
  - Namen je preprečiti progres JZ med zdravljenjem TU DČ pri ASIMPTOMATSKIH bolnikih
    - Predvsem pri resekcijah DČ z visokim tveganjem.
    - Dehiscenca anastomoze pomembno podaljša čas do resekcije jeter ali KT.
- 'colon-first'
  - Simptomatski tumorji
    - Stenoze, krvavitev…

Metahroni JZ

- Boljša prognoza
- Resektabilni – OP
- Neresektabilni
  - Down-sizing s KT
  - Drugi postopki, ki spremene JZ v resektabilne.





Adam R et al. JCO 2009;27:1829-1835

Ponovne resekcije

- Kadar je R0 resekcija možna, so rezultati 5-letnega preživetja podobni rezultatom primarnih resekcij.

Reference /year	Number of patients	Overall Survival	Median Survival (In months)
Que,FG /1994[6]	21	43 % ,4 year	41
Fong ,Y/1994	25	44 % , 2 year	30
Nordlinger ,B/1994	116	33%, 3 year	24
Fernandez-Trigo,V/1995	170	32%,5 year	34
Tuttle,TM/1997	23	32%,5 year	40
Adam,R/1997	64	41%,5 year	46
Yamamoto,J/1999	90	31%, 5 year	31
Muratore,A/2001	29	35%,3 year	NR
Petrowsky,H/2002	126	34%,5year	37
Nagakura S/2002	28	42%,5 year	27
Tanaka ,K/2004	26	48%DFS ,5 year	NR
Pessaux,P:2006	42 (2^{nd} n=42) (3^{rd} n=11)(4^{th} n=2)	55%,21%,36%,5year	41,25,16
Ishiguro,S/2006	111	41 %,5 year	43 months
Cunha,A/2007	40	31%,5 year	NR

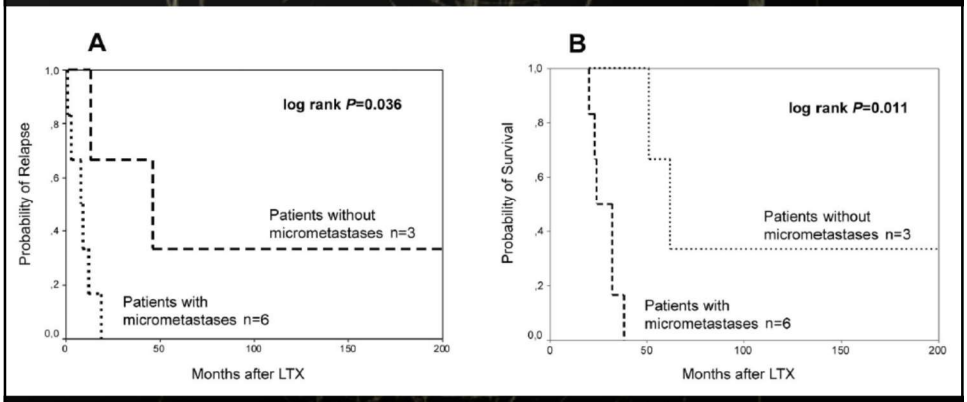
Peritonejektomija in HYPEC

- Izbrani bolniki z nizkim PCI (<12) in brez sistemske bolezni imajo podaljšano preživetje.
- Samo izbrani centri

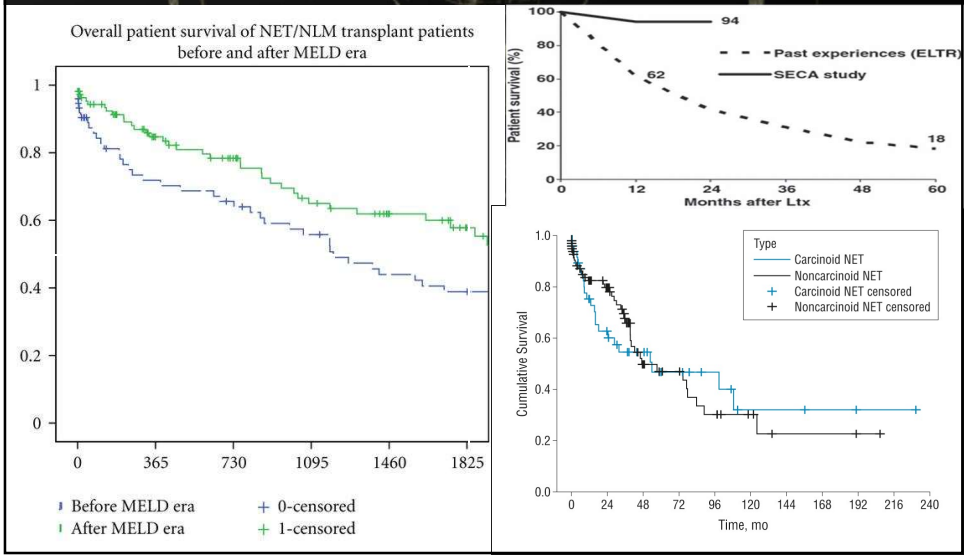
Presaditev

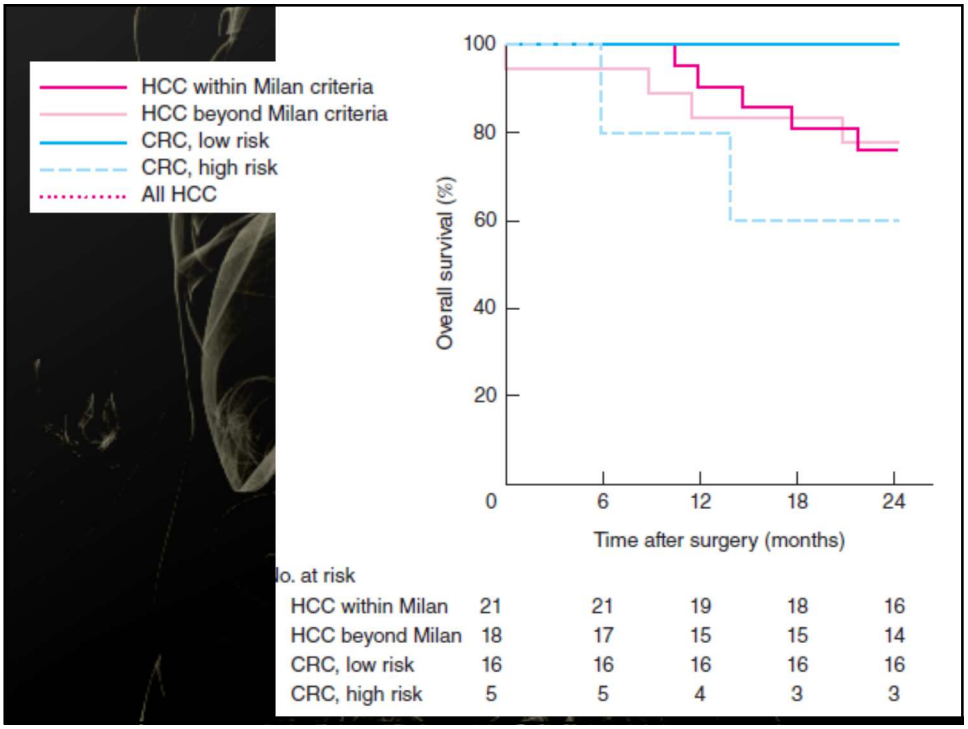
- DANES NE
- JUTRI??
- Odgovor 2027!!!

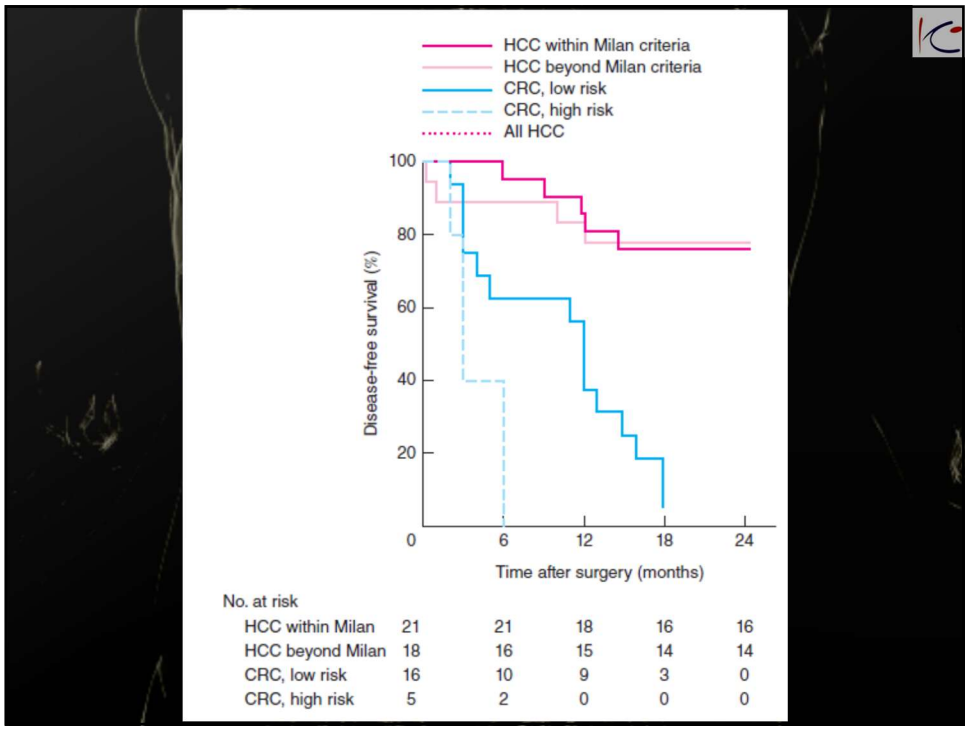
9/25 negativne bezgavke ob op zaradi KRR



mNET- DA, mCRC- Ne še!






HCC within Milan criteria
HCC beyond Milan criteria
CRC, low risk
CRC, high risk
All HCC
Disease-free survival (%)
100
80
60
40
20
0
6
12
18
24
Time after surgery (months)
No. at risk
HCC within Milan 21 21 18 16 16
HCC beyond Milan 18 16 15 14 14
CRC, low risk 16 10 9 3 0
CRC, high risk 5 2 0 0 0


special articles
Annals of Oncology
Annals of Oncology 27: 1386–1422, 2016
doi:10.1093/annonc/mdw235
Published online 5 July 2016
ESMO consensus guidelines for the management of patients with metastatic colorectal cancer
E. Van Cutsem[1*], A. Cervantes[2], R. Adam[3], A. Sobrero[4], J. H. Van Krieken[5], D. Aderka[6], E. Aranda Aguilar[7], A. Bardelli[8], A. Benson[9], G. Bodoky[10], F. Ciardiello[11], A. D'Hoore[12], E. Diaz-Rubio[13], J.-Y. Douillard[14], M. Ducreux[15], A. Falcone[16,17], A. Grothey[18], T. Gruenberger[19], K. Haustermans[20], V. Heinemann[21], P. Hoff[22], C.-H. Köhne[23], R. Labianca[24], P. Laurent-Puig[25], B. Ma[26], T. Maughan[27], K. Muro[28], N. Normanno[29], P. Österlund[30,31], W. J. G. Oyen[32], D. Papamichael[33], G. Pentheroudakis[34], P. Pfeiffer[35], T. J. Price[36], C. Punt[37], J. Ricke[38], A. Roth[39], R. Salazar[40], W. Scheithauer[41], H. J. Schmoll[42], J. Tabernero[43], J. Taïeb[25], S. Tejpar[1], H. Wasan[44], T. Yoshino[45], A. Zaanan[25] & D. Arnold[46]
22.11.2019, OI, 9. Šola tumorjev prebavil

Table 2. Contraindications to hepatic resection in patients with CRC liver metastases (adapted from Adam et al. [148] with permission from AlphaMed Press)

Category	Contraindication
Technical (A)	
1. Absolute	Impossibility of R0 resection with ≥30% liver remnant Presence of unresectable extrahepatic disease
2. Relative	R0 resection possible only with complex procedure (portal vein embolisation, two-stage hepatectomy, hepatectomy combined with ablation[a]) R1 resection
Oncological (B)	
1.	Concomitant extrahepatic disease (unresectable)
2.	Number of lesions ≥5
3.	Tumour progression

Patients should be categorised as A1 or A2/B1, B2 or B3.
[a]All methods, including radiofrequency ablation.

Vsak pacient bi moral biti opredeljen kot:

Npr. A1/B2

Table 5. Historical ESMO groups for treatment stratification of fit patients with metastatic CRC [3]

	Group 0 Resectable	Group 1 Potentially resectable	Group 2 Not resectable	Group 3 Not resectable
Clinical presentation	Clearly resectable R0 liver and/or lung disease	Unresectable liver/lung-limited disease which might become resectable after response to conversion therapy	Multiple metastases/sites Tumour-related symptoms Able to withstand intensive therapy	Asymptomatic Multiple metastases Never able to undergo resection Unsuitable for intensive therapy Frail with co-morbidities
Treatment goal	Cure (NED)	Maximum tumour shrinkage	Clinically relevant tumour shrinkage Disease control	Halt/slow tumour progression Tumour shrinkage less relevant Tolerability most relevant
Treatment intensity	*Surgery* Immediate surgery with no prior chemotherapy or moderate (FOLFOX) perioperative chemotherapy	*Intensive treatment approach* Upfront most active combination regimen	Upfront active combination (at least a chemotherapy doublet)	*Less intensive treatment approach* Treatment selected according to patient preference Sequential approach (start with single agent or doublet with low toxicity) FOLFOX an exception

CRC, colorectal cancer; FOLFOX, infusional 5-fluorouracil, leucovorin, oxaliplatin; NED, no evidence of disease.

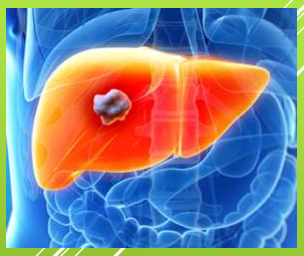
Kirurga zanimajo:

- (A) Bolniki s takoj resektabilni zasevki
- (B) Bolniki, ki postanejo resektabilni s konverzijo

Pravila

- Tehnična resektabilnost in prognostični dejavniki vplivajo na perioperativno KT
- Takojšnja resekcija le pri tistih kjer dosežemo z lahkoto R0 in ugodnimi prognostičnimi dejavniki – vsi drugi KT

SBRT JETERNIH ZASEVKOV



Irena Oblak

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

STEREOTAKTIČNA RADIOTERAPIJA

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

KRITERIJI ZA SBRT

- Gibanje:

a).dihanje: jetra ob dihanju tudi 4 cm sup-inf (mediana 1.8 cm) {4-DCT, abdominalna kompresija ali ABC sistem};

b). Različna polnjenost votlih organov

- Slaba vidljivost zasevkov na CT, ki se uporablja med RT za detekcijo tarče:

Vstavitev 3 zlatih zrn (3-D projekcija)

TEHNIČNO ZAHTEVNA TEHNIKA

12.05.2017

METODA JE ŠE POSEBEJ PRIMERNA ZA:

- Zasevke, ki ležijo blizu večjih žil;
- Za bolnike, ki niso primerni za ostale ablativne metode;
- Za bolnike, ki niso operabilni zaradi komorbiditete, neresektabilnega zasevka ali OP odklonijo.

IZSLEDKI RAZISKAV

Study	Year	% patients with grade 1–2 toxicity	% patients with grade 3–5 toxicity	1-year local control	2-year local control
Lee *et al.*	2009	Not reported	13%	71%	Not reported
Rusthoven *et al.*	2009	Not reported	3%	95%	92%
Vautravers-Dewas	2011	Not reported	2%	90%	86%
Rule *et al.*	2011	Not reported	0%	100% (50 Gy cohort)	89% (50 Gy cohort)
Scorsetti *et al.*	2014	78%	0%	95%	91%
Mendez Romero *et al.*	2016	96%	20%	100% (metastases only)	86% (metastases only)
Meyer *et al.*	2016	Not reported	0%	100%	100%
Goodman *et al.*	2016	54%	0%	77%	Not reported
Anstadt *et al.*	2018	26%	0%	86%	80%

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

CRC in rak dojke ima daljše preživetje v primerjavi z ostalimi raki

- **Swaminath, 2011:**

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

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

LC 94%

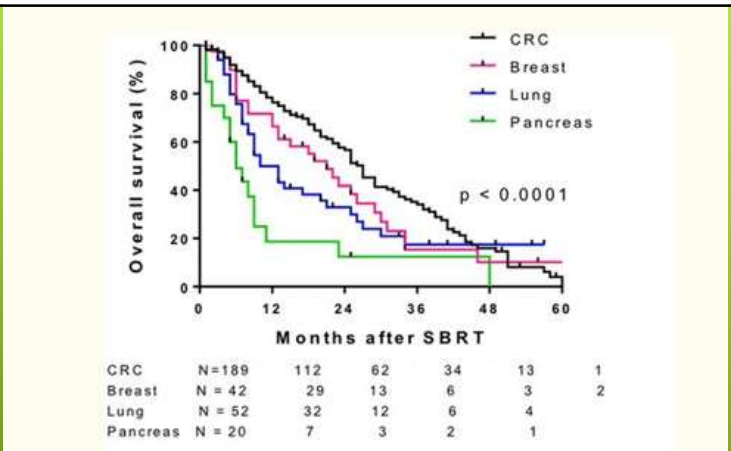
UGOTOVITVE NEKATERIH RAZISKOVALCEV

- Omogoča 70-100% LC in 60-90% OS pri 2 letih.
- Boljša LC pri:

- manjših zasevkih;
- uporabi BED ≥ 100Gy;
- uporabi sistemov za kontrolo dihanja;
- zasevkih CRC ali raka dojke.

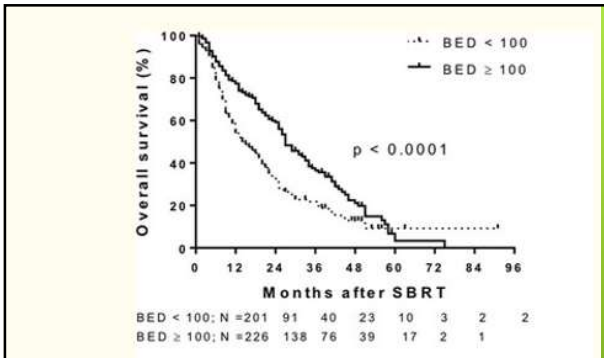
REZULTATI ZDRAVLJENJA S SBRT

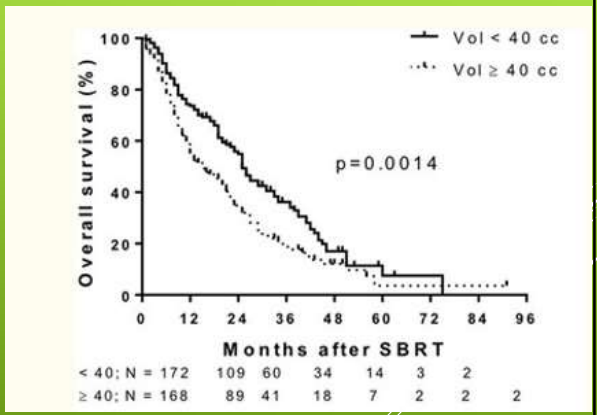
Mahadevan A, et al. Stereotactic Body Radiotherapy (SBRT) for liver metastasis - clinical outcomes from the international multi-institutional RSSearch® Patient Registry. Radiat Oncol 2018; 13: 26.
Andratschke N, et al. The SBRT database initiative of the German Society for Radiation Oncology (DEGRO): patterns of care and outcome analysis of stereotactic body radiotherapy (SBRT) for liver oligometastases in 474 patients with 623 metastases. BMC Cancer 2018; 18: 283.



IZID ZDRAVLJENJA GLEDE NA PATOHISTOLOŠKI PODTIP

Mahadevan A, et all. Stereotactic Body Radiotherapy (SBRT) for liver metastases – clinical outcomes from the international multi-institutional RSSearch® Patient Registry. Radiat Oncol 2018;13-26.





IZID ZDRAVLJENJA GLEDE NA BED IN VELIKOST

Mahadevan A, et all. Stereotactic Body Radiotherapy (SBRT) for liver metastases – clinical outcomes from the international multi-institutional RSSearch® Patient Registry. Radiat Oncol 2018;13-26.

APRIL 2018-SEPTEMBER 2019

Obsevanih 21 bolnikov:

- 14 jetra (pri 2 bolnikih 2 leziji, 1 bolnik z lezijo 2r:9cm)
- 7 pancreas

SBRT JETER

DG primarnega TU:

- 5 CRC
- 2 Ca dojke
- 1 Ca anusa
- 1 holangioCa
- 1 Ca pancreas
- 2 HCC
- 1 LeiomioSA
- 1 Origo (2x ca pljuč, hipernefrom, Ca mehur, Ščitnica?

AKUTNA TOKSIČNOST- BREZ G3-4

nauzea	bruhanje	utrujenost	bolečine	inapetenca
7 (33,3%)	1 (4,7%)	6 (28,6%)	3 (14,3%)	3 (14,3%)

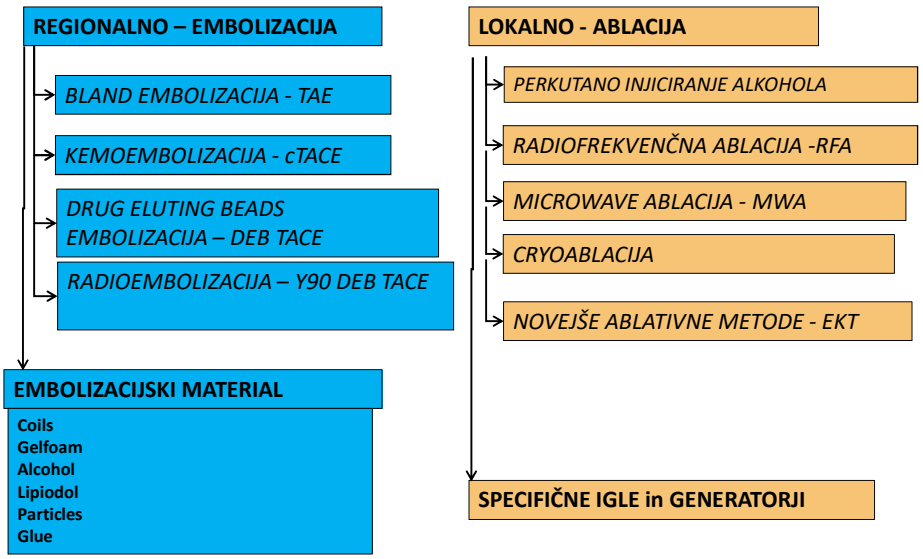
ODGOVOR NA ZDRAVLJENJE

Kompletni	Parcialni	Stagnacija	Progres
7	3	1	0

NEKIRURŠKO LOKALNO ZDRAVLJENJE JETRNIH ZASEVKOV

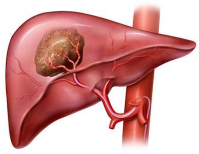
Nina Boc, dr. med.

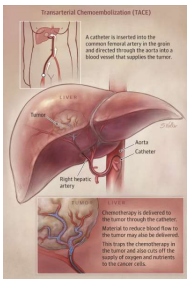
MINIMALNO INVAZIVNO ZDRAVLJENJE SPREMEMB



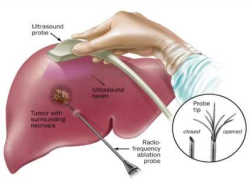
MINIMALNO INVAZIVNO ZDRAVLJENJE sprememb - pristopi

- Perkutani žilni pristopi – REGIONALNA TERAPIJA = EMBOLIZACIJA





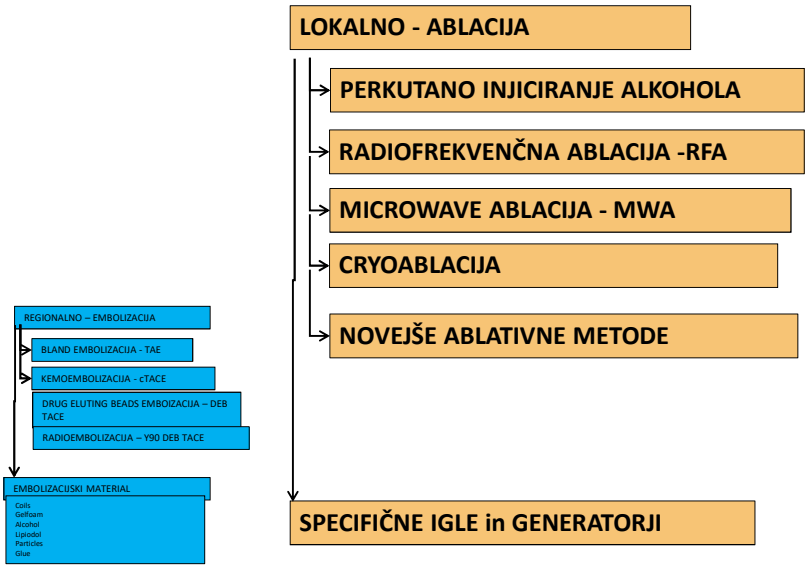
- Perkutani nežilni pristopi – LOKALNA TERAPIJA = ABLACIJA



MINIMALNO INVAZIVNO ZDRAVLJENJE

- HCC
- metastaze mehka tkiva, jetra, pljuča, kosti/primarni tumorji
  - nevroendokrini
  - kolorektalni
  - dojka
  - melanom
  - RCC
  - pljuča
  - prostata

MINIMALNO INVAZIVNO ZDRAVLJENJE SPREMEMB

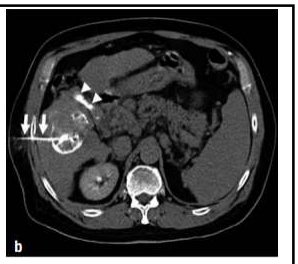


ABLACIJA

- direktno injiciranje (alkohol, vroča FR.)
- vročina (RFA, MWA, HIFU..)
- zmrzovanje (krioablacija)

- prednosti v primerjavi s kirurgijo:
  - manjša morbiditeta in mortaliteta
  - nižji stroški hospitalizacije

PEI



- perkutano injiciranje alkohola – kemična koagulativna nekroza
- dobra lokalna kontrola pri psevdoinkapsuliranih tumorjih velikosti do 2 cm
- srednje preživetje 3 in 5 let 50% do 80% in 28% do 48% *
- ni enakovreden ablativnim metodam, vendar ima manj zapletov

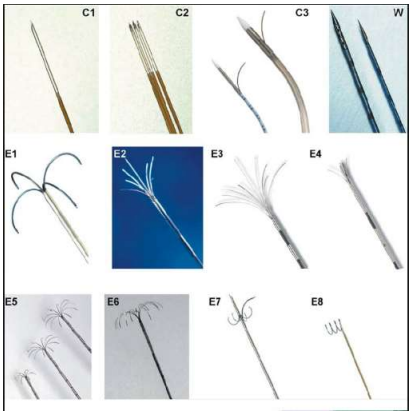
*Arii S, Yamaoka Y, Futagawa S et al.: Results of surgical and nonsurgical treatment for smallsized hepatocellular carcinoma: a retrospective and nation wide survey in Japan. The Liver Cancer Study Group of Japan. Hepatology 2000; 32: 1224–9

RADIOFREKVENČNA ABLACIJA - RFA

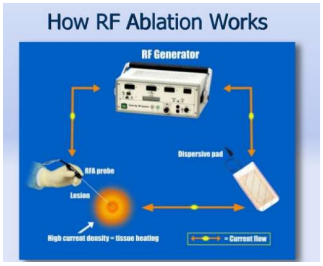
- termična citotoksičnost
- INDIKACIJE:
  - Neresektabilni tumorji (primarni/sekundarni)
  - Multiple lezije ≤3
  - Velikost ≤ 5 cm
- KONTRAINDIKACIJE:
  - Koagulopatije, PM
  - Ascites (perkutani pristop)
  - Neugoden položaj lezije (perkutani pristop)
  - Bližina pomembnih struktur (žolčni vodi, velike žile)
  - Ekstrahepatična bolezen
- ZAPLETI
  - 3,5% vseh zapletov, 0,04% smrti, 0,47% infarkt, 0,19% absces, 0,67% poškodba žolčnih vodov (**Koda et al)

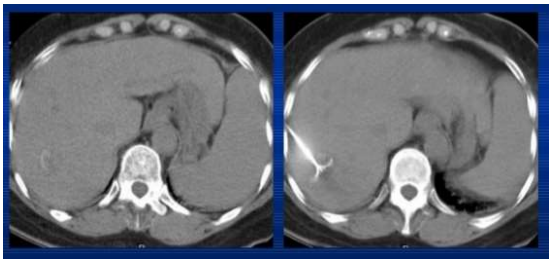
*Lau et. Al. Annals of Surgery 2003
**Koda M et al. Complications of radiofrequency ablation for hepatocellular carcinoma in a multicenter study: An analysis of 16346 treated nodules in 13283 patients. Hepatol Res 2012; 42

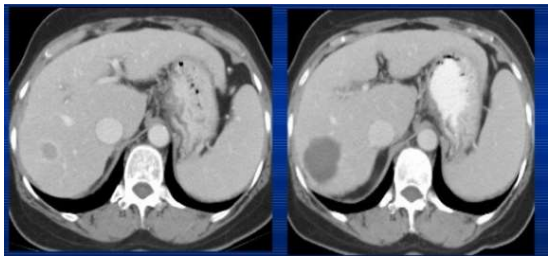
RFA GENERATOR in IGLE



RADIOFREKVENČNA ABLACIJA - RFA







RFA VS. KRG RESEKCIJA

Author	DX	RX	N	Local Recurrence (OR)	Overall survival (OR)
Wu *et al*[1]	CLM	LR RFA	273 574	- 4.89, 95% CI: 1.73-13.87, *P* = 0.003	0.41, 95% CI: 0.22-0.90, *P* = 0.008(5 yr) -
Amerongen et al [2]	CLM	RFA LR	1060 1817	1.66, 95% CI = 1.15–2.40, P = 0.007	2.35, 95% CI = 1.49–3.69, P = 0.001(5 yr)

- RFA je minimalno invazivna tehnika z manj komplikacijami kot krg. resekcija
- RFA ima več recidivov in manjši DFS in OS in je le za bolnike, ki niso kandidati za krg

Radiofrequency ablation compared to surgical resection for curative treatment of patients with colorectal liver metastases – a meta-analysis

Martinus J. van Amerongen[1]*, Sjoerd F.M. Jenniskens[1], Peter B. van den Boezem[2], Jurgen J. Fütterer[1,3], Johannes H.W. de Wilt[2]

J Gastrointest Surg. 2011 Feb;15(2):311-20. doi: 10.1007/s11605-010-1372-y. Epub 2010 Oct 30.

Radiofrequency ablation versus surgical resection for hepatocellular carcinoma in Childs A cirrhotics-a retrospective study of 1,061 cases.

Huang J[1], Hernandez-Alejandro R, Croome KP, Yan L, Wu H, Chen Z, Prasoon P, Zeng Y.

RFA VS. RRS

Acta Oncol. 2013 Jun;52(5):971-7. doi: 10.3109/0284186X.2013.766362. Epub 2013 Feb 14.

Percutaneous radiofrequency ablation (RFA) or robotic radiosurgery (RRS) for salvage treatment of colorectal liver metastases.

Stintzing S[1], Grothe A, Hendrich S, Hoffmann RT, Heinemann V, Rentsch M, Fuerweger C, Muacevic A, Trumm CG.

Author information

1 Department of Medical Oncology and Comprehensive Cancer Center, Klinikum Grosshadern, LMU, Munich, Germany. sebastian.stintzing@med.uni-muenchen.de

- RRS – single session robotic radiosurgery
- Boljša lokalna kontrola DFS 34.4 mes vs. 6.0 mes; p < 0.001
- median FFDR (freedom to distant reccurence) 11.4 mes RRS vs. 7.1 mes RFA p = 0.25
- Ponovitev 67% RRS in 63% RFA, p > 0.99

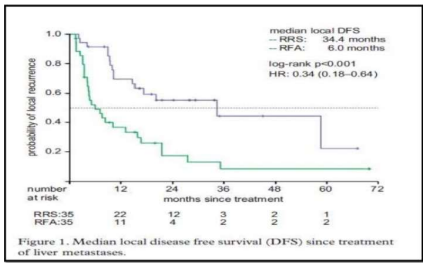
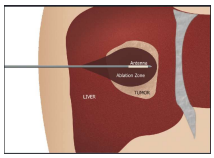


Figure 1. Median local disease free survival (DFS) since treatment of liver metastases.

MICROWAVE ABLACIJA - MWA



- INDIKACIJE (podobne kot za RFA)
  - Velikost je lahko večja kot pri RFA do 5 cm
- KONTRAINDIKACIJE – enake kot RFA
- ZAPLETI
  - Pomembne komplikacije 4,6% (RFA 4,1%), smrtnost 0,23% (RFA 0,15%), krvavitev, tromboza portalne vene, bilomi, abscesi, plevralni izlivi, tumor seeding

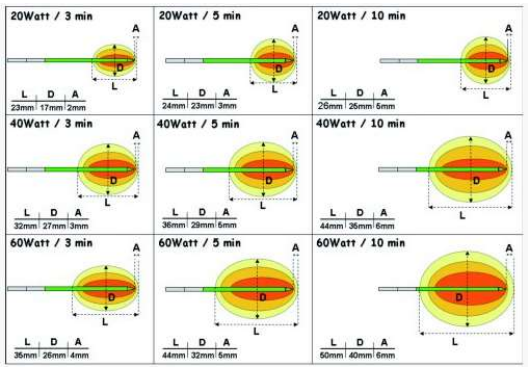
MWA VS. KRG

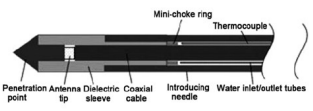
- MWA je minimalno invazivna tehnika z manj komplikacijami kot krg. Resekcija in nekoliko več komplikacijami kot RFA
- MWA ima več recidivov *(46% v 14 mesecih) in manjši DFS in OS in je le za bolnike, ki niso kandidati za krg

* **Surgical ablation of hepatocellular carcinoma with 2.45-GHz microwave: a critical appraisal of treatment outcomes.**
Lee KF[1], Hui JW, Cheung YS, Wong JS, Chong CN, Wong J, Yu SC, Lai PB

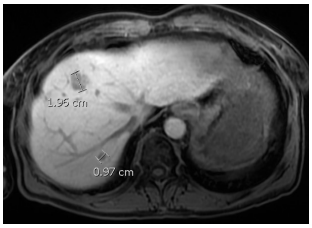
** Lahat E et al. Complications after percutaneous ablation of liver tumors: a systematic review. Hepatobiliary Surg Nutr 2014;

MWA GENERATOR IN IGLE

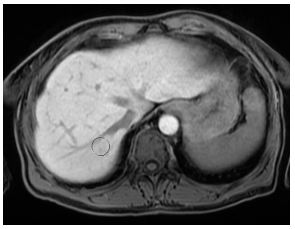




PRIMER MWA



21.08.2018



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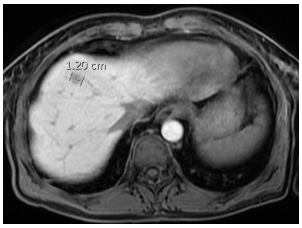

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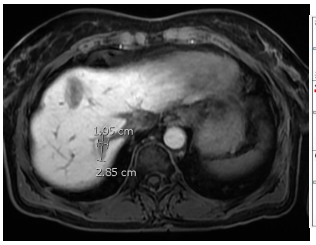

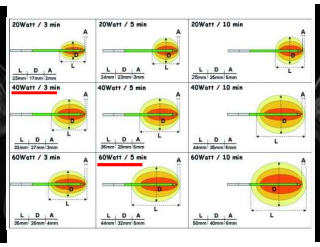

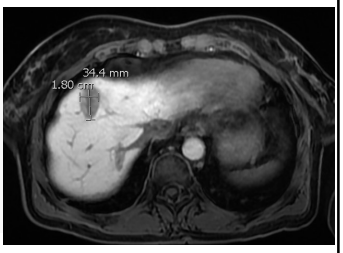

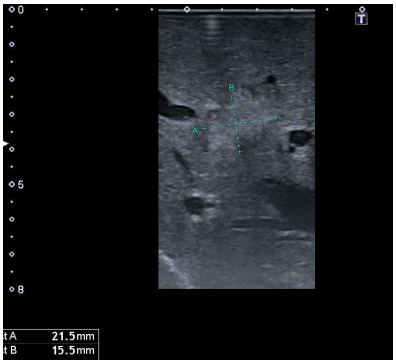

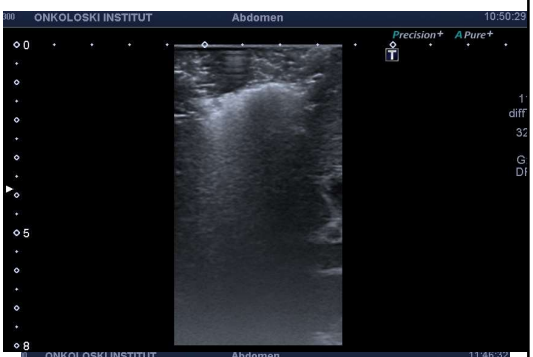

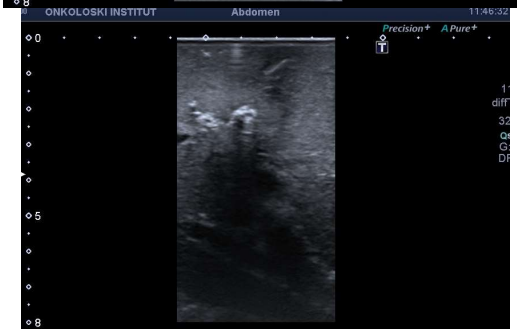

ORIGINAL RESEARCH

Microwave ablation compared with radiofrequency ablation for treatment of hepatocellular carcinoma and liver metastases: a systematic review and meta-analysis

Authors Glassberg MB, Ghosh S, Clymer JW, Qadeer RA, Ferko NC, Sadeghirad B, Wright GWJ, Amaral JF
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Accepted for publication 29 June 2019
Published 12 August 2019 Volume 2019:12 Pages 6407—6438

MWA VS. RFA

- 1379 študij
- Lokalna kontrola tumorjev je boljša – za 30% manj lokalnega progresa tumorja pri MWA vs RFA in 45% (samo randomizirane študije)
- Varnost je enaka
- Boljši outcome pri MWA pri večjih tumorjih ≥2,5 cm

Research | Open Access | Published: 10 June 2019

Microwave ablation compared with hepatic resection for the treatment of hepatocellular carcinoma and liver metastases: a systematic review and meta-analysis

Mrudula B. Glassberg, Sudip Ghosh, Jeffrey W. Clymer, George W. J. Wright, Nicole Ferko & Joseph F. Amaral

World Journal of Surgical Oncology 17, Article number: 98 (2019) | Cite this article
1197 Accesses

MWA VS. KRG

- 1845 študij
- Lokalna ponovitev signifikantno višja pri MWA (risk ratio =2,49; P=0,016)
- Krg resekcija signifikantno boljši 3- in 5- letni OS (RR=0,94; P= 0,03 in RR=0,88; P=0,01)
- MWA krajša hospitalizacija, manjša izguba krvi, manj komplikacij

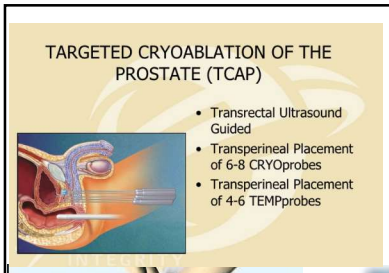
IZZIVI

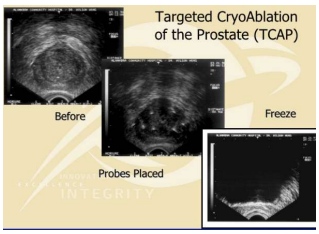
- Malo študij primerjave lokalnih tehnik – največ pri HCC
- lokalni recidivi – v literaturi okrog 10% (2-60% - zlasti pri lezijah ob žilah)
- MWA ima manjši vnetni odgovor na lokalno terapijo
- kirurška resekcija = zlati standard!

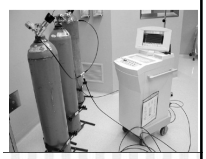
KRIOABLACIJA

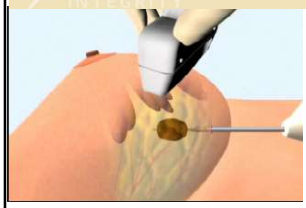
- INDIKACIJE (enake kot za RFA)
- KONTRAINDIKACIJE
  - enake kot za RFA
- SLABOSTI
  - Variabilna velikosti – multiple krioprobe
  - Manjši zmrzovalni efekt ob hepatačnih žilah
  - Boljša lokalna kontrola kot pri RFA
- PREDNOSTI
  - Boljša vizualizacija ledene krogle med posegom
- ZAPLETI – več pomembnih zapletov v primerjavi z RFA (29% vs. 8% ali 41% vs. 3%)
  - Krvavitve, poškodbe žolčnih vodov (lahko tudi pozni zapleti), priležnih organov – kriošok (izplavljanje citokinov – sistemski odziv z vročino, tahikardijo, tahipnejo)
  - Manjše komplikacije 48.6% - vročina, bolečina, plevralni izliv, AV fistula

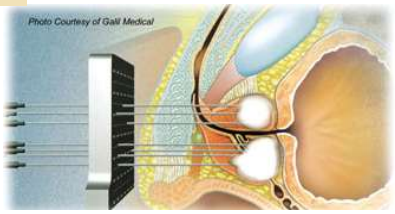
Adam et.al. A comparison of percutaneous cryosurgery and percutaneous radiofrequency for unresectable hepatic malignancies. Arch Surg 2002

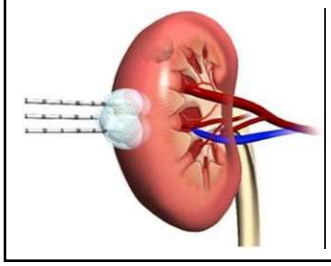








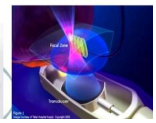




(ŠE)NOVEJŠE METODE

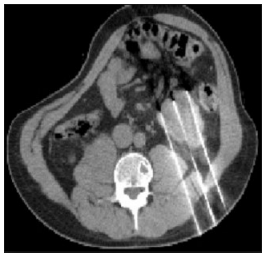
(MR-) HIFU
high-intensity
focused
ultrasound

The Sonablate® 500 is a medical device that uses HIFU to thermally ablate the prostate.



Ideal HIFU candidate:
- Localized prostate cancer
- PSA < 10
- Gleason ≤ 7
- Prostate Volume 40 cc
- Other patients may also qualify and should discuss their specific case with a physician.

- **International HIFU Centers**
  - Toronto, Ontario, Canada
  - Montréal, Québec, Canada
  - **Bucharest, Romania**
  - **Cluj, Romania**
  - **Timisoara, Romania**
  - **Sofia, Bulgaria**
  - **Varna, Bulgaria**
  - Puerto Vallarta, Mexico
  - Cancun, Mexico
  - Nassau, Bahamas



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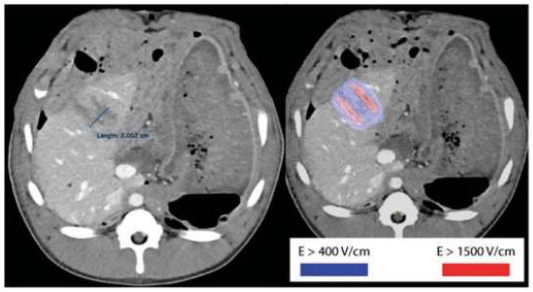
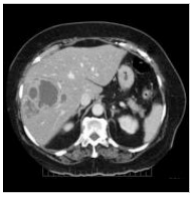
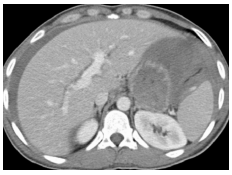


EKT

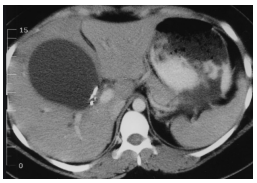
MOŽNI ZAPLETI



absces



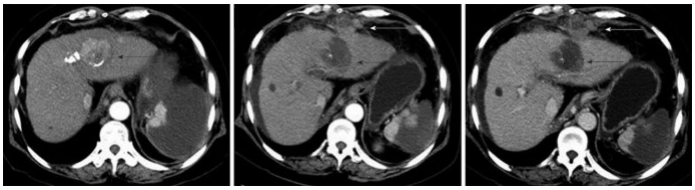
Intraperitonealna krvavitev



Poškodba žolčnih vodov - bilomi

BIOK	S-gamaGT
BIOK	S-bilirubin cel.
BIOK	S-bilirubin dir.
BIOK	S-AST
BIOK	S-ALT
BIOK	S-LDH
BIOK	S-holesteroli
BIOK	S-magnezij
BIOK	S-železo
BIOK	S-transferin
BIOK	S-feritin
BIOK	S-cel.proteini
BIOK	S-albumini

okvara funkcije jeter



tumor seeding

Hepatobiliary Surg Nutr. 2014 Oct; 3(5): 317–323.
doi: 10.3978/j.issn.2304-3881.2014.09.07
PMCID: PMC4207846
PMID: 25392844

Complications after percutaneous ablation of liver tumors: a systematic review

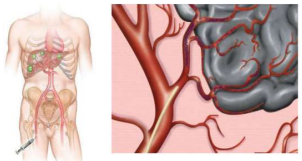
Eylon Lahat,[1] Rony Eshkenazy,[2] Alex Zendel,[3] Barak Bar Zakai,[2] Mayan Maor,[2] Yael Dreznik,[1] and Arie Ariche[2]*

Author information ▸ Article notes ▸ Copyright and License information Disclaimer

MINIMALNO INVAZIVNO ZDRAVLJENJE SPREMEMB (PRETEŽNO) V JETRIH

REGIONALNO – EMBOLIZACIJA

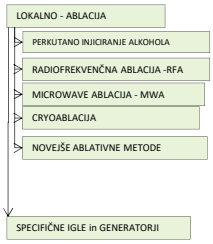
- **BLAND EMBOLIZACIJA - TAE**
- **KEMOEMBOLIZACIJA - cTACE**
- **DRUG ELUTING BEADS EMBOLIZACIJA – DEB TACE**
- **RADIOEMBOLIZACIJA – Y90 DEB TACE**



Catheter is placed via a transfemoral approach with tip within the selected hepatic artery

EMBOLIZACIJSKI MATERIAL

Coils
Gelfoam
Alcohol
Lipiodol
Particles
Glue



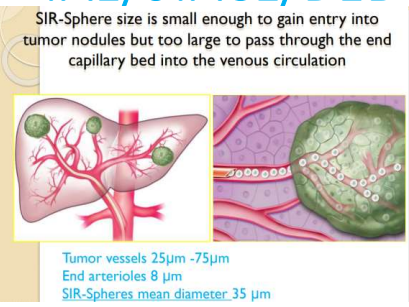
TRANS-ARTERIJSKA EMBOLIZACIJA

- Bland embolizacija (TAE) -> lipiodol
- Konvencionalna kemoembolizacija (cTACE)-> lipiodol+c
- Drug-eluting BEADS kemoembolizacija (DEB-TACE) -> d ik
- Radioembolizacija -> delci + Y sevalec
- Princip = embolizacija feeding arterije in citostatik/sevalec lokalno
- Kemoembolizacija in radioembolizacija = paliativno zdr
- Lahko kombiniramo z ostalimi ablativnimi tehnikami

TAE/cTACE/DEB-TACE

- INDIKACIJE
  - Tumorji, ki niso primerni za druge ablativne metode
- KONTRAINDIKACIJE
  - Obsežne metastaze v jetrih
  - Encefalopatija
  - Obsežna ekstrahepatična bolezen
- RELATIVNE KONTRAINDIKACIJE
  - Tromboza vene porte
  - Jetrna ali ledvična okvara
  - Koagulopatija
  - AV shunti
- ZAPLETI
  - Postembolizacijski sindrom: bolečina, hipertenzija, slabost, bruhanje, ↑ WBC,
  - Netarčna embolizacija (AV shunti, flow related)
  - Reakcije na KS
  - Poškodba žil

TAE/cTACE/DEB-TACE



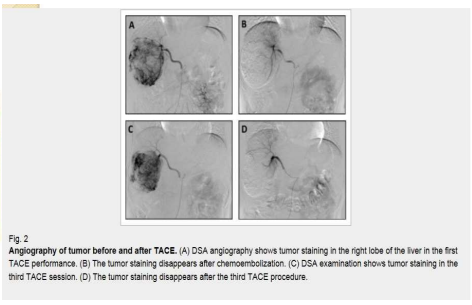
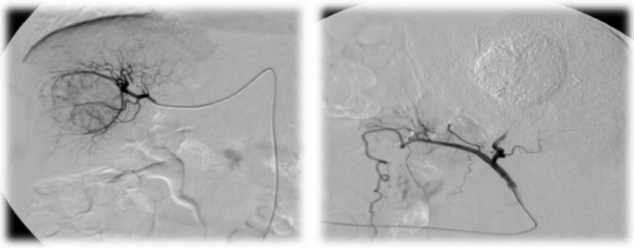
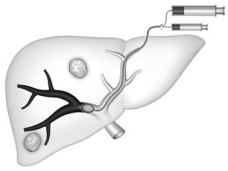


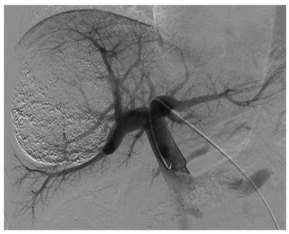
Fig. 2
Angiography of tumor before and after TACE. (A) DSA angiography shows tumor staining in the right lobe of the liver in the first TACE performance. (B) The tumor staining disappears after chemoembolization. (C) DSA examination shows tumor staining in the third TACE session. (D) The tumor staining disappears after the third TACE procedure.

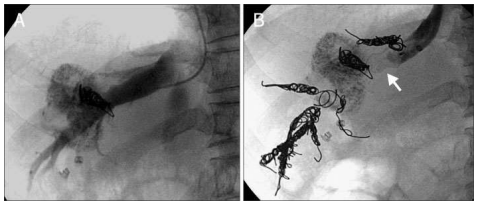
Llovett et. Al Lancet 2002
1,2 in 3 letno preživetje HCC
Podporno zdravljenje
63%, 27% in 17%
Gelfoam embolizacija
75%, 50% in 29%
Kemoembolizacija
82%, 63% in 29%

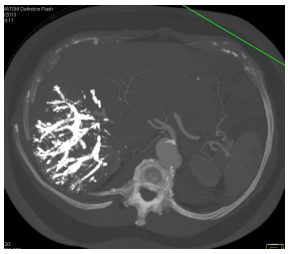


PVE – portal vein embolization









PRIPRAVA BOLNIKA

- TEŠČ 6 ur
- WBC/ANC
- Trombociti >70.000
- PČ/INR <1,5
- Analgezija pri DEBIRI
- Zaščita z antibiotikom

Premedikacija DEBIRI:

slabost/bruhanje

Tropisteron 5 mg pred posegom in 6 ur po posegu

Dexa 8 mg zj. In zvečer in nato še 5 dni

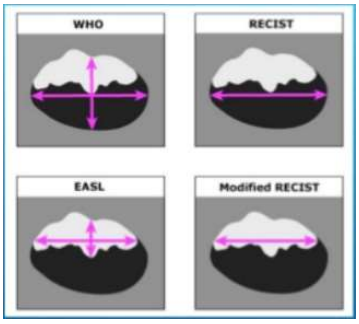
bolečina

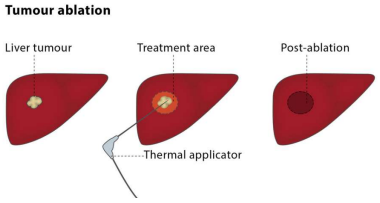
Morfin 10 mg 30 min pred posegom in 6 ur po posegu

infekcija

Cefazolin 2000 mg zj in zv. nato še 2 dni (po potrebi dalj časa)

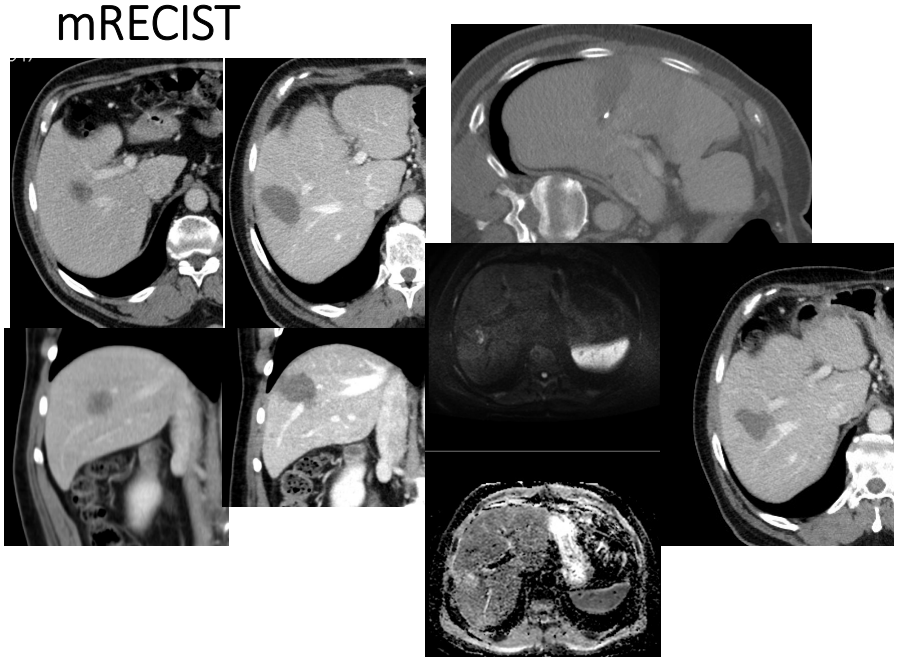
OCENA UČINKA TERAPIJE



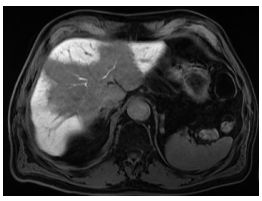


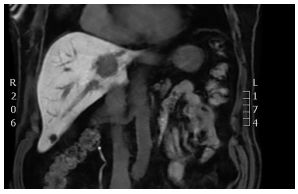
Target lesions		
Response category	RECIST	mRECIST
CR	Disappearance of all target lesions	Disappearance of any intratumoral arterial enhancement in all target lesions
PR	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum of the diameters of target lesions	At least a 30% decrease in the sum of the diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions
SD	Any cases that do not qualify for either PR or PD	Any cases that do not qualify for either PR or PD
PD	An increase of at least 20% in the sum of the diameters of target lesions, taking as reference the smallest sum of the diameters of target lesions recorded since treatment started	An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started
Non-target lesions		
Response category	RECIST	mRECIST
CR	Disappearance of all non-target lesions	Disappearance of any intratumoral arterial enhancement in all non-target lesions
IR/SD	Persistence of one or more non-target lesions	Persistence of intratumoral arterial enhancement in one or more non-target lesions
PD	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions
mRECIST recommendations		
Pleural effusion and ascites	Cytopathologic confirmation of the neoplastic nature of any effusion that appears or worsens during treatment is required to declare PD.	
Porta hepatis lymph node	Lymph nodes detected at the porta hepatis can be considered malignant if the lymph node short axis is at least 2 cm.	
Portal vein thrombosis	Malignant portal vein thrombosis should be considered as a non-measurable lesion and thus included in the non-target lesion group.	
New lesion	A new lesion can be classified as HCC if its longest diameter is at least 1 cm and the enhancement pattern is typical for HCC. A lesion with atypical radiological pattern can be diagnosed as HCC by evidence of at least 1 cm interval growth.	

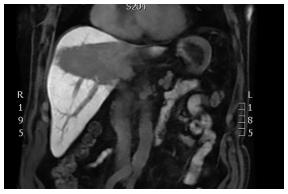
mRECIST

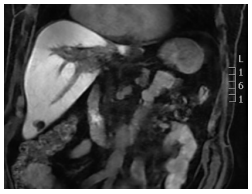


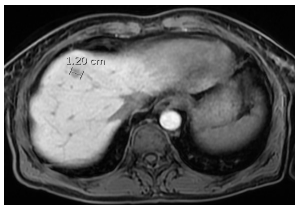
SBRT vs. MWA

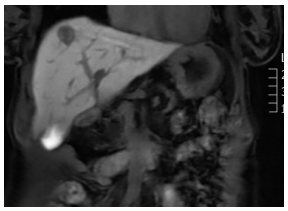


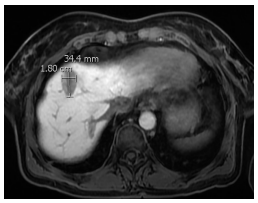






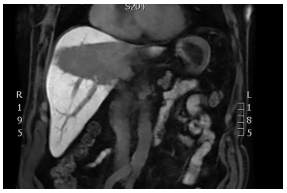


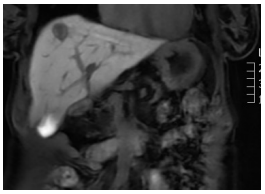


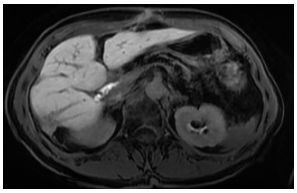


ZAKLJUČEK

- Odločitev na multidisciplinarnem konziliju







Vloga neoadjuvantnega zdravljenja raka trebušne slinavke

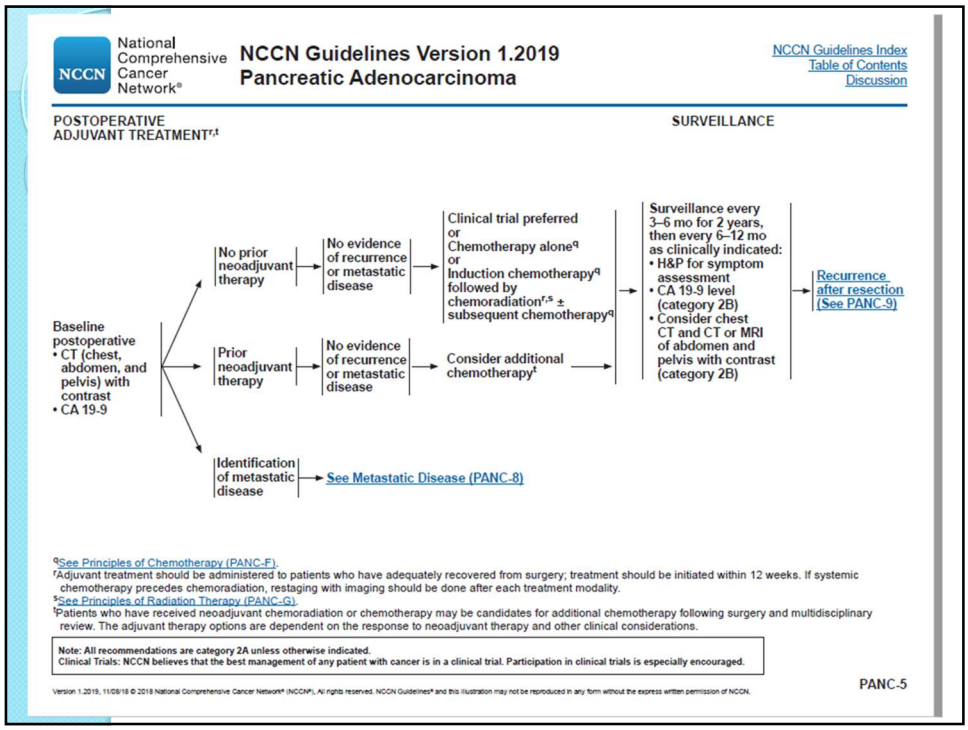
Janja Ocvirk

Ljubljana, 22.11.2019

Limitations of adjuvant treatment

- Approximately 20% of patients with PC are candidates for surgery at diagnosis
- R0 resection rates for resectable PC is 50–70%
- This percentage is lower in borderline disease
- Administration of planned adjuvant chemotherapy may be limited by post-operative complications and early relapse
- It is reported that between 25-50% of patients received no post-operative chemotherapy

Versteijne et al, BJS 2018;
Ducreuz et al, Ann Oncol 2015.



Adjuvant therapy

R0 resection

- Gemcitabin + capecitabine - PS (2)
- mFOLFIRINOX - PS (0-1)

R1 resection

- RT+ChT
- mFOLFIRINOX - PS (0-1)

Adjuvant therapy

- Results of numerous randomized trials and meta-analysis: survival is prolonged if patients are resected after R0 and additionally treated with adjuvant Cht

Objectives of neo-adjuvant treatment

- Increase the rate of R0 resections
- Increase OS in these patients
- Early treatment of micrometastatic disease
- May reduce unnecessary surgical resection in patients with aggressiv disease that develop early recurrence

However…

- Tumour tissue is needed before treatment; this can be difficult
- Biliary drainage with a metal stent may be needed

OS, overall survival.

Neoadjuvant treatment

- Data on neoadjuvant therapy are limited
- Schemes vary: most recommended

  m- FOLFIRINOX

  gamcitabine + nab-paclitaxel

FOLFIRINOX versus gemcitabine/nab-paclitaxel for neoadjuvant treatment of resectable and borderline resectable pancreatic adenocarcinoma:

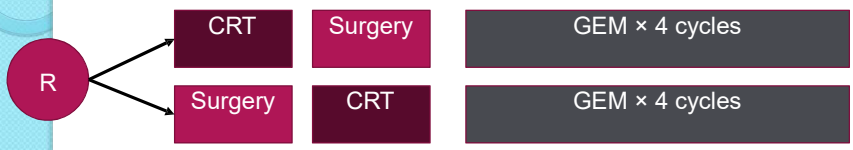
- In a propensity matched analysis of 166 patients using the same preoperative variables, the average treatment effect of FOLFIRINOX was to increase OS by 4.9 months above G-nP (P=0.012).
- Conclusions: FOLFIRINOX and Gem Abraxane are viable options for neoadjuvant treatment of PDA. In this study, FOLFIRINOX was associated with a 4.9 month improvement in OS when compared to G-nP in the neoadjuvant setting after adjusting for covariates.

Dhir M, Zenati MS, Hamad A, et al: FOLFIRINOX versus gemcitabine/nab-paclitaxel for neoadjuvant treatment of resectable and borderline resectable pancreatic adenocarcinoma: A propensity matched analysis. 2018 Society of Surgical Oncology Annual Cancer Symposium. Abstract 7. Presented March 23, 2018.

- We do not have data from many randomised phase III trials
- Most studies reported an incremental change in the rate of R0 resections with neo-adjuvant treatment
- However, most studies were with old or less effective chemotherapy
- Available data for active, modern regimens come from single-centre trials

What is the best treatment option?

Neo-adjuvant versus Adjuvant – chemoradiation (CRT)



N=110 BRPC planned, N=57 BRPC enrolled, Primary endpoint: 2-year survival

	Neoadjuvant CRT	Adjuvant CRT	
2-year survival – ITT	40%	26%	P=0.004
Median OS (months) - ITT	21	12	HR 1.97; P=0.028
R0 resection rate - ITT	51%	26%	P=0.004
R0 resection rate - resected	82%	33%	P=0.010
Positive lymph nodes	0.5±0.9	1.9±1.6	P=0.004

Jang J-Y, et al. Annals of Surgery 2018.

Neoadjuvant therapy utilization for pancreatic cancer among high volume surgical centers: Is it a marker of quality?

- Of 20,119 patients undergoing resection at 107 high volume centers, 2,952 (14.7%) received neoadjuvant therapy.
- These five hospitals had the longest median OS at 28.9 months, compared to 21.1 months for low neoadjuvant utilizers ($p<0.0001$). R0 resection occurred more frequently at high neoadjuvant centers (86% vs 77% at low neoadjuvant centers, $p<0.0001$).

Fisher A, Abbott D, Campbell-Flohr S, et al: Neoadjuvant therapy utilization for pancreatic cancer among high volume surgical centers: Is it a marker of quality? 2018 Society of Surgical Oncology Annual Cancer Symposium. Abstract 59. Presented March 23, 2018.

Randomized phase II/III trial of neoadjuvant chemotherapy with gemcitabine and S-1 versus upfront surgery for resectable pancreatic cancer (Prep-02/JSAP-05)

PRESENTED AT: 2019 Gastrointestinal Cancers Symposium | #GI19

Presented by: Michiaki Unno, Tohoku University

Presented By Michiaki Unno at 2019 Gastrointestinal Cancer Symposium

Prep-02/JSAP-05 phase II/III study

Resectable PDAC

R

Standard Arm

Surgery + Adjuvant (S-1) — Up-S — N=180

Stratification
- CA19-9
- Institutions

Primary endpoint
- Overall survival in PIII
- Resection rate in PII

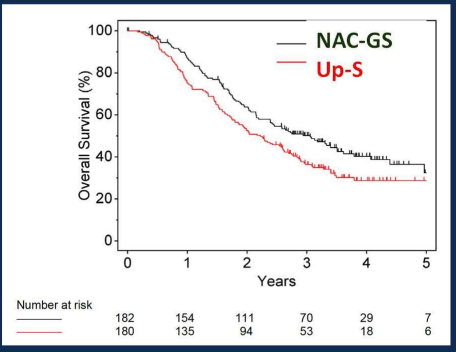
Test Arm

Neoadjuvant (GS) + Surgery + Adjuvant (S-1) — NAC-GS — N=180

Enrollment was started on Jan. 4th , 2013

Presented By Michiaki Unno at 2019 Gastrointestinal Cancer Symposium

Overall Survival (ITT)



- Overall survival
  - NAC-GS: 36.72 months (28.68 – 43.32)
  - Up-S: 26.65 months (21.00 – 31.32)
  - HR: 0.72 (95%CI: 0.55– 0.94)
  - stratified log-rank test: p=0.015
- 2-year OS
  - – 63.7% vs 52.5%

Presented By Michiaki Unno at 2019 Gastrointestinal Cancer Symposium

Summary

- The median OS was 36.72 months in NAC-GS group as compared with 26.65 months in Up-S group (HR for death, 0.72, 95%CI 0.55-0.94, p=0.015).
- Grade 3 or 4 adverse events frequently (72.8%) observed in NAC-GS were leukopenia or neutropenia. However, NAC-GS was safe and feasible.
- Lymph node metastasis was significantly decreased in NAC-GS group (59.6% vs 81.5%)

Presented by: Michiaki Unno, Tohoku University

Presented By Michiaki Unno at 2019 Gastrointestinal Cancer Symposium

How do we define borderline resectable PC?

- A **multidisciplinary team** is required for definition of borderline resectable pancreatic cancer
- **Borderline resectable** lesions can be defined as those where there is a high likelihood of an **incomplete resection**

National Comprehensive Cancer Network (NCCN) Guidelines, Version 3.2017 Pancreatic Adenocarcinoma. www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf. Accessed 28 September 2017.

Borderline resectable

Neoadjuvant treatment

- mFOLFIRINOX
- (Gemcitabine based ChT)
- RT+ChT

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2019
Pancreatic Adenocarcinoma

NCCN Guidelines Index
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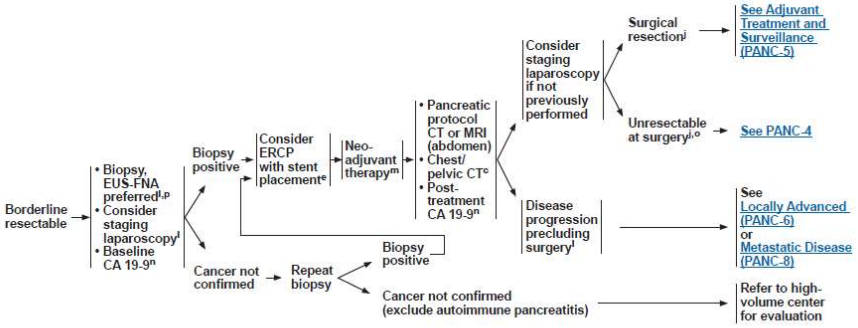
Discussion

BORDERLINE RESECTABLE[l,l] NO METASTASES — **TREATMENT**



[c]Imaging with contrast unless contraindicated.
[e]See Principles of Stent Management (PANC-B).
[l]See Criteria Defining Resectability Status (PANC-C).
[l]See Principles of Surgical Technique (PANC-D) and Pathologic Analysis: Specimen Orientation, Histologic Sections, and Reporting (PANC-E).
[l]See Principles of Diagnosis, Imaging, and Staging (PANC-A).
[m]There is limited evidence to recommend specific neoadjuvant regimens off-study, and practices vary with regard to the use of chemotherapy and chemoradiation. See Principles of Chemotherapy (PANC-F) for acceptable neoadjuvant options. Subsequent chemoradiation is sometimes included; see Principles of Radiation Therapy (PANC-G). Most NCCN Member Institutions prefer neoadjuvant therapy at or coordinated through a high-volume center.
[n]Elevated CA 19-9 does not necessarily indicate cancer or advanced disease. CA 19-9 may be elevated as a result of biliary infection (cholangitis), inflammation, or obstruction, benign or malignant. In addition, CA 19-9 will be undetectable in Lewis antigen-negative individuals (See Discussion).
[o]See Principles of Palliation and Supportive Care (PANC-H).
[p]Core biopsy recommended, if possible, to obtain adequate tissue for possible ancillary studies.

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

Conclusions

- Pancreatic cancer surgery requires and experienced team and high-volume centres
- Adjuvant treatment is still the standard, although neo-adjuvant treatment has a good rationale
- Adjuvant treatment in super-fit patients: mFOLFIRINOX, in remaining patients gemcitabine (+/- CPC in R0) can be considered
- Patients have to be discussed in multidisciplinary groups.
- Neo-adjuvant treatment is preferred, with active chemotherapy treatments

Pancreatic resections for adenocarcinoma of the pancreas

-Results from Maribor-

Stojan Potrč, Matjaž Horvat, Arpad Ivanecz, Tomaž Jagrič, Urška Marolt, Vid Pivec, Bojan Ilijevec

Surgical Clinic, UCC Maribor Slovenia

Standard surgical tratment for adenocarcinoma of the pancreas

Incidence almost equals mortality

Presently the standard treatment:

- Radical R0 resection +/- Administration of adjuvant chemotherapy

  → *5-year survival: 7-25% (median of 15 - 20 mo)*

How many pts amenable for resection?

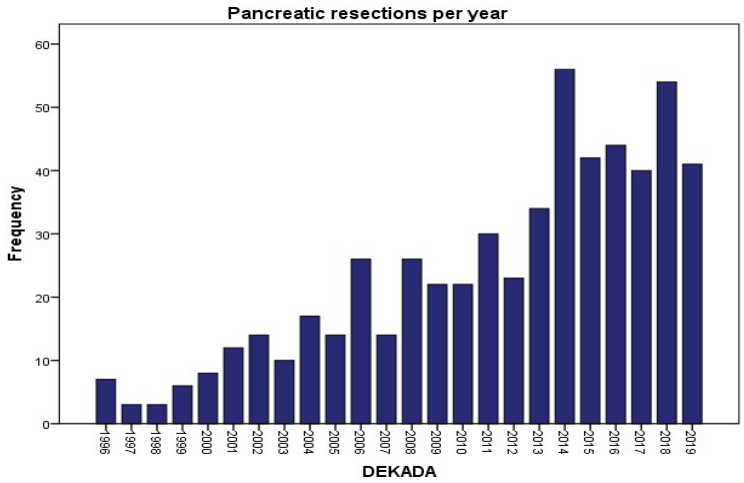
- EU and USA *(from the reports)* → 15 - 20% resectable

Cancer Registry of SLO 2015:

- Incidence 18/100.000 → 370/Y
- If 20% resectable → 70-80 resections for ACP/Y

Annual incidence of pancreatectomies

UKC MB (1997- 2018)



Problems in treatment of pancreatic cancer

15-20% resectable

↓

Recurrence rate → >85%

↓

* ***"Any proposed treatment must not be worse than the disease itself"***

↓

Important → to keep MM low not to compromise the survival

* *Rosenberg L et al. Treatment of pancreatic cancer. Int J of Pan. V 22;Oct 1997*

Outcome of pancreatectomies for adenocarcinoma of the pancreas

UMC MB: January 1, 2000 - June 31, 2017

- Prospective stored E-database → altogether 568 pancreatic resections,
- Analyzed 223 patients resected for pancreas adenocarcinoma January 1st, 2000 to June 31st, 2017, 2 ASA 4 excluded,
- Median follow-up 21 months,
- The follow-up was obtained by our own outpatient follow-up and by the National Cancer Registry of Slovenia.
- Aim: incidence of M&M, impact factors for M&M, survival, to compare two chronologically successive groups of patients (P1: 2000-2009; P2: 2010-2017) in this issue.

Factors studied for correlations with M&M and survival

- Age, Age < &> 70 year
- General performance (ASA 1, 2, 3)
- CEA, Ca 19-9
- Preop. Bilirubin level
- EBD - Y/N
- Amylase on drains > 7ukat/l
- Size of tumour
- Type of resection (Total Vs. PD Vs. LP)
- Resection of the VP/VMS - Y/N
- Period of the study (P1 Vs. P2)

Demographic data:
(n=223)

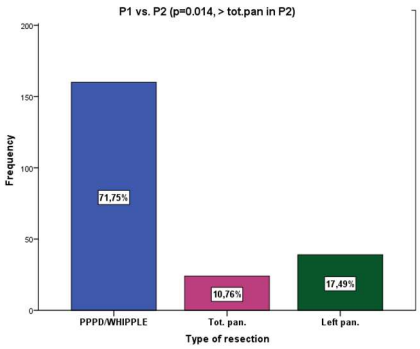
		P1	P2	All	p
Gender (n = 223)	Male	42 (50.6%)	70 (50%)	112 (50.2%)	0.521
	Female	41 (49.4%)	70 (50%)	111 (49.8%)	
Age (n = 223)	Mean (years)	64.04 ± 9.6	65.61 ± 9.2	65.03 ± 9.4	0.227
ASA (n = 223)	1	27 (32.5%)	40 (28.6%)	67 (30%)	0.524
	2	35 (42.2%)	70 (50%)	105 (47.1%)	
	3	21 (25.3%)	30 (21.4%)	51 (22.9%)	
Hospital stays (n = 216)	Mean CD < 3a (days)	16.2 ± 9.1	16.0 ± 8.1	16 ± 8.7	0.950
	Mean CD < 3a (days)	19.98 ± 15	20.12 ± 15	20.07 ± 15	
Preop. Tot. bili. (n = 206)	Mean (mmol/l)	95.8 ± 11	72.2 ± 7	80.6 ± 6	0.066
EBD (n = 223)		17 (20,5%)	35 (25%)	52	0.274
CEA (n = 214)	Median (ug/l)	5.9	6.1	6.04	0.917
Ca 19-9 (n = 211)	Median (ku/l)	240	259	258	0.459

T and N stage in P2
(N=223)

	n %
T1a	1 (0.4%)
T1b	0
T1c	37 (16.6%)
T2	125 (56.1%)
T3	61 (26.5%)
T4	1 (0.4%)

	n %
N0	59 (26.5%)
N1	131 (58.7%)
N2	33 (14.8%)

Type of pancreatic resection
(n = 223)



		P1	P2	All	p
Type of resection (n = 223)	PD	66	94	160	0.014
		79.5%	67.1%	**71.7%**	
	TP	3	21	24	
		4.2%	**15%**	**10.8%**	
	LP	14	25	39	
		16.9%	17.9%	**17.5%**	

Perioperative Morbidity:
Data from the literature – high „powered“ studies (2014 and later)

References	Number of patients	Morbidity
Swanson RS et al., Ann Surg 2017 **(mc USA)**	**21.482 pancreatectomies**	**36%**
Nimitsch U. et al., et al. Ann Surg 2016 **(mc all D)**	**50.003 pancreatectomies**	**37.5%**
Kagedan DJ. Et al., J Gastroitst Surg. 2017 **(mc CDN)**	**2563 W/PPPD**	**50%**
Jose E. et al., PLoS One 2017 **(mc E)**	**4088** all types of resection	**45%**
Yoshioka R. et al Br J Surg 2014 **(mc all J)**	**10.652 PD**	**45%**
Ceppa EP. et al J Am Coll Surg 2015 **(sc USA)**	**1,163: (**66%) **PD,** (32%) LP, (2%)**TP**	**57% vs 46%**
Mise Y. et al., J Gastroitst Surg. 2015 **(sc USA)**	**833:** (74,2%) **PD**, 257 (22.9%)**LP**, 18 (1.6%) **TP,** 15 (1.3%) cent. res.	**15%-**
Xiong J. et al. Int J Surg. 2017 **(sc)**	**325** (86,7%) PD vs **50** (13,3%) TP	***31,4% vs 52%**
Truty MJ et al. Ann Surg. 2019 **(sc)**	**194** PD	**36%**
Pedziwiatr M. et al. Surg Oncol. 2018 **(meta)**	**21 295:** 3824 **older** pts > 80 yrs, 17471 **younger** pts < 80 yrs	**47% vs 39%**

Clavien-Dindo (90-day)

Resections for pancreatic cancer (n=223)

(n=223)	CD n (%)	CD > I n (%)	CD > IIIa n (%)
I	132 (59.2%)		
II	31 (13.9%)	91 (40.8%)	
IIIa	9 (4.0%)		
IIIb	19 (8.5%)		51 (22.9%)
IVa	2 (0.9%)		
IVb	14 (6.3%)		
V	16 (7.2%)		

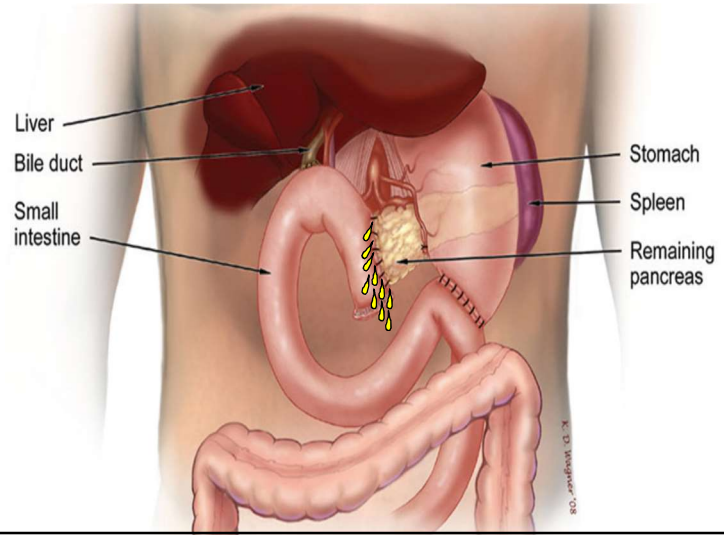
Morbidity after all pancreatic resections

Correlations (all, n = 223)

X^2 CD > IIIa			p
ASA 3 VS. 1,2 (impact)	38.8% vs. 18.4%		0.003
EBD (impact)	32.7% vs. 19.4%		0,044
Binary logistic CD > IIIa			
ASA (independant predictor)	p = 0.015	HR: 2.377	95% CI: 1.182 – 4.778
Hospital stay (consequence)			
CD > I	31.4 ± 2 vs. 13.6 ± 0,3 days		< 0.0001
CD > IIIa	39 ± 4 vs. 16.2 ± 0.7 days		< 0.0001

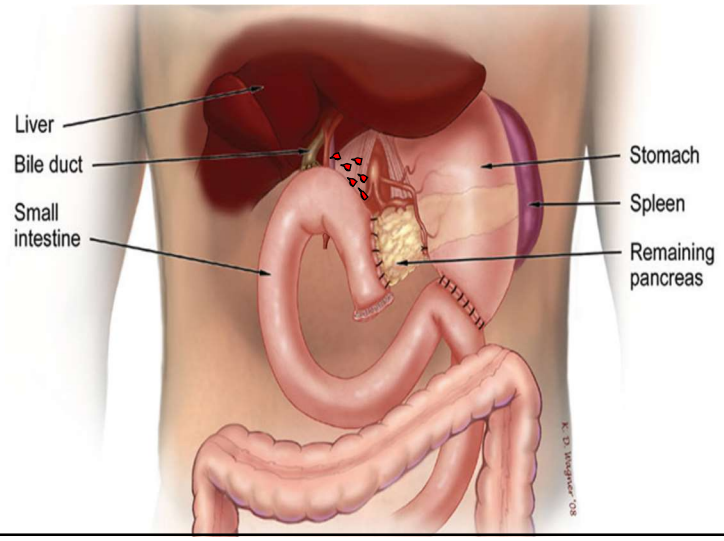
Problem of Morbidity & Mortality

Achilles' heel of pancreas head resection: leak on the PJA



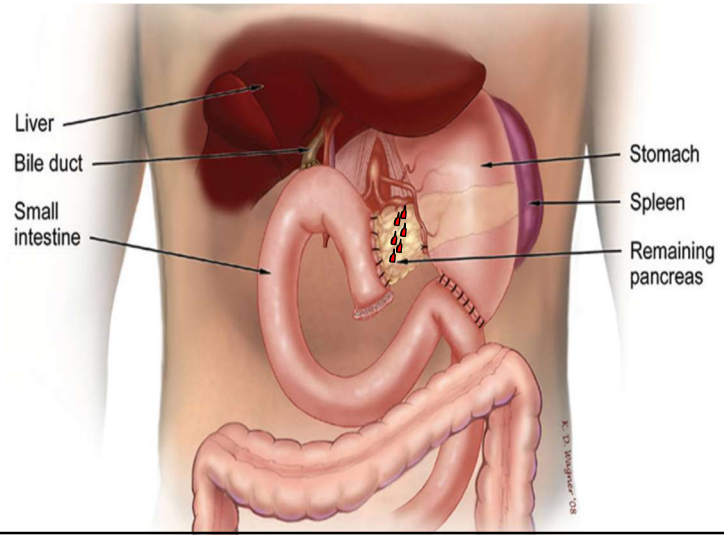
Problem of Morbidity & Mortality

Potentially catastrophic cosnequence – bleeding from CHA



Problem of Morbidity & Mortality

Potentially catastrophic cosnequence – bleeding from SA

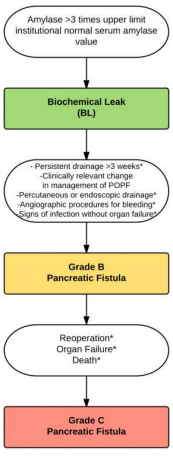


Problem of Morbidity & Mortality

Definition of PF according to ISgPF (2017)

- Definition → amylase 3x normal
- Incidence of PF → 5-30 %
- ISgPF → 16,2% (PF B in C), 5,2% bleeding!!!

Event	BL (NO POPF)	Grade B POPF*	Grade C POPF*
Increased amylase activity > 3 times upper limit institutional normal serum value	YES	YES	YES
Persisting peripancreatic drainage > 3 weeks	NO	YES	YES
Clinically relevant change in management of POPF#	NO	YES	YES
POPF percutaneous or endoscopic specific interventions for collections	NO	YES	YES
Angiographic procedures for POPF related bleeding	NO	YES	YES
Reoperation for POPF	NO	NO	YES
Signs of infection related to POPF	NO	YES, without organ failure	YES, with organ failure
POPF related organ failure^	NO	NO	YES
POPF related death	NO	NO	YES



*Treatment/Event POPF related

Pancreatic fistula after PPPD/PRPD for pancreatic adenocarcinoma
(n=160)

PPPD/PRPD for pancreatic adenocarcinoma (n = 160)	n	%	90-day mortality
Biochemical leak	13	7.5%	0
PF B	10	6.3%	0
PF C	13	**8.1%**	**35.7% (5 pts)**

Pancreatic fistula after pancreatic head resection
Correlations (PD only; n=160)

Amylase > 7ukat/l		**p**
T 1 vs.T > 1 (impact factor)	35.5% vs. 18.6%	0.04
PF C		
ASA (impact factor)	1.9% vs. 9.3% vs. 15.6%	0.022
Age, Vascular resect., EBD…	→	*No correlation*

Bleeding (consequence of PF)	44.4% vs. 6%	0.0001
Hospital stay (consequence of PF C)	30.7 vs. 13.4 days	0.0001

Type of morbidity and 90-day mortality

(all, n = 223, * PD, n=160)

Type of complication	n	n 90-day mortality
No complications	133 (59.6%)	0
Leaking PJA (+/-bleeding)	24 (10.7%) *(*14.3%)*	5
Bleeding – non-PF	6 (2.2%)	2
Leaking of BDA	5 (2.2%)	0
Leaking of GEA	4 (1.8%)	0
Disruption of laparotomy	4 (1.8%)	0
Abdominal abscess (amylase < 7)	8 (3.6%)	0
Delayed gastric emptying	3 (1.3%)	0
Thrombosis of vascular prothesis	2 (0.9%)	0
Cardio-respiratory failure	7 (1.3%)	4
Pulmonary embolism	2 (0.8%)	1
Mycotic sepsis	5 (1.3%)	0
Other	6 (2.2%)	1
Cirrhosis	1 (0.4%)	1
Died after dissmisal while on chemo (on day 60)	1 (0.4%)	1
Died after dismissal (on day 42) – reason not known	1 (0.4%)	1
PF A	12 (7,2%)	0

Perioperative Mortality :

data from the literature – high „powered“ studies (2014 and later)

References	Number of patients	Mortality
Swanson RS et al., Ann Surg 2017 **(mc USA)**	**21.482** pancreatectomies	**3.7%** 30 day **7.4%** 90 day
Nimitsch U. et al., et al. Ann Surg 2016 **(mc all D)**	**50.003** pancreatectomies	**10.1**% (hospital mort)
Kagedan DJ. Et al., J Gastroitst Surg. 2017 **(mc CDN)**	**2563** W/PPPD	Low vol.→ **2.5%** & **5.2%** Med. vol.→**3.9** & **6.3** High vol. → **1.5%** & **2.7%**
Jose E. et al., PLoS One 2017 **(mc E)**	**4088** all types of resection	Low vol. → **11%** High vol. →**7%**
Yoshioka R. et al Br J Surg 2014 **(all J)**	**10.652** PD	Low vol.→ **5%** High vol.→ **1.5%**
Ceppa EP. et al J Am Coll Surg 2015 **(sc USA)**	**1,163:** (66%) PD, (32%) LP, (2%)TP	**2.9%** (hospital)
Krautz C et al., Ann Surg 2017 **(mc D)**	**60.500** PD	<16 PD → **10-13%** >48 PD → **6-8%**
Mise Y. et al., J Gastroitst Surg. 2015 **(sc USA)**	**833:** (74,2%) PD, **257** (22.9%)LP, **18** (1.6%) TP, **15** (1.3%) cent. res.	**1.2%** 90 day **Only 9% NPC´s**
Xiong J. et al. Int J Surg. 2017 **(sc)**	**375:** 325 (86,7%) PD, 50 (13,3%) TP	**2,7% vs 6%**
Truty MJ et al. Ann Surg. 2019 **(sc)**	**194** PD	**6,7%** 90 day
Pedziwiatr M. et al. Surg Oncol. **2018 (meta)**	**21 295:** 3824 **older** pts > 80 yrs, 17471 **younger** pts < 80 yrs	**4,54%** **2,26%**

30 and 90-day mortality

Incidence (all, n=223)

Resection for pancreatic adenocarcinoma (n=223)	P1	P2	p
30-day mortality	6%	**2.1%**	0.129
90-day mortality	12%	**4.3%**	**0.016**

Correlations for 30 and 90-day mortality – all resections

X^2 (all, n = 223)

Variable	30-day mortality	p	90-day mortality	p
ASA 3 vs. 1 and 2	10.2% vs. 1.7%	0.034	20.2% vs. 3.9%	0.001
CD > 1	12% vs. 0%	0,001	19% vs. 2%	< 0.0001
CD > IIIa	20% vs. 0%	0.0001	34.3% vs. 0.8%	< 0.0001

Binary Regression (all, n = 223)

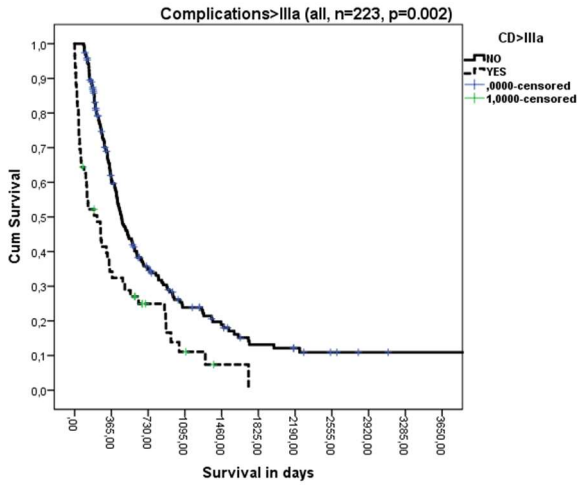
Variable	Mortality	HR	95% CI	p
ASA 3 (independant predictor)	30-day mortality	6.221	1.400 – 27.533	0.016
	90-day mortality	5.917	1.495 – 23.419	0.011
CD > IIIa (independant predictor)	90-day mortality	90.500	10.564 – 775.286	< 0.0001

Correlations for 30 and 90-day mortality - PPPD/PRPD

Binary Regression (PD, n = 160)

Variable	Mortality	HR	95% CI	p
PF C	30-day mortality	32.727	3.134 – 341.755	0.004
ASA 3	90-day mortality	8.451	1.882 – 37.945	0.005
CD > IIIa	90-day mortality	90.500	10.564 – 775.286	< 0.0001

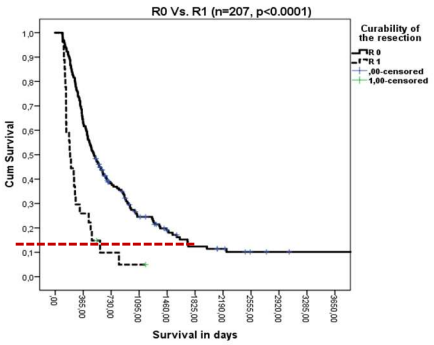
Impact of complications CD > IIIa on survival



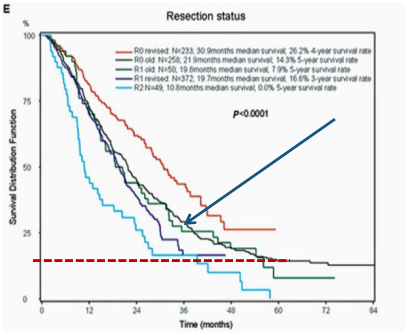
Currability of the resection:

R0 vs. R1 (all, n = 223)

	P1	P2	All	p
R 0 resection	73	125	194	0.806
(n = 223)	88.3%	**89.3%**	**88.8%**	



16.7 vs. 6.5 months, Log Rank < 0.0001



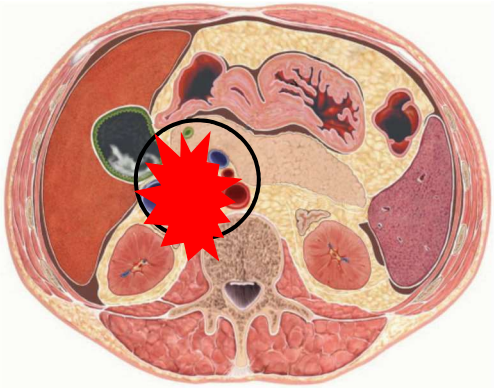
Pancreatic Cancer Surgery in the New Millennium

Better Prediction of Outcome

Werner Hartwig, MD, Thilo Hackert, MD,* Ulf Hinz, MSc,* Alexander Gluth,* Frank Bergmann, MD,† Oliver Strobel, MD,* Markus W. Büchler, MD,* and Jens Werner, MD**

Survival → critical points in pancreatic resection

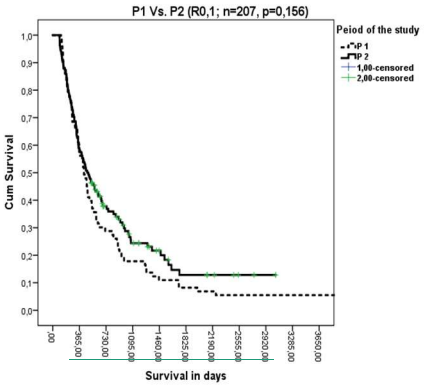
Problem of growth through dorsal pan. capsule: → R1

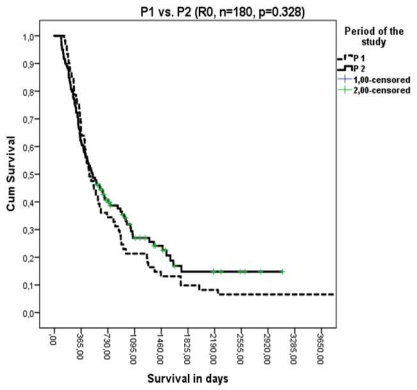


R1	25 pts (11.2%)	**„Dorsal“ R1**	19/25 (8.5%)

Survival

P1 vs. P2 (all R, n = 207; R0, n = 180)



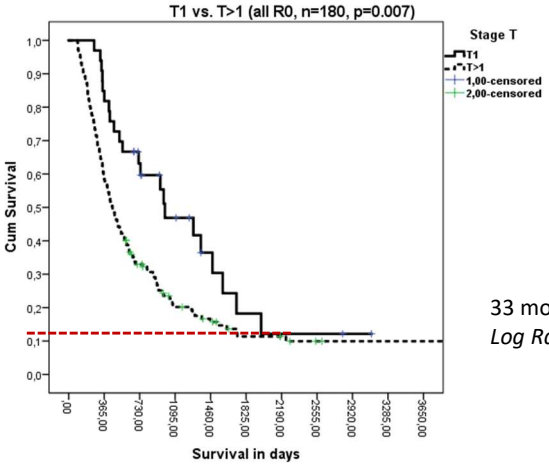


14.2 months (P1) vs. 15.7 months (P2)
Log Rank = 0.16

16 months (P1) vs. 17.4 months (P2)
Log Rank = 0.328

Survival

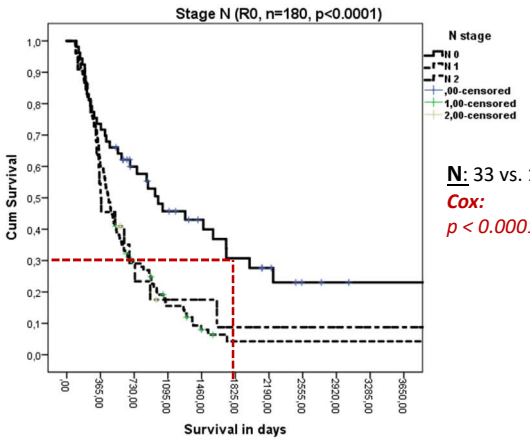
T stage 1 vs. T > 1 (all R0, n = 180)



33 months (T1) vs. 15 months (T>2)
Log Rank = 0.007

Survival Cox regression

N stage (all R0, n = 180)



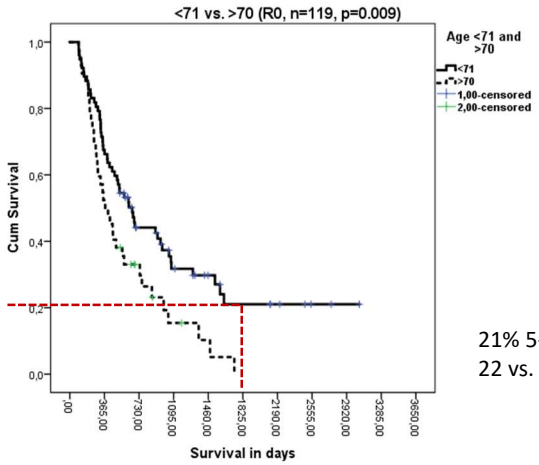
N: 33 vs. 15 vs. 15 mo;

Cox:

p < 0.0001, HR: 2.312, 95% CI: 1.558 – 3.430

Survival: < 71 vs. >70

(P2, R0, n = 119)

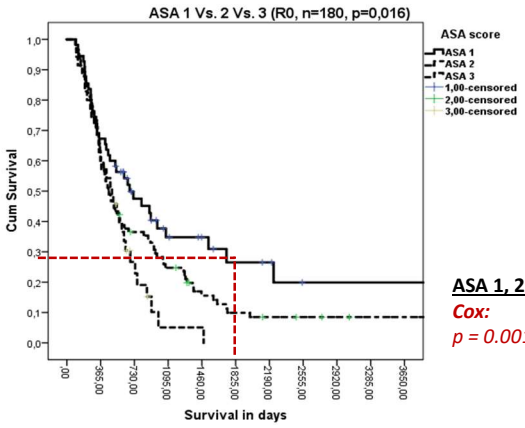


21% 5-year survival

22 vs. 15.7 months, Log Rank = 0.009

Survival Cox regression

ASA and N stage (all R0, n = 180)



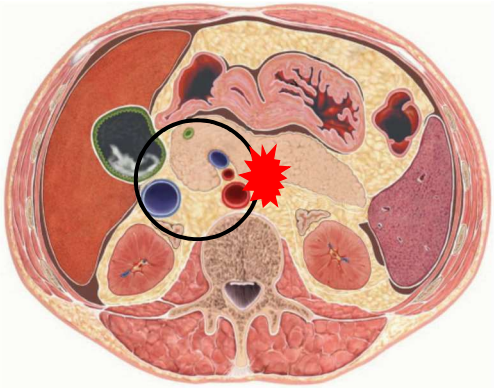
ASA 1, 2, 3: 22.6 vs. 15 vs. 16.3 mo

Cox:

p = 0.001, HR: 1.505, 95% CI 1.173 – 1.930

Survival → critical points in pancreatic resection

Infiltration of arteries CHA, SMA, COELIAC TRUNC



Curability of the resection and long term survival

Definitions: resectable, borderline resectable, locally advanced (Katz)

	SMV/PV	SMA	CHA	CT
Resectable	< 180^0, no occlusion	No contact	No contact	No contact
Borderline	> 180^0, without/with occlusion	< 180^0	Reconstructable	< 180^0
Locally advanced	180^0, technically not amenable for resection	> 180^0	Not reconstructable	> 180^0

Optimizing the outcomes of pancreatic cancer surgery

Oliver Strobel[1], John Neoptolemos[2], Dirk Jäger[3] and Markus W. Büchler[1]*

Box 2 | **Anatomical resectability criteria**[41]

Resectable
- SMV/PV: no tumour contact or unilateral narrowing
- SMA, CA and CHA: no tumour contact

Borderline resectable
Subclassified according to SMV/PV involvement alone or arterial involvement
- BR-PV (SMV/PV alone)
  - SMV/PV: tumour contact ≥180° or bilateral narrowing and/or occlusion not exceeding the inferior border of the duodenum
  - SMA, CA and CHA: no tumour contact
- BR-A (arterial involvement)
  - SMA and CA: tumour contact of <180° without deformity and/or stenosis
  - CHA: tumour contact without showing tumour contact of the PHA and/or CA

Unresectable
Subclassified according to the status of distant metastasis

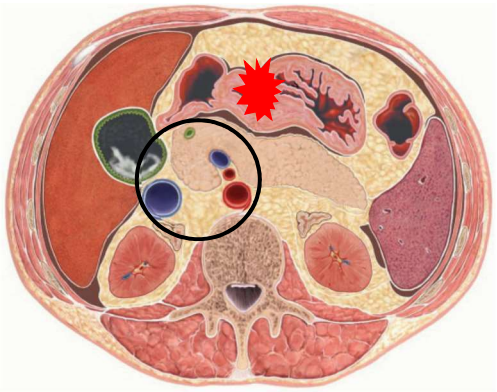
Locally advanced
- SMV/PV: bilateral narrowing and/or occlusion, exceeding the inferior border of the duodenum.
- SMA and CA: tumour contact ≥180°
- CHA: tumour contact extending to PHA and/or CA
- Aorta: tumour contact or invasion of the aorta

Metastatic
Distant metastasis (incuding para-aortic and extra-abdominal lymph node metastasis)

CA, coeliac artery; CHA, common hepatic artery; PHA, proper hepatic artery; PV, portal vein; SMA, superior mesenteric artery; SMV, superior mesenteric vein. Adapted with permission from REF[41], Elsevier.

Survival → critical points in pancreatic resection

Infiltration of SMV

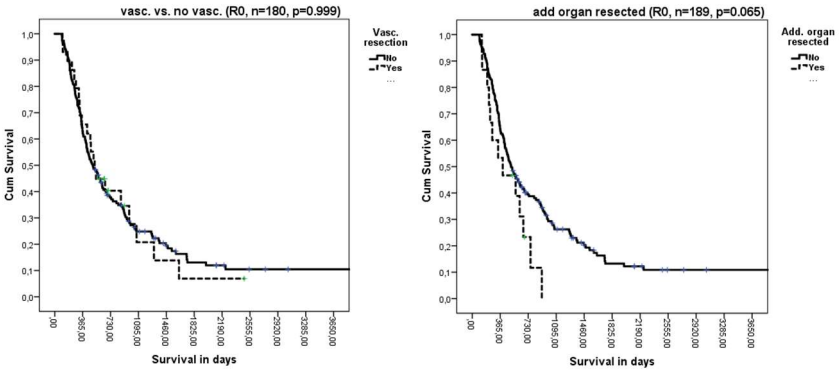


To provide R0 if infiltration of VMS suspected:
(all, n = 223)

	P1	P2	All	p
Resection of VMS/VP/CHA(2) (n=223)	10 (12%)	35 **(25%)**	45**(20.2%)**	**0.014**
Type of vascular reconstruction	9 (10.8%)	21 (15%)	**30 (13.5%)**	**0.009**
- Direct suture	1 (1.2%)	**14 (10%)**	**15 (6.7%)**	
- Interposition vascular graft				

	P1	P2	All	p
Resection of other organ	7 (8.4%)	13 (9.3%)	20 (9%)	0.518

Survival: vascular res. and res. of add. Organs
(R0, n = 180)



Meta-analysis comparing upfront surgery with neoadjuvant treatment in patients with resectable or borderline resectable pancreatic cancer

E. Versteijne[1], J. A. Vogel[2], M. G. Besselink[2], O. R. C. Busch[2], J. W. Wilmink[3], J. G. Daams[4], C. H. J. van Eijck[5], B. Groot Koerkamp[6], C. R. N. Rasch[1] and G. van Tienhoven[1], on behalf of the Dutch Pancreatic Cancer Group

Median survival after upfront resection
data from the literature

Table 3 Median overall survival, resection rate and R0 rate after upfront surgery reported in 12 studies

Reference	No. of patients	Median age (years)	Median OS (months)	Resection rate, ITT (%)	R0 rate* (%)	Patients with positive lymph nodes (%)*
Casadei *et al.*[15]	20	67·5	19·5	75	33	87
Golcher *et al.*[16]	33	65·1	14·4	70	70	57
Bao *et al.*[17]	78	68†	17·9	77	75	58
Raptis *et al.*[18]	102	64‡	12	32·7	n.r.	n.r.
Tzeng *et al.*[19]	52	61·9	25·3	92	81	81
Fujii *et al.*[20]	71	63	13·1	70	40	92
Fujii *et al.*[21]	233	67	23·5	87·6	70·1	71
Barbier *et al.*[22]	85	64	17	79	67	64
Papalezova *et al.*[23]	92	65†	13	74	79	62
Kato *et al.*[24]	624	63·8	12·6	86·4	65·9	57
Hirono *et al.*[25]	331	R: n.r. BR-V: n.r. BR-A: 69§	R: 20·9 BR-V: 16·3 BR-A: 12·4	R: 89·5 BR-V: 92 BR-A: 83·1	R: n.r. BR-V: n.r. BR-A: 62·1	R: n.r. BR-V: n.r. BR-A: 74·8
Murakami *et al.*[26]	25	67§	11·6	92	17	78
Total	1746	Range 61·9–69	14·8	81·3 (79·4, 83·1)	66·9 (64·2, 69·6)	64·8 (62·0, 67·5)

Values in parentheses are 95 per cent confidence intervals. *Among patients who underwent resection of pancreatic cancer. †Mean age. ‡Including patients with unresectable pancreatic tumours, who were not reported separately. §Including patients who received neoadjuvant treatment. OS, overall survival; ITT, intention to treat; R, resectable; n.r., not reported; BR-V, borderline resectable with venous involvement; BR-A, borderline resectable with arterial involvement.

14.2 months (P1) vs. 15.7 months (P2)
Log Rank = 0.16

Adjuvant oncological treatment
(n = 206)

	P1	P2	All	p
Oncotherapy received	25 34.7%	86 **64.1%**	111 **49.5%**	**< 0.0001**

Type of chemotherapy	n
Gemcitabine	106
Gemcitabine + Nab-Paclitaxel	3
Folfirinox	2

37 completed
42 not completed
32 not started

Median survival after neoadjuvant oncoth

data from the literature

Meta-analysis comparing upfront surgery with neoadjuvant treatment in patients with resectable or borderline resectable pancreatic cancer

E. Versteijne[1], J. A. Vogel[2], M. G. Besselink[2], O. R. C. Busch[2], J. W. Wilmink[3], J. G. Daams[4], C. H. J. van Eijck[3], B. Groot Koerkamp[3], C. R. N. Rasch[1] and G. van Tienhoven[1], on behalf of the Dutch Pancreatic Cancer Group

Table 4 Median overall survival, resection rate and R0 rate after neoadjuvant treatment reported in 35 studies

Reference	No. of patients	Median age (years)	Median OS (months)	Resection rate ITT (%)	R0 rate (%)*	Patients with positive lymph nodes (%)*
Palmer et al.[27]	50	66	13·6	54	74	56
Casadei et al.[28]	18	71·5	22·4	61	64	55
Golcher et al.[16]	33	62·5	17·4	58	90	32
Evans et al.[29]	86	65·8	22·7	74	89	38
Heinrich et al.[29]	28	59	26·5	89	80	64
Le Scodan et al.[30]	41	59·3	9·4	63	81	50
Turrini et al.[31]	34	61·5†	15·5	50	100	24
Small et al.[32]	17	62‡	R: 10·2 BR: 11·2	R: 43 BR: 30	n.r.	0
Esnaola et al.[33]	13	60	24·1	69	92	n.r.
Kim et al.[34]	62	64‡	R: 26·5 BR: 18·4	R: 57 BR: 72	85	44
O'Reilly et al.[35]	38	73	27·2	71	74	67
Shaib et al.[36]	13	64	11	62	n.r.	13
Calvo et al.[37]	15	61	10	60	78	n.r.
Ohigashi et al.[38]	38	66	32	82	97	10
Katz et al.[39]	22	64	21·7	68	93	33
Oh et al.[40]	38	59	21·2	61	78	4
Tzeng et al.[41]	141	63	19·1	59·6	91·7	48·8
Tzeng et al.[19]	115	65·5	28	82·6	89·5	51·5
Fujii et al.[20]	21	66	29·1	86	100	17
Fujii et al.[21]	40	65	24·9	90	86	39
Ielpo et al.[42]	11	61·8†	20	73	100	n.r.
Masui et al.[43]	18	63	21·7	83	87	33
Takai et al.[44]	32	61·8	19·2	75	n.r.	n.r.
Barbier et al.[22]	88	65	15	43	92	29
Patel et al.[45]	18	67	15·6	50	89	n.r.
Papalezova et al.[23]	144	64	15	53·0	78·0	25
Chuong et al.[46]	57	64‡	16·4	56	97	34
Dholakia et al.[47]	50	63·5	17·2	58	93	28
Boone et al.[48]	61	64‡	R: 20 BR: 22	R: 95 BR: 83	R: 86 BR: 70	n.r.
Rose et al.[49]	64	66	23·6	48	87	58
Moningi et al.[50]	14	67·2‡	14·4	29	100	n.r.
Sho et al.[51]	99	R: 66·4† BR-V: 66·3† BR-A: 66·0†	R: 50·2 BR-V: 26·6 BR-A: 18	R: 100 BR-V: 97 BR-A: 84	R: 98 BR-V: 97 BR-A: 81	n.r.
Rashid et al.[52]	121	67	17	45·5	98·4	63·6
Hirono et al.[25]	46	69§	18	87	80	78
Murakami et al.[26]	53	67‡	27·4	66	72	30
Total	1738	Range 59–73	18·8 months	66·0 (63·7, 68·2)	86·8 (84·6, 88·7)	43·8 (40·6, 47·1)

Neo adj. Onco:

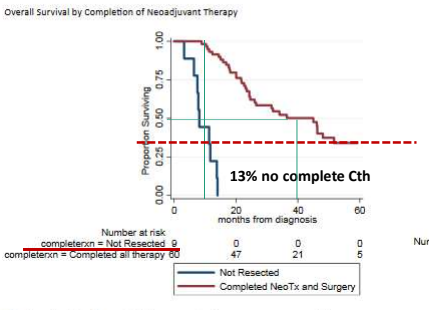
- Less resections
- Younger pts ???
- More R0
- Less N+
- Improved long-term survival

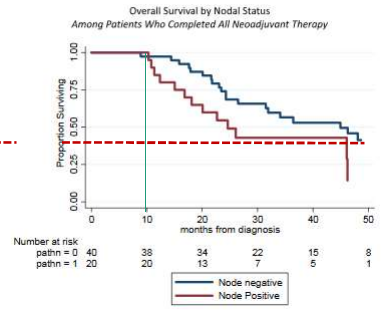
Neoadjuvant treatment

data from the literature

Survival of patients with resectable pancreatic cancer who received neoadjuvant therapy.

Citation data: Surgery, ISSN: 1532-7361, Vol: 159, Issue: 3, Page: 893-900
Publication Year: 2016

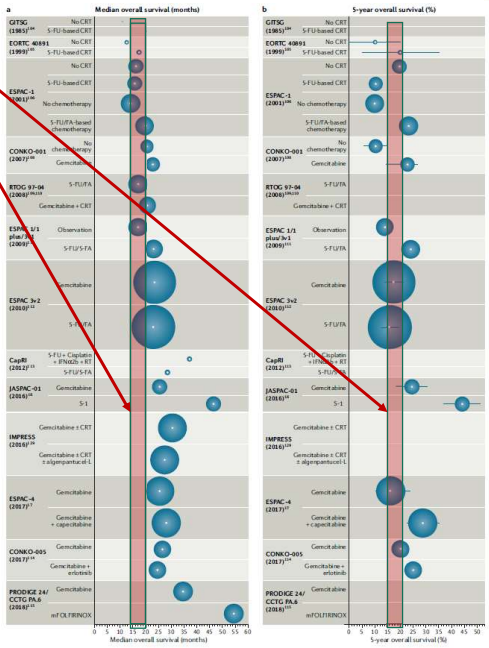




Where are we ???

Optimizing the outcomes of pancreatic cancer surgery

Oliver Strobel[1], John Neoptolemos[2], Dirk Jäger[3] and Markus W. Büchler[1]*



Has survival improved ???

The American Journal of Surgery

Review

Has survival improved following resection for pancreatic adenocarcinoma?

Kenneth Luberice, Darrell Downs, Benjamin Sadowitz, Sharona Ross, Alexander Rosemurgy*

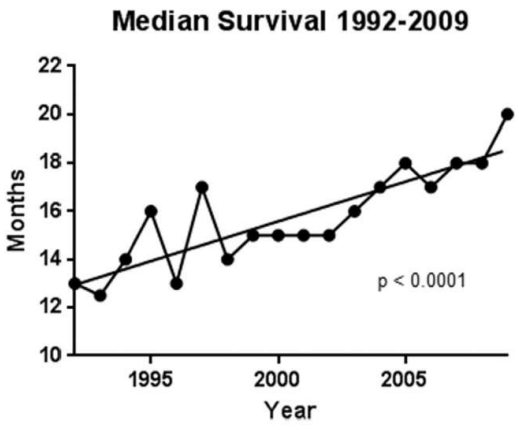


Fig. 3. Median survival for patients undergoing pancreatectomy for pancreatic adenocarcinoma from 1992 to 2009.

Has survival improved ???

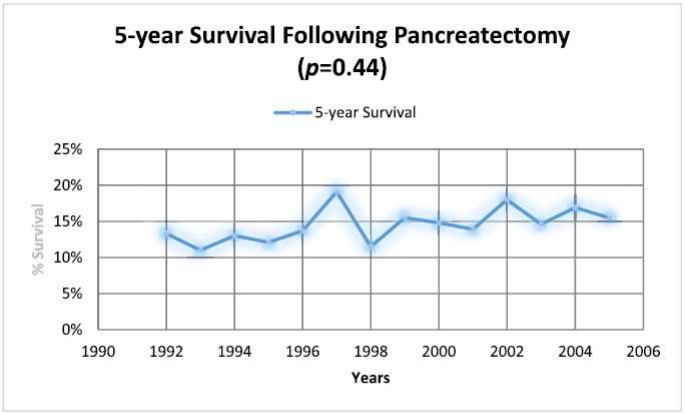


Fig. 5. Percentage of patients reaching 5-year survival following pancreatectomy for pancreatic adenocarcinoma.

The indications for TP (n=33):

- postoperative bleeding from the pseudo-aneurism of the proximal part of the AHC and leak on PEA (1 pts)
- PAC and main duct IPMN (9 pts)
- diffuse main duct IPMN (1 pts)
- very soft pancreas (10 pts) and in 5 pts vascular resection
- positive resection margins (5 pts)
- tumor extending to the body of the pancreas (5 pts)
- and formerly removed left pancreas (2 pts)

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research article

Impact factors for perioperative morbidity and mortality and repercussion of perioperative morbidity and long-term survival in pancreatic head resection

Stojan Potrc[1], Arpad Ivanecz[1], Vid Pivec, Urska Marolt[1], Sasa Rudolf[2], Bojan Iljevec[1], Tomaz Jagric[1]

[1]Department of Abdominal Surgery, Surgical Clinic, University Medical Centre Maribor, Maribor, Slovenia
[2]Department of Radiology, University Medical Centre Maribor, Maribor, Slovenia

Radiol Oncol 2018; 52(1): 54-64.

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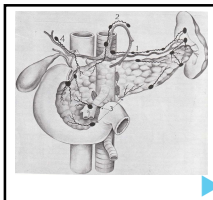
Disclosure: No potential conflicts of interest were disclosed.

VLOGA RADIOTERAPIJE PRI RAKU TREBUŠNE SLINAVKE

Izr.prof.dr.Irena Oblak, dr.med.



KARCINOM TREBUŠNE SLINAVKE

- Incidenca narašča;
- Prognoza bolnikov se zadnjih 20 let ni bistveno spremenila;
- Le slabih 5% bolnikov vključenih v raziskave;
- 15-20% bolnikov ima ob DG omejeno obliko raka, resektabilno bolezen;
- 30-40% bolnikov ima ob DG lokalno napredovalo bolezen in 40% oddaljene zasevke;
- Po OP se bolezen ponovi lokalno v 50-80%, z oddaljenimi zasevki v 75%;
- 5-letno preživetje <5% , po R0 OP 20%.

Vloga RT pri raku trebušne slinavke

- Adjuvantno zdravljenje
- Neoadjuvantno zdravljenje
- Definitivna RT pri lokalno napredovalem raku
- Ponovitev bolezni
- Paliativno zdravljenje

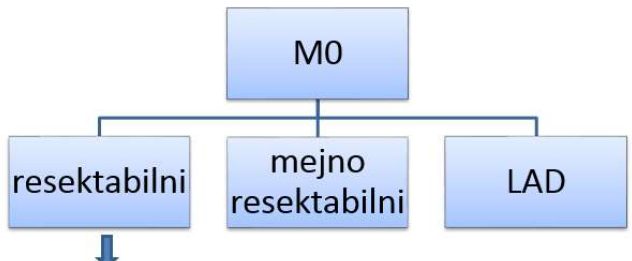
Resektabilna bolezen

- M0;
- Ne vrašča v druge organe;
- Ni vraščanja v pomembne arterije, vene;
- <50% obraščanje AMS,…

Mejno resektabila bolezen

- Opredelitev je odvisna od kirurga;
- Visoko rizični za okultne M+;
- R0?;
- Pogosto potrebne obsežne OP z vaskularnimi resekcijami in različne rekonstrukcije;
- Potreba po neoadjuvantnem zdravljenju

ALGORITEM ZDRAVLJENJA RAKA TREBUŠNE SLINAVKE BREZ ODDALJENIH ZASEVKOV (ASCO, NCCN, ESMO)-1

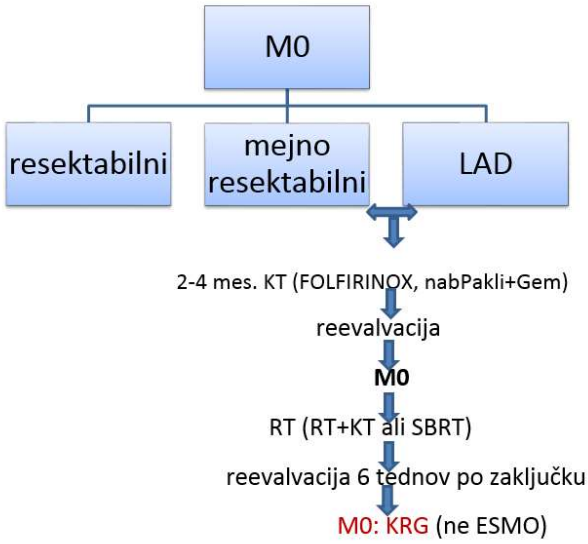


a). Neoadjuvantno TH?

b). če≥ pT1N0→ POOP TH

(KT ali RT+KT)

ALGORITEM ZDRAVLJENJA RAKA TREBUŠNE SLINAVKE BREZ ODDALJENIH ZASEVKOV (ASCO, NCCN, ESMO)-1



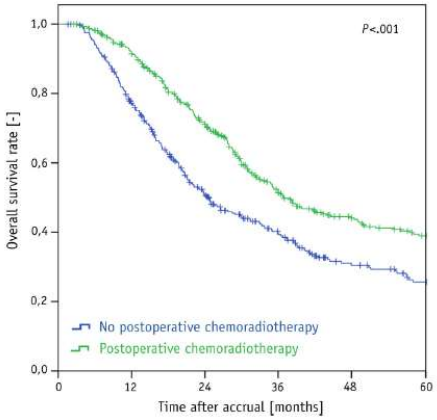
VLOGA RT V SKLOPU ADJUVANTNEGA ZDRAVLJENJA

- Kontradiktorni izsledki raziskav;
- Korist adjuvantne RT?;
- Pri izbranih bolnikih po R+ resekciji ali N+ = ↑rizični za LR

1. *Morganti AG, Falconi M, et al. Multi-institutional pooled analysis on adjuvant chemoradiation in pancreatic cancer. Int J Radiat Oncol Biol Phys 2014;*
2. *Kooby DA, Gilespie TW, et al. Impact od adjuvant radiotherapy on survival after pancreatic cancer resection: an appraisal of data from the national cancer data base. Ann Surg Oncol 2013; 20: 3634-42.*
3. *RTOG trial 0848 še teče- zaključena 2020*

Adjuvantna RT+KT

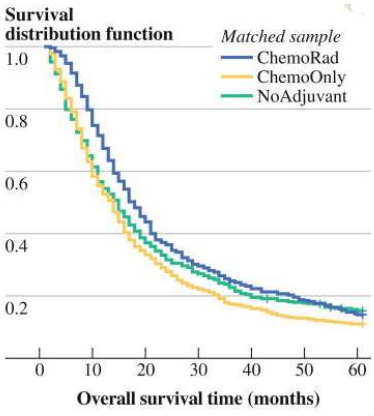
- 1995-2008: 1.120 bolnikov po OP;



Morganti AG, Falconi M, et al. Multi-institutional pooled analysis on adjuvant chemoradiation in pancreatic cancer. Int J Radiat Oncol Biol Phys 2014;

Adjuvantna RT+KT

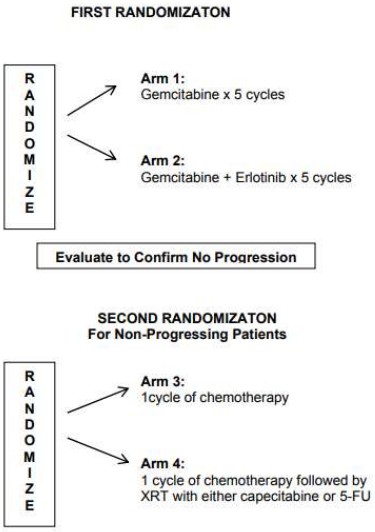
- 1982-2002: 11.526 bolnikov po OP;
- RT mora biti del adjuvantnega zdravljenja



Kooby DA, Gilespie TW, et al. Impact of adjuvant radiotherapy on survival after pancreatic cancer resection: an appraisal of data from the national cancer data base. Ann Surg Oncol 2013

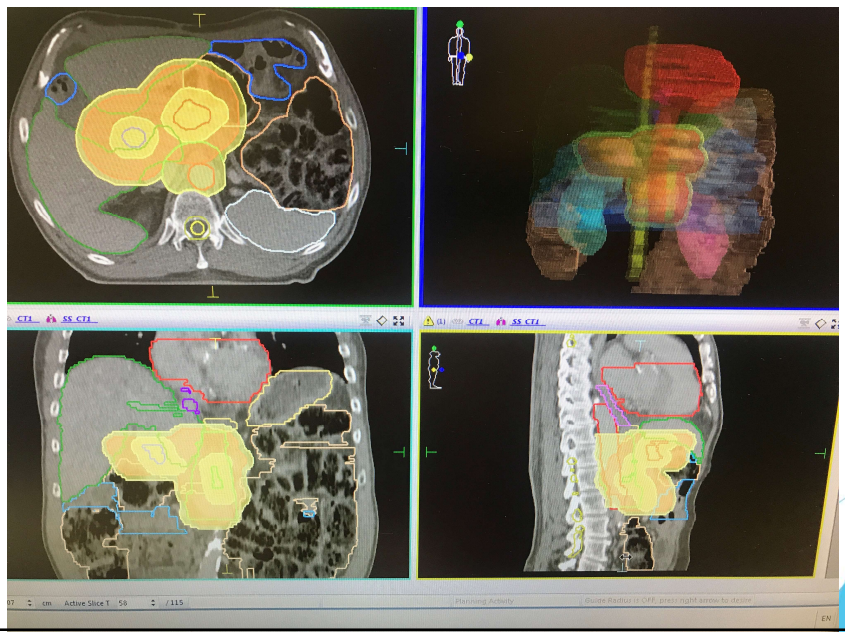
Adjuvantno zdravljenje z RT

- 1000 bolnikov po OP glave trebušne slinavke;
- Rezultati 2020



RTOG trial 0848

Primer poOP RT



Namen neoadjuvantnega zdravljenja

- ↑ selekcija bolnikov, ki jim OP ne bi koristila in nudila ↑ preživetja (hitro v progres z M+ med predOP zdravljenjem);
- ↑ R0 resekcij;
- Zgodnje TH mikro-zasevkov.

Neoadjuvantno zdravljenje

- Pred tem nujna patohistološka potrditev bolezni;
- Določitev Ca 19-9 pred TH in če povišan: na 1-3 mes. med TH
- ?dolžina, vrsta neoadjuvantnega zdravljenja;
- ? Opredeliti odgovor na predOP zdravljenje

Ocena odgovora na neoadjuvantno TH
RECIST kriteriji ne sovpadajo z odgovorom!

- Predvsem ne za RT;
- MRI?, PETCT ?

Katz MH, et al. Response of borderline resectable pancreatic cancer to neoadjuvant therapy is not reflected by radiographic indicators. Cancer 2012; 118:5749.

VLOGA RT V SKLOPU NEOADJUVANTNEGA ZDRAVLJENJA PRI MEJNO RESEKTABILNIH TU

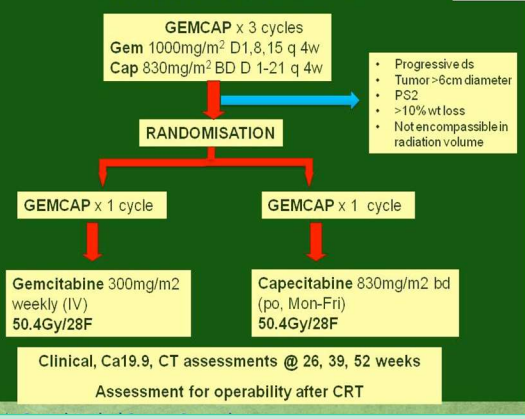
4-6 mesecev KT ⟶ RT+KT (derivati 5-FU) (Scalop trial) ali SBRT

- Poveča verjetnost R0 resekcije;
- VMAT > 3-D konformalna RT (50,4 Gy v 28 fr): boljša D distribucija, eskaliranje D, ↓ SE;
- GTV +1 cm, ABC sistem;
- SBRT 25-30 Gy v 5-6 frakcijah (↓OTT-manj prekinitve sistemske TH).

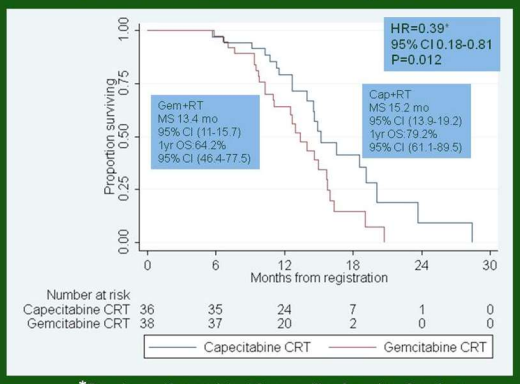
Katz MH, Crane CH, et al. Management of bordeline resektable pancreatic cancer. Semin Radiat Oncol 2014

Ob RT derivati 5-FU> Gemcitabin

SCALOP SCHEMA



K-M curve of OS by arm



*Pre-planned log-rank test for equality of survivor functions

RT s kapecitabinom ↓toksična in ↑ učinkovita

SCALOP raziskava: Mukherjee , ASCO GI 2013

VLOGA RT V SKLOPU DEFINITIVNEGA ZDRAVLJENJA PRI LOKALNO NAPREDOVALIH TU

- Ni konsenza glede optimalnega zdravljenja;
- KT+RT > KT (ne velja ob FOLFIRINOX-u);
- Odloži lokalni progres, ni ↑OS;
- Predvsem za bolnike, kjer ni možno, da postanejo OP.

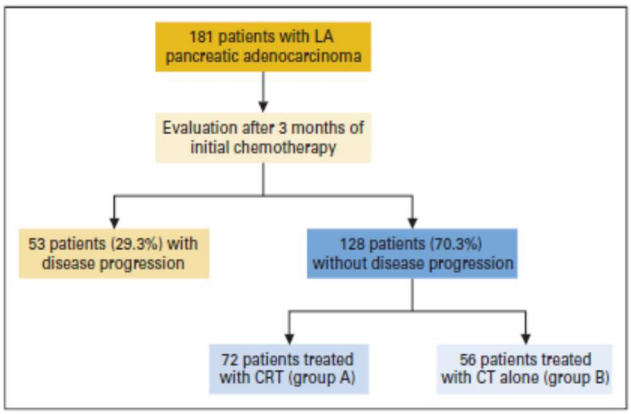
a). 4-6 mesecev KT ➡ RT+KT ali SBRT- če M0

b). Če ni kandidat za KT: RT+KT ali SBRT- če M0

1.Tempero MA, Malafa MP, et al. Pancreatic adenocarcinoma, version 2.2014: featured updates to the NCCN guidelines J Natl Compr Canc Netw. 2014;12:1083-1093.
2.LAP07 raziskava: Hammel P, Huguet F, et al. Effect of chemoradiotherapy vs chemotherapy on survival. JAMA 2016

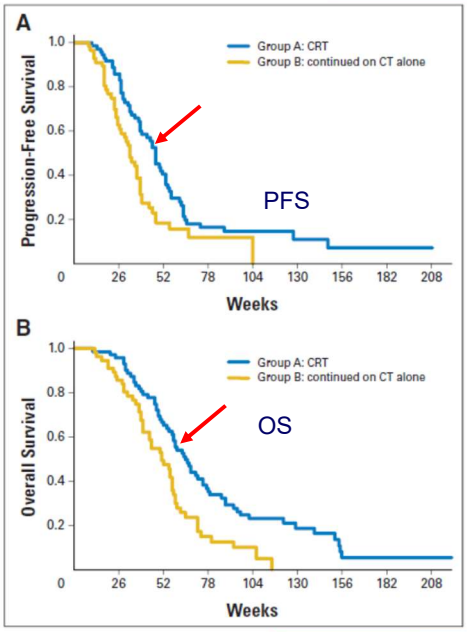
Radiokemoterapija pri lokalno napredovalem raku trebušne slinavke

Retrospektivna analiza



RT+KT bi lahko bila pomembna po uvodni KT za vsaj stabilizacijo bolezni

Huguet JCO 2007



RT pri lokalno napredovalem raku trebušne slinavke

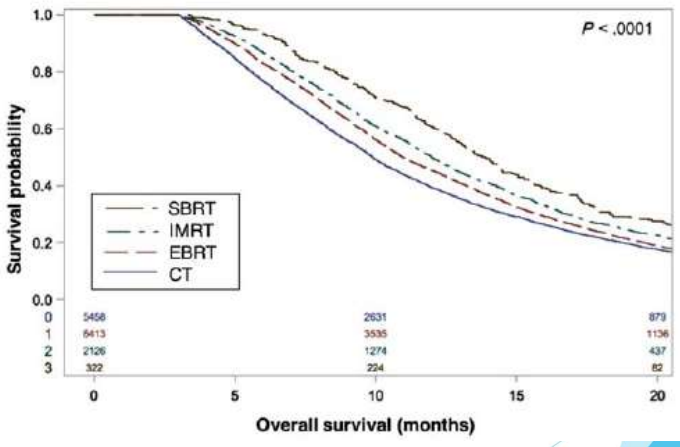
14.331 bolnikov:

a. 38 %KT,

b. 44% KT+3-D RT,

c. 15% KT+IMRT,

d. 3% KT+SBRT



De Geus SWL, Eskander MF, et al. Stereotactic Body Radiotherapy for Unresected Pancreatic Cancer: A Nationwide Review. Cancer 2017

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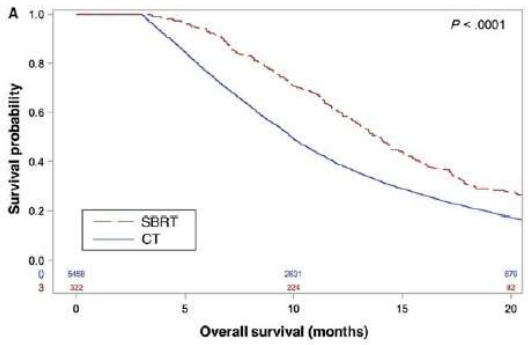

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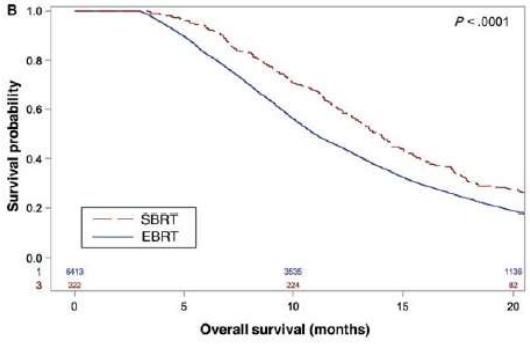

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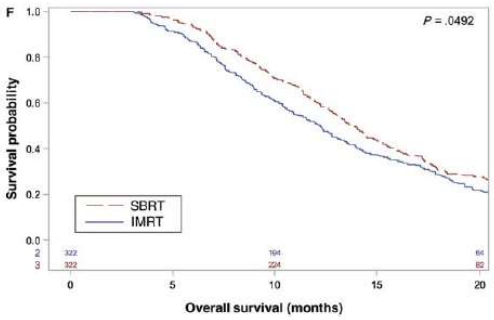

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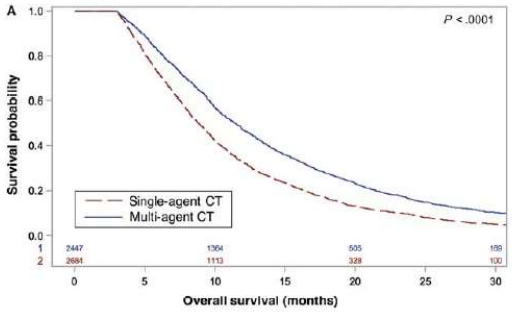


De Geus SWL, Eskander MF, et al. Stereotactic Body Radiotherapy for Unresected Pancreatic Cancer: A Nationwide Review. Cancer 2017

VLOGA RT V SKLOPU ZDRAVLJENJA LOKALNE PONOVITVE BOLEZNI ALI V SKLOPU „SECOND LINE“ ZDRAVLJENJA

a). RT+/- KT

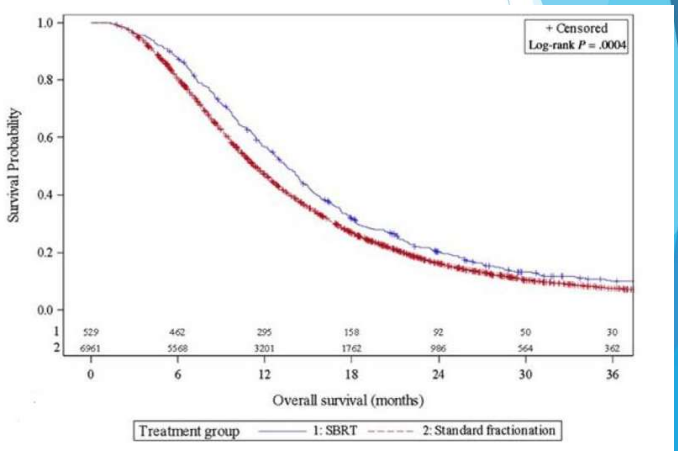
b). SBRT

VLOGA RT V SKLOPU PALIATIVNEGA ZDRAVLJENJA

- Protibolečinsko
- Hemostiptično
- Zmanjšanje obstrukcije,…

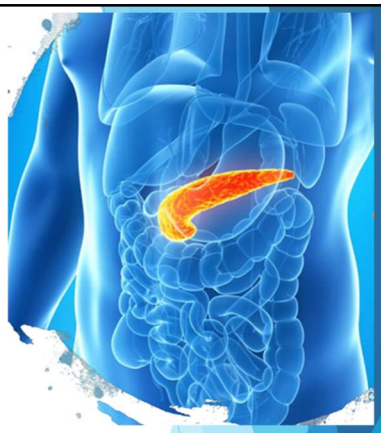
SBRT

- SBRT>konvencionalno RT: ↑mediano S in OS_2 (21.7% vs 16.5%)



Zhong J, Patel K, *et al*. **Outcomes for Patients With Locally Advanced Pancreatic Adenocarcinoma Treated With Stereotactic Body Radiation Therapy Versus Conventionally Fractionated Radiation** *2017*

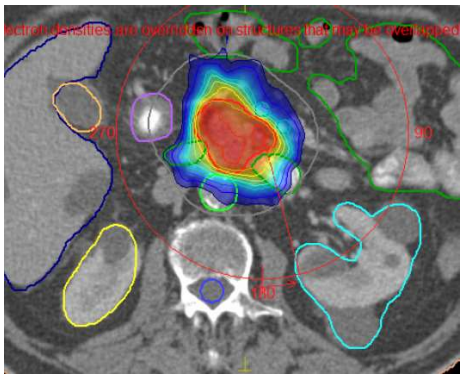
SBRT

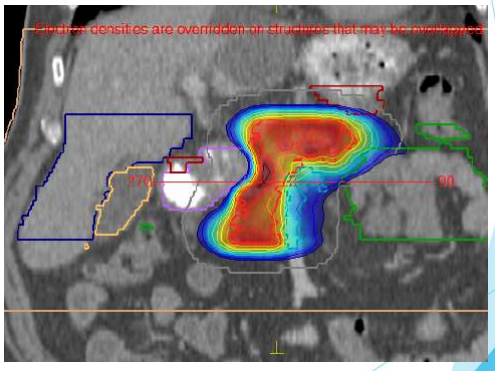


Indikacije:

- Patohistološka verifikacija;
- Velikost lezije <5 cm;
- M0;
- PS 0-2 po WHO
- >2 mm stran od želodca ali dvanajstnika;
- V okviru neoadjuvantnega zdravljenja (KT);

Primer bolnika





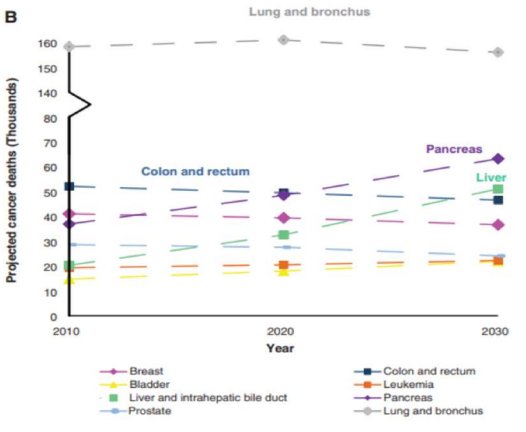
Atene, november 2018

VLOGA SISTEMSKE TERAPIJE PRI NAPREDOVALEM KARCINOMU TREBUŠNE SLINAVKE

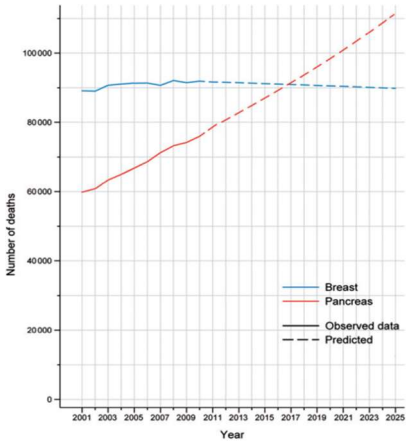
asist. mag. Zvezdana Hlebanja, dr.med.
specialistka internistične onkologije

RAK TREBUŠNE SLINAVKE

- Zahrbten, pozno odkrit, hitro potekajoč, smrten



Rahib L, et al. *Cancer Res.* 2014;74(11):2913-2921.



Ferlay J, et al. *Acta Oncol.* 2016;55(9-10):1158-1160.

PANCREATIC CANCER AWARENESS

ZAHRBTEN, POZNO ODKRIT, HITRO POTEKAJOČ, SMRTEN…








PANCREATIC CANCER AWARENESS

RAK TREBUŠNE SLINAVKE

- V Sloveniji zboli cca 400 bolnikov letno (žensk več kot moških)
- Zdravljenje zahteva multidisciplinarni pristop
- Edino kurativno zdravljenje je kirurško (15-20 %)
- 5-letno preživetje manj kot 10 %
- Večinoma je zdravljenje paliativno (54 % bolnikov odkritih v napredovalem stadiju - 5-letno preživetje <2 %)
- Za določitev stadija bolezni CT prsnega koša in trebuha
- Pred uvedbo zdravljenja določitev tumorskega markerja CA19-9
- Histološka verifikacija (ni vedno potrebna)

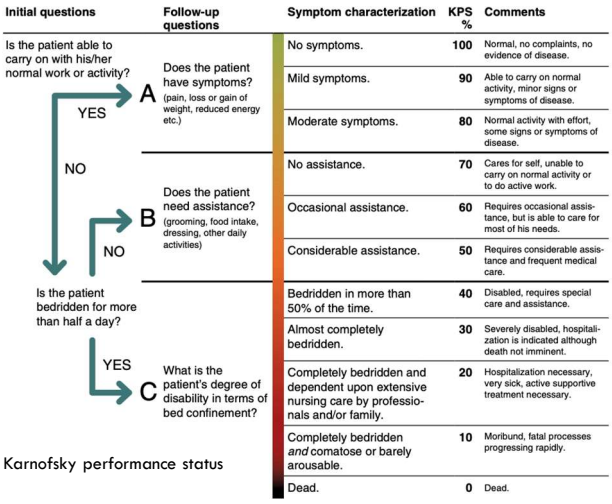
PANCREATIC CANCER AWARENESS

SISTEMSKO ZDRAVLJENJE NAPREDOVALEGA RAKA TREBUŠNE SLINAVKE

- 15-20 % operabilnih
- Ostali lokalno napredovali ali metastatski
- mOS 8-12 mesecev za lokalno napredovale in samo 3-6 mesecev za metastatske
- Vrsto citostatskega zdravljenja določajo:
  - PS bolnika
  - Genske značilnosti
  - Molekularne značilnosti
  - Pridružene bolezni
  - Bolnikove preference
  - Predhodni načini zdravljenja

PANCREATIC CANCER AWARENESS

STANJE ZMOGLJIVOSTI BOLNIKA



Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Péus et al. BMC Medical Informatics and Decision Making 2013

PANCREATIC CANCER AWARENESS

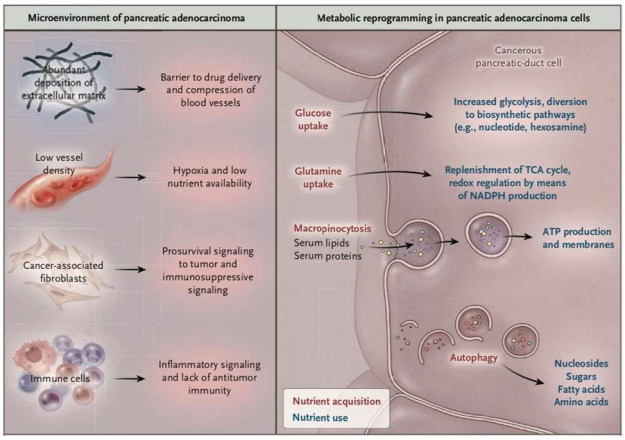
SISTEMSKO ZDRAVLJENJE NAPREDOVALEGA RAKA TREBUŠNE SLINAVKE

- Nobena kemoterapija ne ozdravi metastatskega raka trebušne slinavke
- Njen namen je olajšati simptome bolezni, upočasniti napredovanje bolezni in podaljšati preživetje
- Pred odločitvijo o vrsti kemoterapije 1. reda najnovejša priporočila svetujejo gensko in molekularno testiranje za vse metastatske bolnike

PANCREATIC CANCER AWARENESS

GENETSKE SPREMEMBE IN POTENCIALNI BIOMARKERJI ZA RAK TREBUŠNE SLINAVKE

- **BRCA 1,2, PALB 2**
- KRAS - Na mutacije KRAS vplivajo **vnetni signali** (morda povezani s prehrano z veliko maščobami)
- **Mikrookolje tumorja** (fibroblasti, povezani s stromo/rakom)
- Mismatch repair deficiency (**Lynch syndrome**) napoveduje učinkovitost imunoterapije
- **Neraziskani/nepoznani biomarkerji za rak trebušne slinavke**

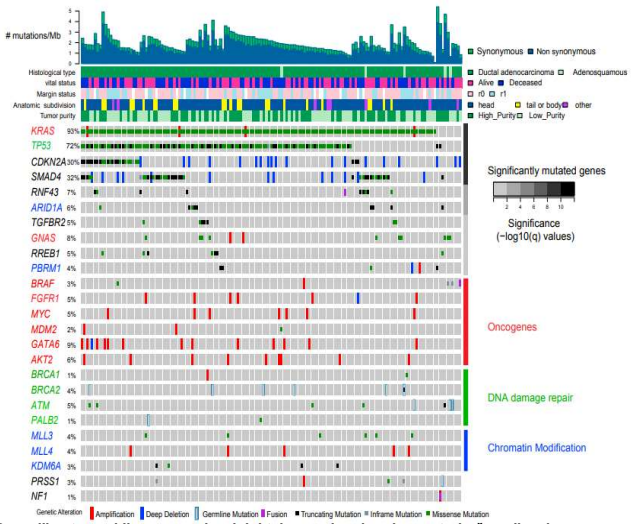


Ryan et al., N Engl J Med 2014; Jones et al., Science 2008; Philip et al., Gastroenterology 2013; Puleo et al., Gastroenterology 2018; Le et al., N Engl J Med 2015; Lee et al., Cancer Discov 2017.

POGOSTE MUTACIJE PRI RAKU TREBUŠNE SLINAVKE

- Rak trebušne slinavke je rezultat **velikega števila genskih mutacij**
- Genske mutacije se združujejo **na omejenem številu poti in procesov**
- Sestavni deli poti, ki so se v posameznem tumorju spremenili, se zelo razlikujejo

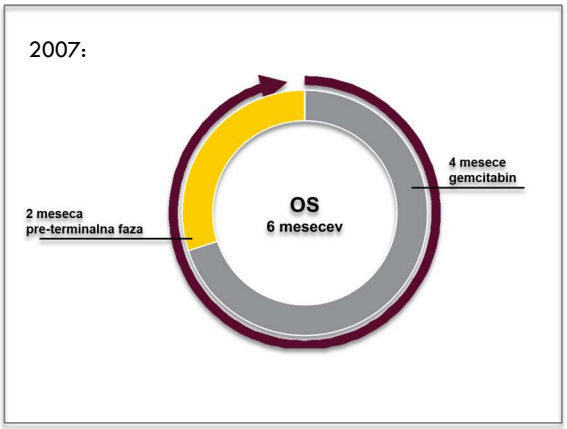
- Odkrivanje učinkovin, ki delujejo na spremenjene poti in procese, lahko ponudi ključna prijemališča za zdravljenje

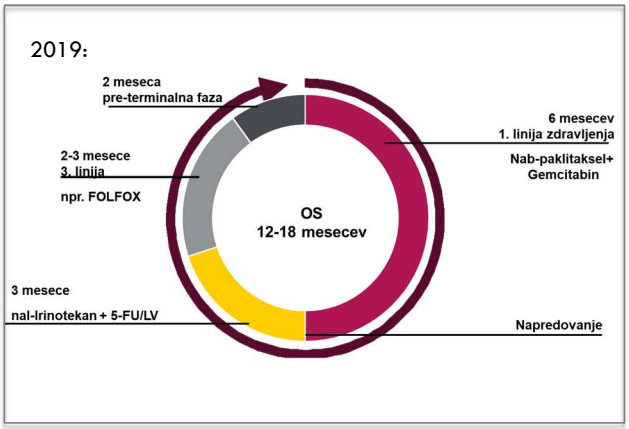


Raznolikost genskih sprememb pri duktalnem adenokarcinomu trebušne slinavke

Cancer Genome Atlas Research Network. Cancer Cell 2017; 32:185-203.

PA VENDARLE SE PREMIKA …





PA VENDARLE SE PREMIKA …

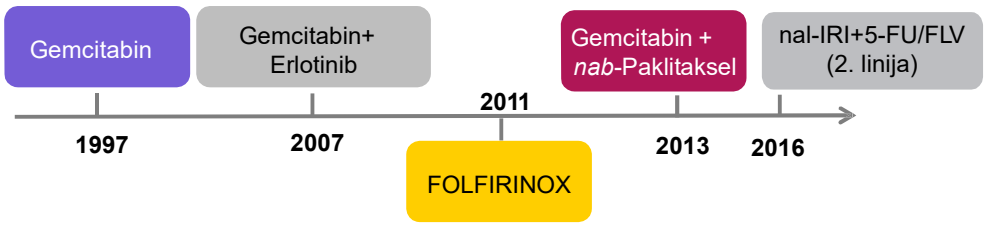
❖ Prvič v desetletjih se vendarle kaže trend izboljšave preživetja, najverjetneje na račun:

- Ozaveščenosti o bolezni
- Napredka v diagnostiki
- Napredka v načinih adjuvantnega zdravljenja
- Napredka v izbiri pravih kandidatov za pravo zdravljenje glede na PS
- Napredka v genskem in molekularnem testiranju
- Zgodnjega vključevanja v paliativno oskrbo

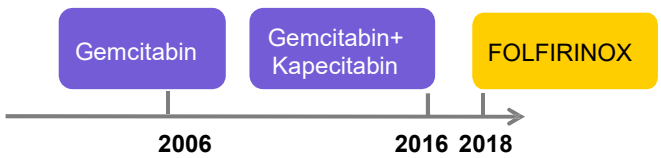
PANCREATIC CANCER AWARENESS

MOŽNOSTI ZDRAVLJENJA RAKA TREBUŠNE SLINAVKE V LETU 2019

Paliativno zdravljenje

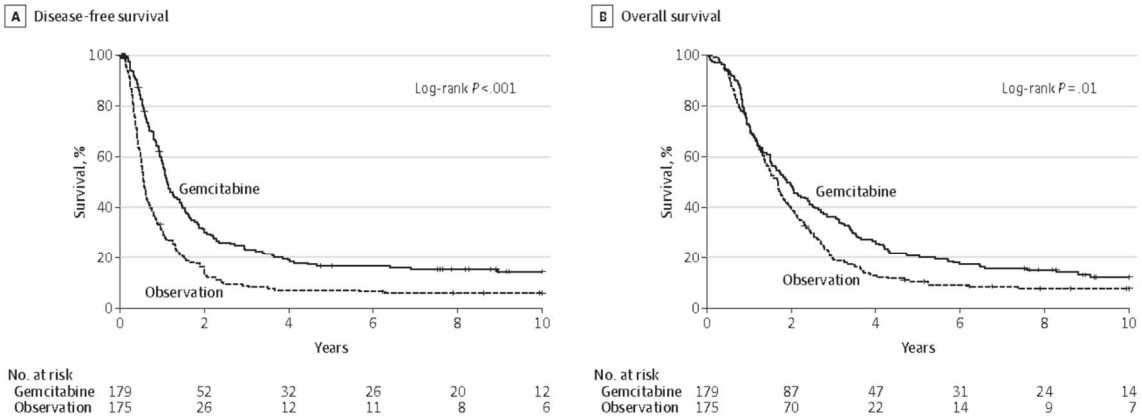


Adjuvantno zdravljenje



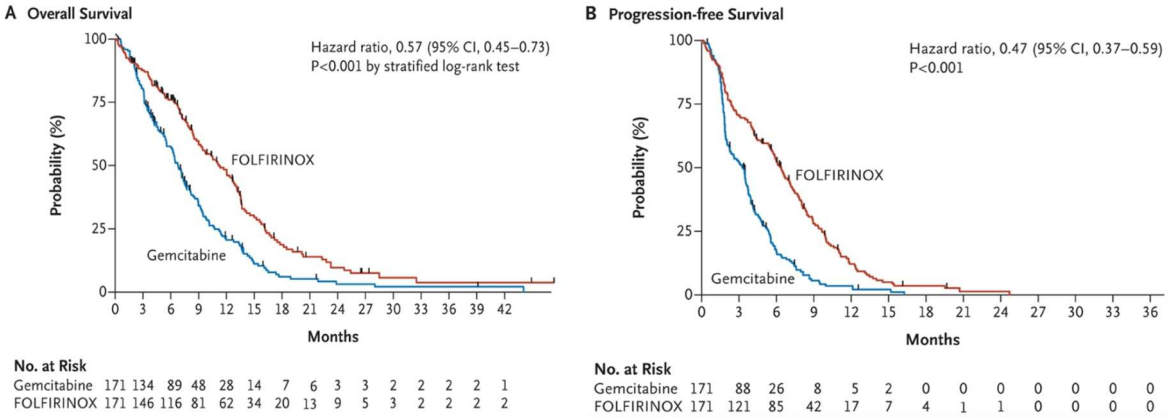
PANCREATIC CANCER AWARENESS

CONKO - 001

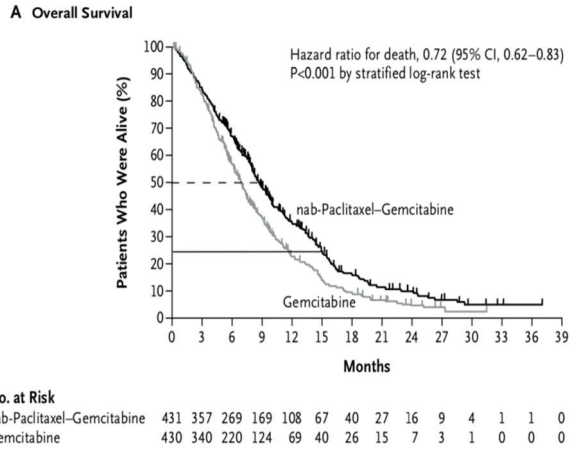


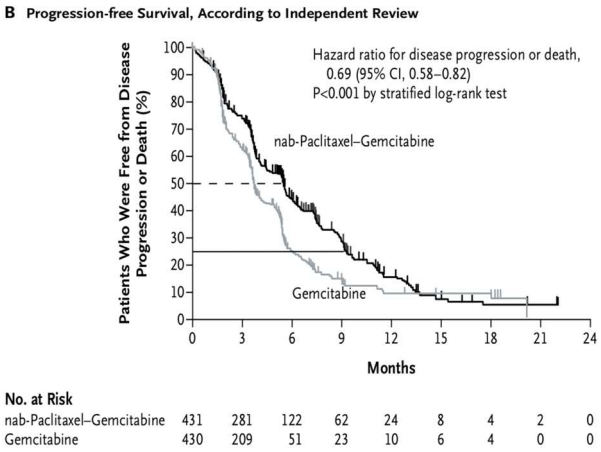
A, Median disease-free survival was 13.4 months (95% CI, 11.6-15.3 months) in the gemcitabine group compared with 6.7 months (95% CI, 6.0-7.5 months) in the observation group (hazard ratio, 0.55 [95% CI, 0.44-0.69]). B, Median group compared with 20.2 months (95% CI, 17.7-22.8 months) in the observation group (hazard ratio, 0.76 [95% CI, 0.61-0.95]). Vertical lines on curves indicate patients censored on the date of their last follow-up.

ACCORD 11



ŠTUDIJA MPACT





ZDRAVLJENJE METASTATSKE BOLEZNI – I. LINIJA

- Ločimo zmogljive od nezmogljivih bolnikov
- Opravimo gensko testiranje in molekularni profil
- Gensko testiranje – odkrije cca 17 % mutacij, več kot polovica le-teh v genih, ki sodelujejo v popravilu DNA (zato derivati platine!)
- Molekularno testiranje – odkriva napake v MMR mehanizmih (1 %) in MSI status – ti bolniki so kandidati za zdravljenje z imunoterapijo po I.-linijskem zdravljenju
- Poleg tega molekularno testiranje lahko odkrije glavno driver mutacijo KRAS in druge mutacije npr. TRK – kandidati za larotrektinib

PANCREATIC CANCER AWARENESS

ZDRAVLJENJE METASTATSKE BOLEZNI – I. LINIJA NOSILCI GENSKIH MUTACIJ

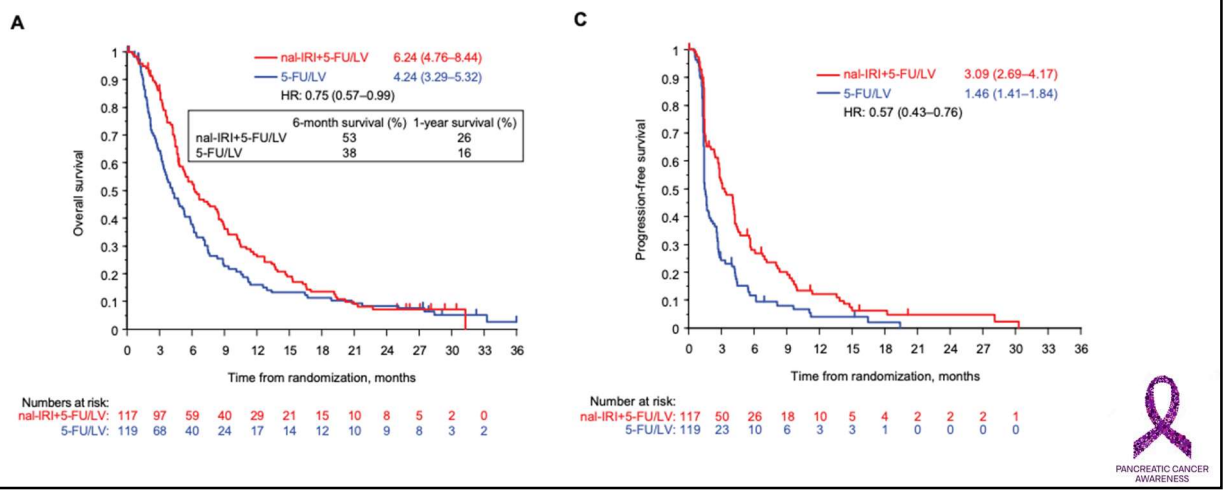
- ❖ Gensko testiranje – noslici BRCA 1,2 ali PALB 2
- ❖ Kemoterapevtski protokoli, ki vsebujejo derivate platine:
- PS 0-1: FOLFIRINOX ali mFOLFIRINOX
- PS > 1: FOLFOX/XELOX ali GEM/CIS (16 tednov), nato vzdrževalno zdravljenje s PARP inhibitorjem (olaparib)

ZDRAVLJENJE METASTATSKE BOLEZNI – I. LINIJA GLEDE NA ZMOGLJIVOST

Brez dokazanih/znanih genskih mutacij (duktalni adenokarcinomi)

- **PS 0-1** (brez komorbidnosti, normalne vrednosti bilirubina – manj kot 1,5 x ULN):
  - FOLFIRINOX ali mFOLFIRINOX
  - Gemcitabin/nab-paklitaksel (manj toksičen, približno enako učinkovit)
  - Za bolnike z bilirubinom >1,5 x ULN - FOLFOX
- **PS > 1** (zmerna komorbidnost, bilirubin manj kot 1,5 x ULN) – gemcitabin mono, lahko GEMCAP, S1, kapecitabin
- **PS 2** (zelo selekcionirani bolniki, visoko tumorsko breme): GEM + nab-pakli
- acinarno-celični karcinom – kemoterapija z derivati platine
- **PS ≥ 3**: podporno zdravljenje

ZDRAVLJENJE METASTATSKE BOLEZNI - II. LINIJA NAPOLI - 1



PANCREATIC CANCER AWARENESS

ZDRAVLJENJE METASTATSKE BOLEZNI – II. LINIJA

- Odločitev o kemoterapiji 2. reda je individualizirana
- Optimalen režim ni dorečen (PS, predhodno zdravljenje)
- BRCA 1,2 + PALB 2 mutirani – GEM/CIS + PARP inhibitorji. Če so tovrstno zdravljenje že dobili v I. liniji ali refraktorni na FOLFIRINOX ali mFOLFOX v I. liniji, naj za II. linijo prejmejo nab-Pakli GEM (PS 0-1), sicer (PS > 1): GEM mono ali GEMCAP ali fluoropirimidini mono
- Če so bili v I. liniji zaradi zvišanega bilirubina zdravljeni s kemoterapijo po shemi FOLFOX, naj v II. liniji prejmejo sheme z liposomskim irinotekanom ali GEM mono ali CAP mono

PANCREATIC CANCER AWARENESS

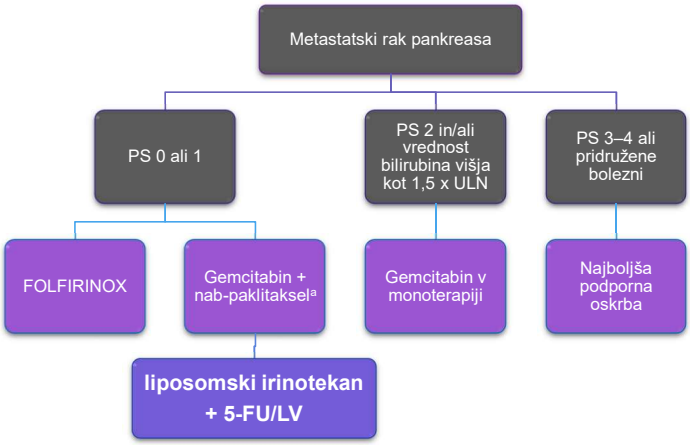
ZDRAVLJENJE METASTATSKE BOLEZNI – II. LINIJA

- Za bolnike, ki so v I. liniji prejeli KT na osnovi GEM in so v PS 0-1, v II. liniji priporočamo 5-FU + oxaliplatin ali 5-FU + liposomski irinotekan
- Za bolnike v slabšem PS, ki so v I. liniji prejeli KT na osnovi GEM, v II. liniji priporočamo monoterapijo s fluoropirimidini (CAP, S1)
- Za bolnike v izrazito slabem PS: podporno simptomatsko zdravljenje
- Za redke bolnike z MSI-H: v 2. liniji imunoterapija

- Za bolnike, ki so v I. liniji prejeli KT na osnovo 5-FU (FOLFIRINOX, mFOLFIRINOX, FOLFOX …), v II.-linij priporočamo KT na osnovi GEM

PANCREATIC CANCER AWARENESS

2015 ESMO SMERNICE ZA ZDRAVLJENJE BOLNIKOV Z METASTATSKIM RAKOM PANKREASA

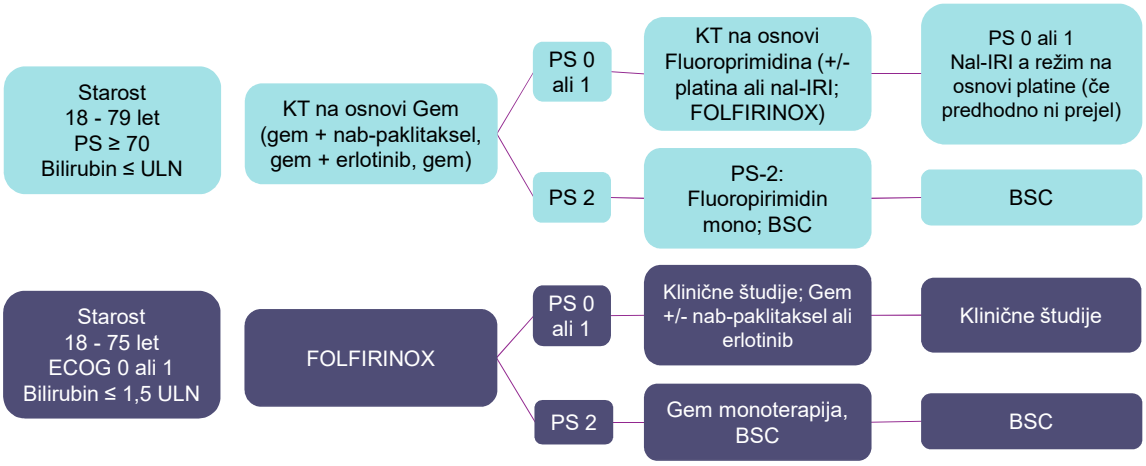


[a] Pri zelo izbranih bolnikih s stanjem zmogljivosti 2 po ECOG lahko zaradi velikega tumorskega bremena gemcitabin in nab-paklitaksel predstavljata najboljšo možnost odziva.

1. Ducreux M, et al. Ann Oncol 2015; 26 Suppl 5:v56-68; 2. E-update, June 2017: http://www.esmo.org/Guidelines/Gastrointestinal-Cancers/Cancer-of-the-Pancreas/eUpdate-Treatment-Recommendations.

PANCREATIC CANCER AWARENESS

METASTATSKI RAK TREBUŠNE SLINAVKE: ZAPOREDNO ZDRAVLJENJE – III. LINIJA



World Congress on GI Cancer 2019: Challenging the experts in advanced pancreatic cancer, what can we do faster and better? Medscape Oncology

NCCN SMERNICE: I. LINIJA ZDRAVLJENJA BOLNIKOV Z METASTATSKIM RAKOM TREBUŠNE SLINAVKE

	Prednostni režimi	Drugi priporočeni režimi
Dobro stanje zmogljivosti	• FOLFIRINOX (kategorija 1)/mFOLFORINOX • Gemcitabin + nab-paklitaksel(kategorija 1) Samo za znane BRCA1/2 ali PALB2 mutacije: • FOLFIRINOX (kategorija 1) /mFOLFORINOX • Gemcitabin + cisplatin	• Gemcitabin + erlotinib (kategorija 1) • Gemcitabin (kategorija 1) • Gemcitabin + kapecitabin • FDR gemcitabin, docetaksel, kapecitabin (GTX režim) (kategorija 2B) • Fluoropirimidini + oksaliplatin (kategorija 2B) (OFF ali CapeOX)

Slabo stanje zmogljivosti	• Gemcitabin
	  • 1000 mg/m2 30 min infuzija tedensko 3 tedne vsakih 28 dni (kategorija 1)
	  • FDR gemcitabine (10mg/m^2/min) namesto standardne infuzije (kategorija 2B)
	• Kapecitabin (kategorija B2)
	• Kontinuirana infuzija 5-FU (kategorija B2)
		• Ni priporočil

Bolniki z metastatsko boleznijo niso kandidati za obsevanje, razen če je to potrebno v paliativne namene

NCCN Guidelines Pancreatic Adenocarcinoma Version 3.2019
FDR gemcitabin: fixed-dose-rate gemcitabine (10 mg/m^2/min); OFF: 5-FU/LV/oksaliplatin

NCCN SMERNICE: II. LINIJA ZDRAVLJENJA BOLNIKOV Z METASTATSKIM RAKOM TREBUŠNE SLINAVKE

	Prednostni režimi	Drugi priporočeni režimi		Uporabni v določenih okoliščinah

Dobro stanje zmogljivosti	Ni priporočil	***Predhodno zdravljenje z gemcitabinom***
		• **Liposomski irinotekan + 5-FU + LV (kategorija 1 za metastatsko bolezen)**
		• 5-FU + LV + irinotekan (FOLFIRI)
		• FOLFIRINOX/mFOLFIRINOX
		• Oksaliplatin/5-FU/LV (OFF)
		• FOLFOX
		• Kapecitabin/oksaliplatin
		• Kapecitabin
		• Kontinuirana infuzija 5-FU
			Predhodno zdravljenje s fluoropirimidini
			• Gemcitabin
			• Gemcitabin + nab-paklitaksel
			• Gemcitabin + cisplatin (za znane BRCA1/2 ali PALB2 mutacije)
			• Gemcitabin + erlotinib
			• **Liposomski irinotekan + 5-FU + LV (brez predhodnega irinotekana)**
				• Pembrolizumab (za MSI-H ali dMMR tumorje)
				• Larotrektinib (pozitiven NTRK fuzijski gen)
				• Obsevanje s kemoterapijo, če ni bilo predhodno uporabljeno za:
				  • Lokalno napredovalo bolezen, če je primarno mesto edino mesto napredovanja
				  • Izbira bolnikov s ponovljeno boleznijo v kombinaciji s sistemskim zdravljenjem

Slabo stanje zmogljivosti	Ni priporočil	• Gemcitabin
		  • 1000 mg/m2 30 min infuzija tedensko 3 tedne vsakih 28 dni (kategorija 1)
		  • FDR gemcitabine (10mg/m^2/min) namesto standardne infuzije (kategorija 2B)
		• Kapecitabin (kategorija 2B)
		• Kontinuirana infuzija 5-FU (kategorija 2B)
				Ni priporočil

NCCN Guidelines Pancreatic Adenocarcinoma Version 3.2019
FDR gemcitabin: fixed-dose-rate gemcitabine (10 mg/m^2/min); OFF: 5-FU/LV/oksaliplatin; dMMR: mismatch repair deficient; MSI-H: microsatellite instability.

VLOGA PODPORNEGA ZDRAVLJENJA

- Rak trebušne slinavke je karcinom, ki bolnikom povzroča hude subjektivne težave
- V ospredju zdravljenja naj bo agresivno lajšanje bolečine, poskrbeti je treba za čim počasnejšo izgubo telesne teže (preprečevati anoreksijo), ustrezno naj se zdravi bolnikova anksioznost in depresija.
- V primeru biliarne obstrukcije poskus vstavitve stentov ali zunanje biliarne drenaže
- Ob zapori pasaže na nivoju dvanajstnika, razmislek o kirurški intervenciji (by pass) ali vstavitev stentov
- Trombembolični zapleti – še pogostejši kot pri drugih malignomih – možnost preventivne uvedbe tromboprofilakse
- Bolniki in svojci morajo razumeti, da je specifično zdravljenje s KT paliativno in ne kurativno

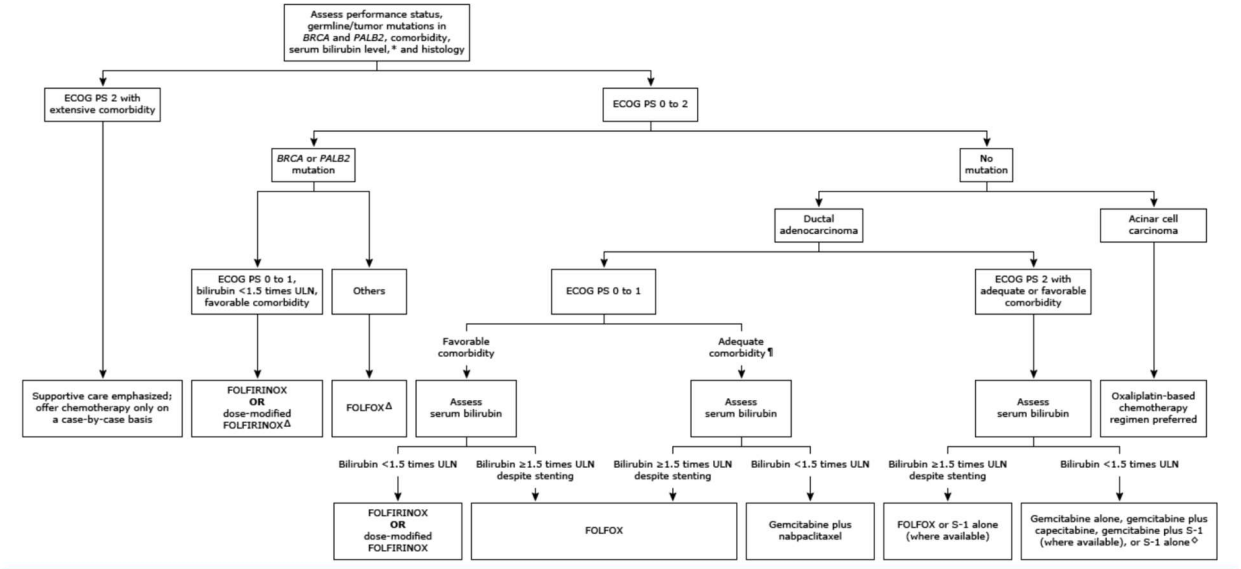
PANCREATIC CANCER AWARENESS

ZAKLJUČKI

- Rak trebušne slinavke je rak z najnižjim 5-letnim preživetjem (8 %)
- Edina možnost ozdravitve je resekcija, za katero je primernih slabih 20 % bolnikov (mOS nezdravljenih, lokalno napredovalih je 8-12 mesecev, mOS nezdravljenih metastatskih bolnikov je 3-6 mesecev)
- Najboljše rezultate preživetja je doseglo zdravljenje po shemi FOLFIRINOX (mOS = 11,1 meseca)
- Preživetja se še podaljšujejo, če bolnikov PS dopušča nadaljevanje zdravljenja z 2. linijo KT
- Zdravljenje s KT tem bolnikom zagotavlja predvsem izbojšano kvaliteto življenja, saj zmanjšuje s tumorjem povezane znake bolezni
- Ključnega pomena je, da bolnike s tovrstnim malignomom takoj vključimo v program podpornega simptomatskega zdravljenja

PANCREATIC CANCER AWARENESS

First-line systemic chemotherapy for metastatic pancreatic adenocarcinoma

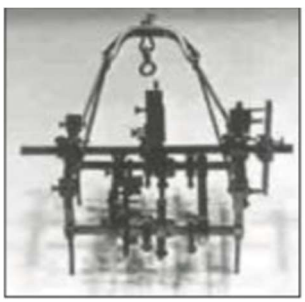


Vloga SBRT pri karcinomu trebušne slinavke s prikazom primera

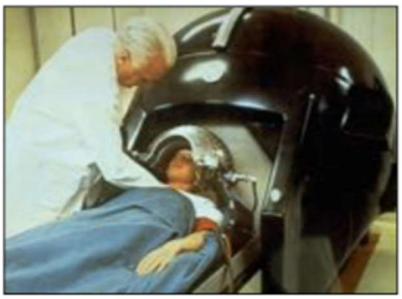
AJRA ŠEČEROV ERMENC

Stereotaktično obsevanje????

- Stereos = rigiden, fiksen
- Taxis = predpis



1908



1950

2019???

Potrebna ustrezna strojna in programska oprema

Usposobljen kader

Predoperativno obsevanje karcinoma pankreasa

Gy = J/kg

1,8 Gy – tumor

TD 45 Gy

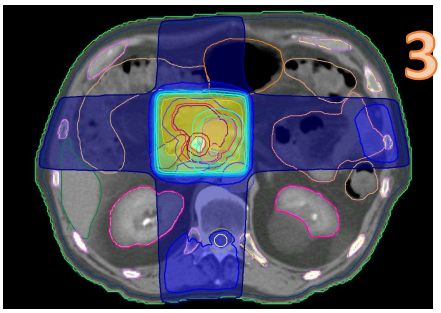
BED 53.1 Gy

Stereotaktično obsevanje karcinoma pakreasa

7 – 10 Gy - tumor

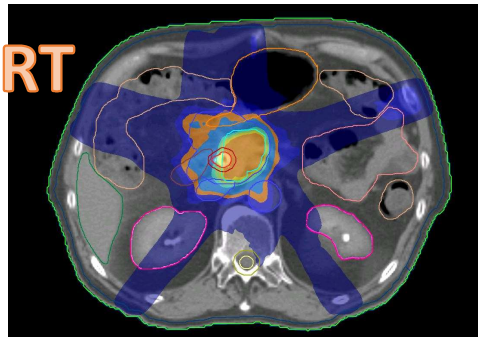
TD 35 – 50 Gy

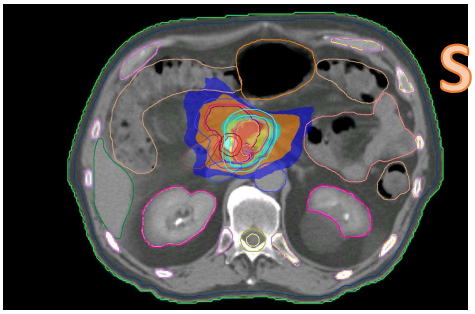
BED 59.5 - 100 Gy



3D

IMRT





SBRT

SBRT in karcinom pankreasa?

Practical Radiation Oncology (2019) 9, 322-332

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ASTRO Guideline

Radiation Therapy for Pancreatic Cancer: Executive Summary of an ASTRO Clinical Practice Guideline

Manisha Palta MD [a,*], Devon Godfrey PhD [a], Karyn A. Goodman MD [b], Sarah Hoffe MD [c], Laura A. Dawson MD [d,e], David Dessert [f], William A. Hall MD [g], Joseph M. Herman MD, MS [h], Alok A. Khorana MD [i], Nipun Merchant MD [j], Arti Parekh MD [k], Caroline Patton MA [l], Joseph M. Pepek MD [m], Joseph K. Salama MD [a,n], Richard Tuli MD, PhD [o], Albert C. Koong MD, PhD [h]

Table 4 Recommendations for sequencing of chemotherapy and RT in patients receiving RT

KQ 3 recommendations	Strength of recommendation	Quality of evidence	Consensus
1. For patients with resected pancreatic cancer receiving adjuvant therapy, delivery of chemoradiation following 4-6 months of systemic chemotherapy is recommended.	**Strong**	**Moderate**	**92%***
2. For patients with borderline resectable pancreatic cancer receiving neoadjuvant therapy, delivery of RT following 2-6 months of systemic chemotherapy is recommended.	**Strong**	**Moderate**	**92%***
3. For patients with unresectable or locally advanced pancreatic cancer without systemic progressionfollowing 4-6+ months of chemotherapy, definitive RT is recommended.	**Strong**	**Moderate**	**85%***

Abbreviations: KQ = key question; RT = radiation therapy.
* The medical physics representative abstained from rating these recommendations.

Večja populacijska raziskava – 14 000 bolnikov s karcinomom pankreasa

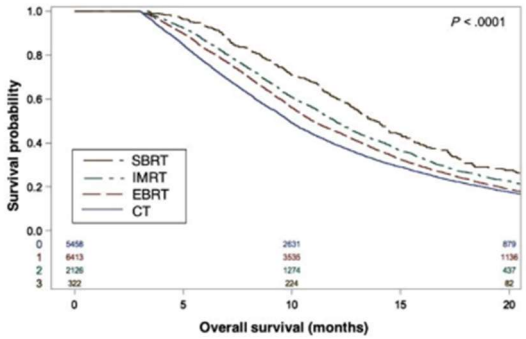
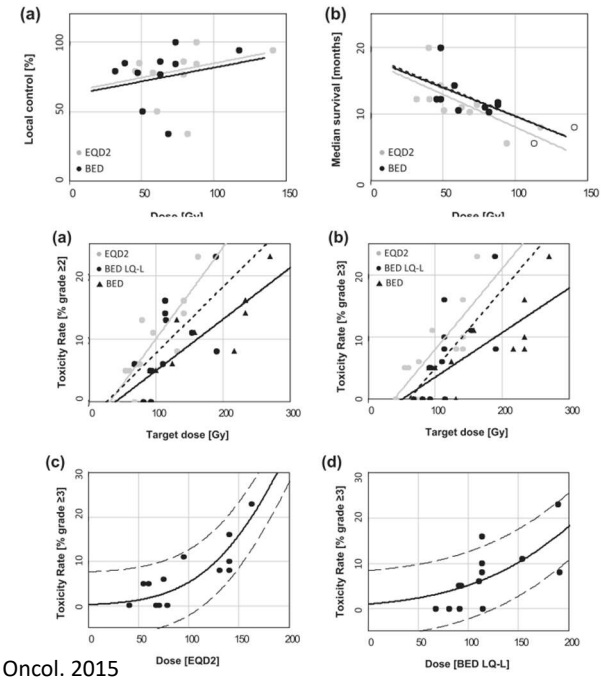


Figure 1. Kaplan-Meier curves of overall survival for patients with unresected pancreatic adenocarcinoma treated with CT alone, EBRT, SBRT, or IMRT. CT indicates chemotherapy; EBRT, external-beam radiotherapy; IMRT, intensity-modulated radiation therapy; SBRT, stereotactic body radiotherapy.

↑ preživetje s SBRT

De Geus et al., Cancer. 2017

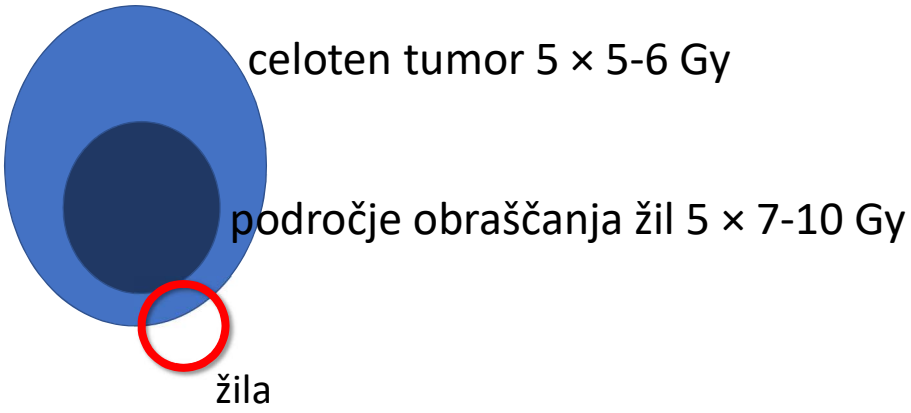


BED
75Gy

5 frakcij

Cevasti organi!!!!

Brunner et al., Radiother Oncol. 2015



Chuong et al., IJROBP. 2013

Inoperabilni lokalno napredovali in mejno resektabilni karcinom pankreasa

- 56.1% mejno resektabilnih tumorjev operiranih, 96.9 % od teh R0 resekcija
- Srednje preživetje bolnikov z mejno resektabilnim tu. 16,4 mesecev v primerjavi z lokalno napredovalim 15 mesecev
- Nič G3 akutna toksičnost, 5.3% G3 pozna toksičnost

Chuong et al., IJROBP. 2013

1-letna LC 81%

Primerni bolniki za SBRT karcinoma pankreasa

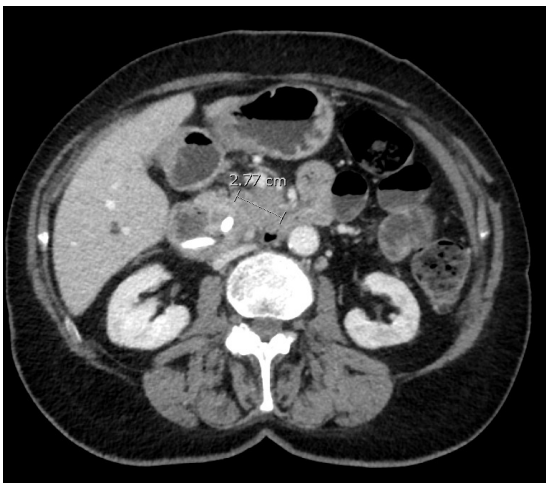
- Histološko/citološko verificiran karcinom pankreasa.
- Karcinom pankreasa brez oddaljenih metastaz (mejno ali neoperabilen tumor ali recidiv).
- Tumor manjši kot 5 cm.
- PS 0 ali 1.
- Tumor oddaljen > 2mm od želodca, dvanajstnika ali drugih cevastih organov.

To je v teoriji, kaj pa praksa…

Bolnica, letnik 1946

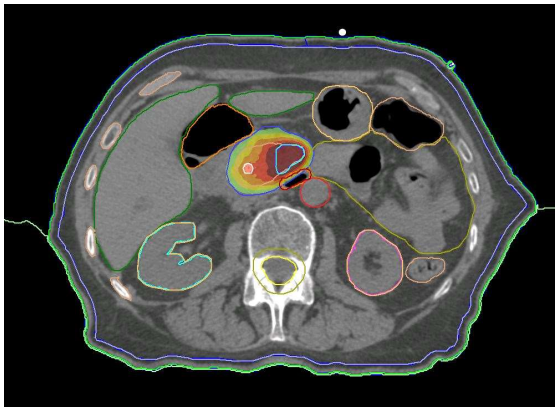
- 2013 Ca dojke, po OP pT1pN0M0, adjuvantno RT in HT- v remisiji
- Avg. 2018 adenokarcinom glave pankreasa
- Med poskusom vstavitve ERCP in stenta pride do manjše perforacije
- Mejno resektabilen (kontakt AMS manj kot 180^{o})
- 1. ciklus KT: FOLFIRINOX - hudi neželjeni učinki
- V tujino po drugo mnenje glede OP in SBRT

Drugo mnenje



- Ob pregledu v tujini visok marker
- Ponovni CT – november 2018 – progres - lokalno napredovali karcinom, brez metastaz
- Laparoskopija izključi karcinozo
- Predlagajo SBRT, sicer zadržani zaradi bližine divertikla duodenuma

SBRT načrt obsevanja



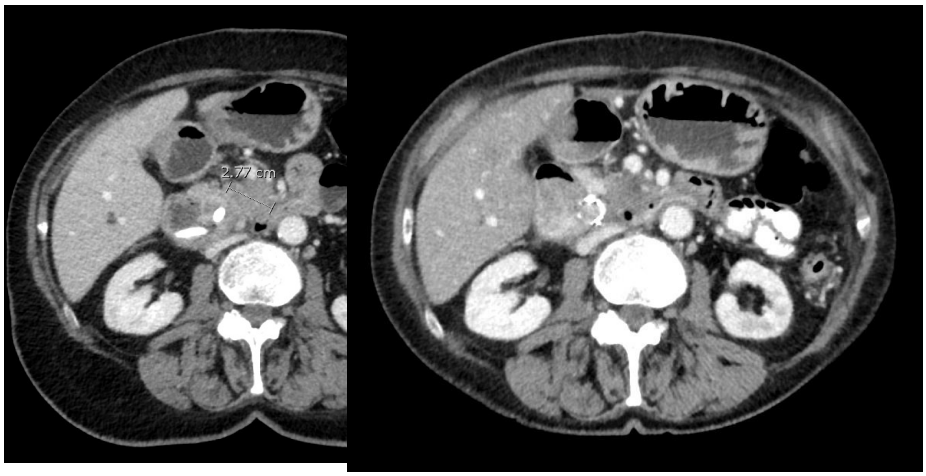
- Februar 2019 obsevanje s SBRT tehniko na OI
- 5 frakcij z dozo 6 Gy na področje obraščanje žilja
- Brez toksičnh sopojavov

Skupina	Preiskava	09.09.19	27.06.19	27.05.19	20.02.19	12.02.19	24.01.19	17.01.19	04.01.19	03.01.19
HEMA	K-Bazofilci (#)	0.01	0.02	0.03	0.03	0.04	0.03	0.05		0.04
HEMA	K-Nezreli Granulociti (#)	0.02	0.01	0.02	0.02	0.04	0.02	0.05		0.02
HEMA	K-Eritroblasti	0.0	0.0	0.0	0.0	0.0	0.0	0.0		0.0
HEMA	K-Eritroblasti (#)	0.00	0.00	0.00						
HEMA	K-Erc-Retikulociti (#)			53.1						
HEMA	K-Erc-Retikulociti (%)			1.6						
HEMA	K- Retikulociti, hemoglobin			34.6						
HEMA	Retikulociti - CHr									
HEMA	K-SR			13	42	49				
HEMA	K-CRP									
HEMA	P-PČ					1.17	1.26			
HEMA	INR					0.86	0.82			
BIOK	S-Na	139	136	139	137	138	135	136		141
BIOK	S-K	5.6	5.3	5.6	4.4	4.8	4.8	4.6		4.9
BIOK	S-Cl	104	100	103	99	101	101	103		105
BIOK	S-glukoza		5.2	5.1	5.1	4.4	4.4	4.4		3.8
BIOK	S-kreatinin	128	128	120	116	122	124	126		129
BIOK	S-sečnina	7.5	9.4	7.6	4.7	6.7	8.0	7.4		8.0
BIOK	S-urat	341	339	341	314	292	339	356		370
BIOK	S-fosfat anorg.	1.05	1.07	1.13	0.98	1.00	0.90	1.05		0.86
BIOK	S-kalcij	2.39	2.39	2.38	2.36	2.50	2.48	2.57		2.44
BIOK	S-kalcij, korig.						2.50	2.57		
BIOK	S-alk.fosfataza	2.70	1.95	1.87	2.95	3.51	14.33	13.43		11.26
BIOK	S-gamaGT	2.40	1.45	1.11	8.37	12.49	57.51	54.33		36.56
BIOK	S-bilirubin cel.	6	5	6	9	8	17	16		19
BIOK	S-bilirubin dir.	3	3				15	15		19
BIOK	S-AST	1.10	0.84	0.71	0.84	0.65	2.51	2.25		1.01
BIOK	S-ALT	0.84	0.57	0.51	0.68	0.58	2.23	1.91		0.88
BIOK	S-LDH	3.26	2.51	2.91	2.56	3.25	2.95	3.42		2.81
BIOK	S-holesteroli			3.7						
BIOK	S-magnezij		0.63	0.73			0.61	0.62		0.69
BIOK	S-železo	19.5		21.1						
BIOK	S-transferin	26		25						
BIOK	S-feritin	507		751						
BIOK	S-cel.proteini	63	62	61			73			
BIOK	S-albumini	42	39	39			43	44		
BIOK	S-CRP	1.5	0.5	0.5	6	9	17	11		15
IMUN	S-CEA	4.3	2.2	2.7		2.5	2.2		1.8	
IMUN	S-CA 19-9	859	317	361		2476	2339		1915	
IMUN	CA 72-4			< 1.5					1.6	
IMUN	S-CA 15-3									
IMUN	S-AFP	2.17								
ZUNA	Krvna skupina in Rh									

- Po SBRT sistemsko zdravljenje na KOGE
- Padec tumorskega markerja

Maj 2019

28.1.2019 25.5.2019



- Tumorska formacija z obraščanjem AMS po obsegu primerljiva, bolj hipodenzne strukture – vitalnost?
- HPB konzilij: sledenje

September 2019

- 3.9.19: PET CT - metaboličen regres malignoma pankreasa, najverjetneje z manjšim vitalnim ostankom malignega infiltrata, suspektne drobne pljučne lezije v blagem porastu
- Kontrola: dobro splošno počutje, porast tumorskega markerja, eventuelno za sistemsko zdravljenje na KOGE

Slikovna diagnostika za sledenje? Oceno resektabilnosti?

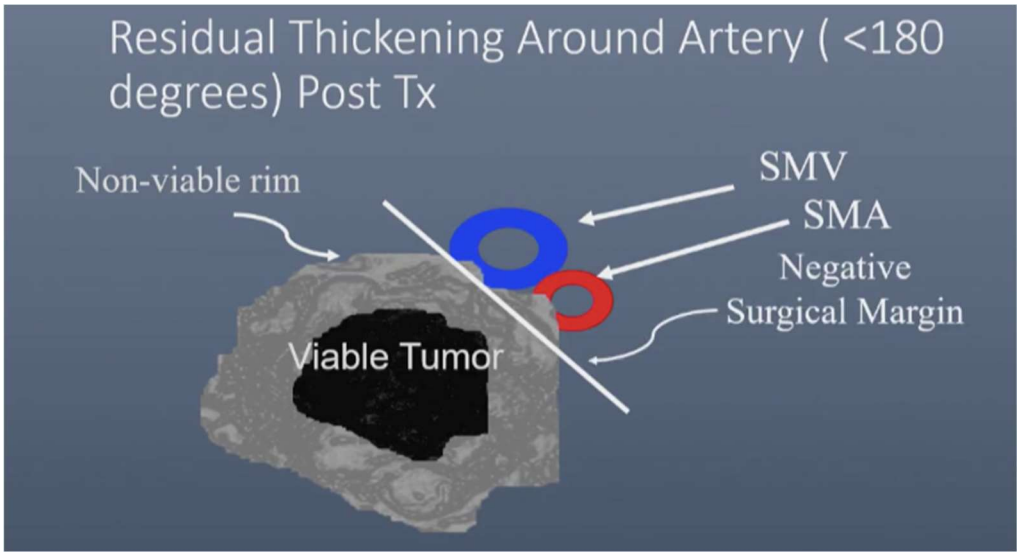
Original Article

Response of Borderline Resectable Pancreatic Cancer to Neoadjuvant Therapy Is Not Reflected by Radiographic Indicators

Matthew H. G. Katz, MD[1]; Jason B. Fleming, MD[1]; Priya Bhosale, MD[2]; Gauri Varadhachary, MD[3]; Jeffrey E. Lee, MD[1]; Robert Wolff, MD[3]; Huamin Wang, MD[4]; James Abbruzzese, MD[3]; Peter W. T. Pisters, MD[1]; Jean-Nicolas Vauthey, MD[1]; Chusilp Charnsangavej, MD[2]; Eric Tamm, MD[2]; Christopher H. Crane, MD[5]; and Aparna Balachandran, MD[2]

- 12% delni odgovor
- Zmanjšanje obraščanja žilja po RT/KT no CT slikah običajno ni vidna
- TODA 95% bolnikov operiranih R0 resekcija

Cancer December 1, 2012



Zaključek

- SBRT je indicirano pri mejno operabilnih in lokalno napredovalih karcinomih pankreasa
- Optimalna slikovna metoda za sledenje?

Vloga perioperativnega in adjuvantnega sistemskega zdravljenja pri karcinomu želodca

Marko Boc, dr.med.

Ljubljana, 22. november 2019

KARCINOM ŽELODCA – AGRESIVNA BOLEZEN

- SKORAJ **2/3** BOLNIKOV OB ODKRITJU Z T3-T4 TUMORJI
  - 85% BOLNIKOV – METASTAZE V LOKOREGIONALNIH BEZGAVKAH
- OPERIRANI BOLNIKI PO R0 RESEKCIJI
  - S_{5y} STADIJ I =70-75%
  - S_{5y} ≥ STADIJ IIB = <35%
- PRI **40-65%** BOLNIKOV PO KURATIVNI OPERACIJI SE BOLEZEN PONOVI
- METASTATSKI BOLNIKI
  - mS 8-11m, S_{5y} <10%

STADIJ	5-letno preživetje
IA	71%
IB	57%
IIA	45%
IIB	33%
IIIA	20%
IIIB	14%
IIIC	9%
IV	4%

40-50% BOLNIKOV

Howlader N, et al. SEER Cancer Statistics Review, 1975-2009

World Journal of Gastroenterology. **20** (7): 1635–49.
Ann Surg. 2005 Jan; 241(1): 27–39.

CILJI PERIOPERATIVNEGA ZDRAVLJENJA

- ZMANJŠANJE OBSEGA BOLEZNI
- VEČJA MOŽNOST RADIKALNE RESEKCIJE (R0)
- ZGODNJE ZDRAVLJENJA MIKROMETASTAZ

VEČJA MOŽNOST OZDRAVITVE, PODALJŠANJE PREŽIVETJA

PRED PRIČETKOM TERAPIJE

MULTIDISCIPLINARNI KONZILIJ (KIRURG, RADIOTERAPEVT, INTERNISTIČNI ONKOLOG, RADIOLOG)

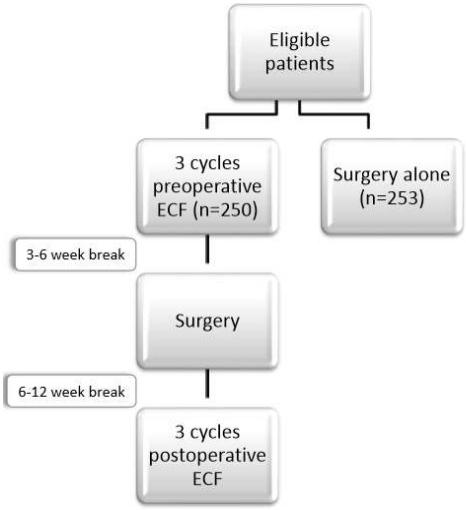
PLAN ZDRAVLJENJA

Smyth EC et al. Ann Oncol (2016) 27 (suppl 5): v38-v49

MOŽNOSTI PERIOPERATIVNEGA ZDRAVLJENJA

- **PERIOPERATIVNA KEMOTERAPIJA (KT ➔KRG ➔ KT)**
- **DOPOLNILNA KEMOTERAPIJA (KRG ➔ KT)**
- PREDOPERATIVNA KEMORADIOTERAPIJA (KT/RT ➔ KRG)
- DOPOLNILNA KEMORADIOTERAPIJA (KRG ➔ KT/RT)

MAGIC (n=503)



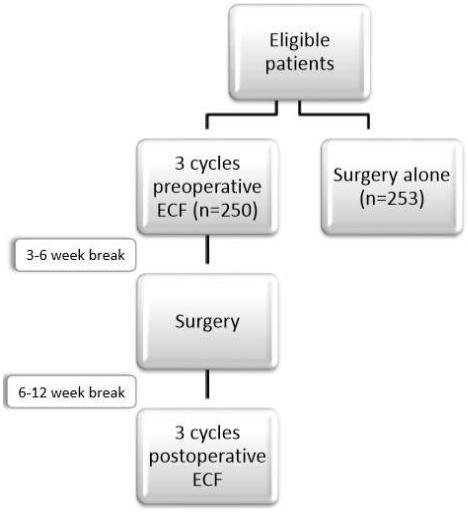
Eligibility criteria
Stage ≥ II gastric, gastroesophageal junction, or lower oesophageal adenocarcinoma (after 1999)
No metastases
ECOG 0-1

MAGIC preoperative patient characteristics		
	Surgery alone	Chemo + surgery
Median age	62	62
Sex Male Female	 191 (75%) 62 (25%)	 205 (82%) 45 (18%)
Site of disease		
Gastric	187 (74%)	185 (74%)
Oesophagus	36 (14%)	37 (15%)
GOJ	30 (12%)	28 (11%)

ECF, epirubicin 50mg/m2, cisplatin 60mg/m2 and continuous 5-fluorouracil 200mg/m2/d

Cunningham D et al. *N Engl J Med* 2006;355:11-20.

MAGIC (n=503)



MAGIC post-operative patient characteristics		
	Surgery alone	Chemo + surgery
Surgery		↑ curative resections
Curative	66/250 (66%)	169/244 (69%)
Palliative	70/250 (28%)	44/244 (18%)
Other	17/250 (6%)	27/244 (13%)
ypT stage		↑ early T stage
T1	16/193 (8%)	27/172 (16%)
T2	55/193 (29%)	62/172 (36%)
T3	106/193 (55%)	75/172 (44%)
T4	16/193 (8%)	8/172 (4%)
ypN Stage (gastric)		↑ early N stage
N0	42/156 (27%)	42/135 (31%)
N1	68/156 (43%)	72/135 (53%)
N2	34/156 (23%)	19/135 (14%)
N3	12/156 (8%)	2/135 (2%)

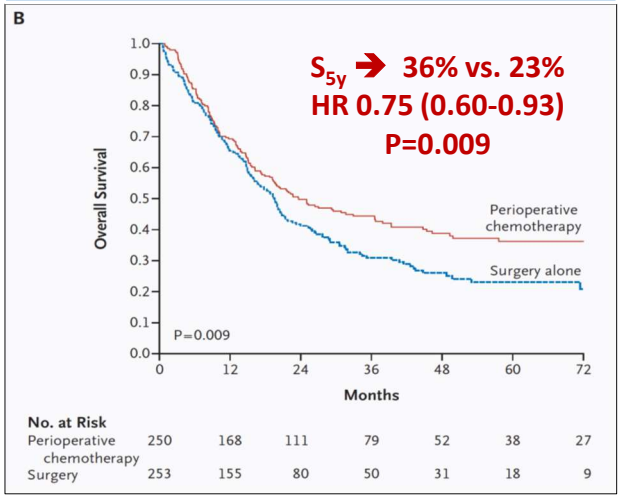
ZMANJŠANJE OBSEGA BOLEZNI

ECF, epirubicin 50mg/m2, cisplatin 60mg/m2 and continuous 5-fluorouracil 200mg/m2/d

Cunningham D et al. *N Engl J Med* 2006;355:11-20.

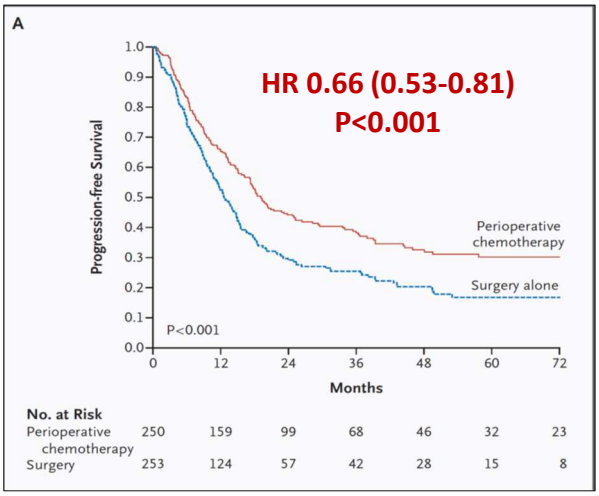
MAGIC (n=503)

OS



S_{5y} ➔ 36% vs. 23%
HR 0.75 (0.60-0.93)
P=0.009

PFS

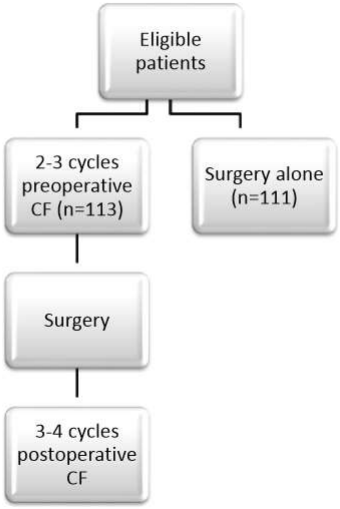


HR 0.66 (0.53-0.81)
P<0.001

LOKALNE PONOVITVE	**14%** vs. 21%
PONOVITVE V OBLIKI ODDALJENIH ZASEVKOV	**24%** vs. 37%

Cunningham D et al. *N Engl J Med* 2006;355:11-20.

FNCLCC (n=224)



Eligibility criteria
Lower oesophageal or GOJ adenocarcinoma (gastric after 1998)
No metastases
ECOG 0-1

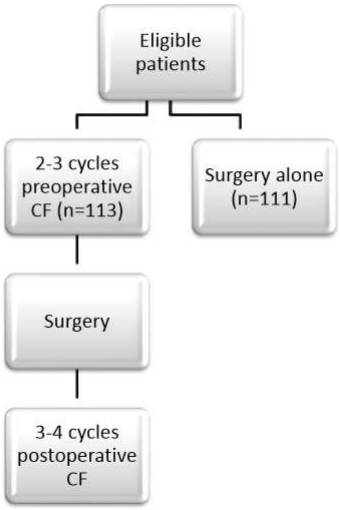
FFCD/ACCORD preoperative patient characteristics

	Surgery alone	Chemo + surgery
Median age	63	63
Sex		
Male	91 (82%)	96 (85%)
Female	20 (18%)	17 (15%)
Site of disease		
Gastric	28 (13%)	27(9%)
Oesophagus	15 (25%)	10 (24%)
GOJ	70 (62%)	74(67%)

CF, cisplatin 100mg/m2 and continuous 5-fluorouracil 800mg/m2/d day 1-5 q 28d

Ychou M et al. *JCO* 2011;29:1715-21.

FNCLCC (n=224)



FFCD/FNCLCC post-operative patient characteristics

	Surgery alone	Chemo + surgery
Surgery		↑ curative surgery
No resection	11 (10%)	7 (6%)
R0	81(74%)	95(87%)
R1	6 (5%)	4 (4%)
R2	11(10%)	2(2%)
Rx	1(1%)	1(1%)
ypT stage		↑ early T stage
T0	(8%)	3 (3%)
T1-2	(29%)	38 (39%)
T3-4	(55%)	57 (58%)
ypN Stage (gastric)		↑ early N stage
N0	17 (20%)	32(33%)
N+	68 (80%)	66(67%)

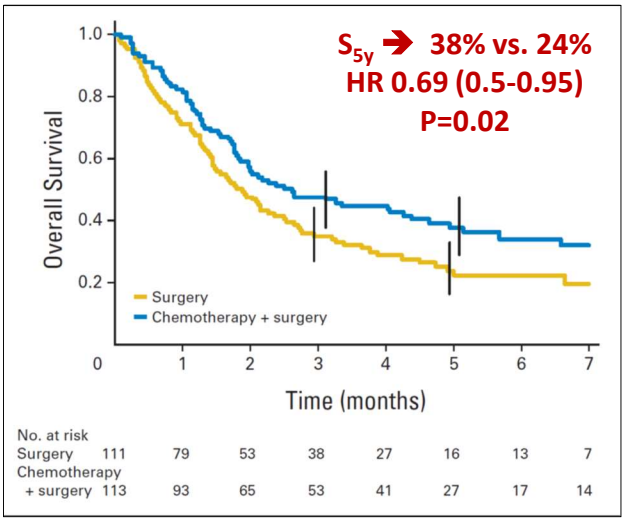
ZMANJŠANJE OBSEGA BOLEZNI

CF, cisplatin 100mg/m2 and continuous 5-fluorouracil 800mg/m2/d day 1-5 q 28d

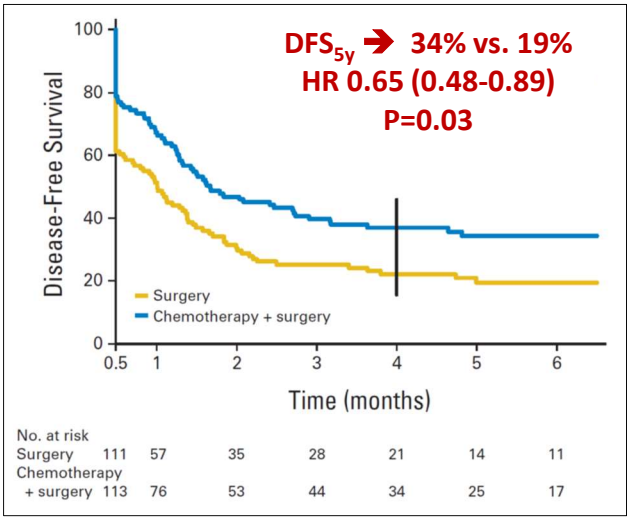
Ychou M et al. *JCO* 2011;29:1715-21.

FNCLCC (n=224)

OS



DFS



VSI BOLNIKI D2 RESEKCIJA

Ychou M et al. *JCO* 2011;29:1715-21.

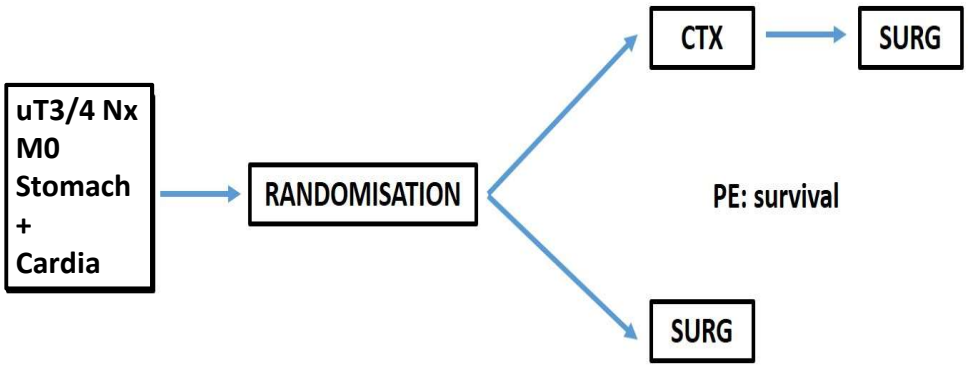
MAGIC & FNCLCC

1. ~10% bolnikov ni končalo predoperativnega zdravljenja
2. ~ 50% ni bilo zmožno pooperativnega zdravljenja

	MAGIC 3 cycles ECF	FFCD/FNCLCC 2-3 cycles CF
Pre-operative chemotherapy	3 cycles: n= 215 (91%)	1 cycle: n=11 (10%) 2 cycles: n=85 (75%) 3 cycles: n= 13 (12%) 87% had minimum 2 cycles
Surgery	229 (92%)	109 (97%)
Post-operative chemotherapy	Any chemotherapy: n=137 (55%) 3 cycles: n= 104 (42%)	Any chemotherapy: n=54 (50%) 1 cycle: n=6 (6%) 2 cycles: n=7 (6%) 3 cycles: n= 16 (15%) 4 cycles: n=25 (23%)

Ychou M et al. *JCO* 2011;29:1715-21.
Cunningham D et al. *N Engl J Med* 2006;355:11-20.

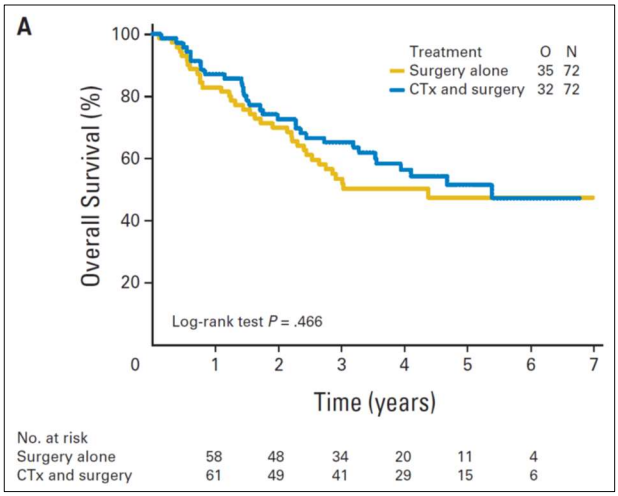
EORTC 40954



Schuhmacher C et al. *JCO* 2010;28:5210-5218.

EORTC 40954

OS



mOS: CTh + surgery = 65m
surgery = 53m
HR 0.84, NS (p=.466)

R0 resection **81.9% vs. 66.7%, p=.036**

$SURG_{group}$ >N+ (76.5% vs. 61.4%, p=.018)
$postOP_{compl}$ > CTX_{group} (27.1% vs. 16.2%, NS)

Schuhmacher C et al. *JCO* 2010;28:5210-5218.

Epirubicin? – MRC OE5

Histologically confirmed adenoCa of lower oesophagus and EGJ (Type I and II)

MDT-resectable desease following EUS and CT

(T1/2 N0 excluded)

→ RANDOM → 2xCF → SURG

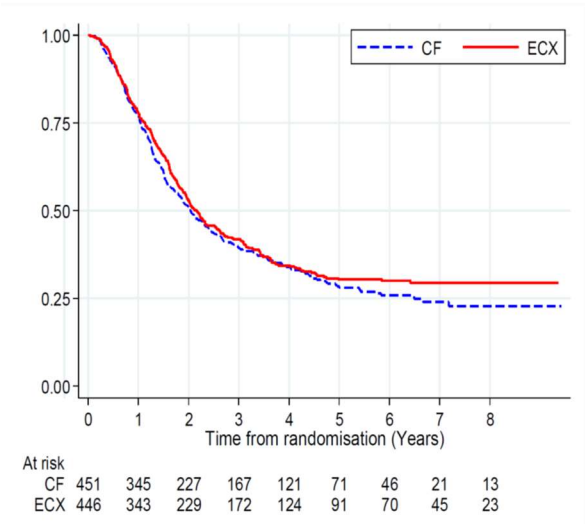
→ RANDOM → 4xECX → SURG

CF: 2x 3w cycles of cisplatin (80mg/m^2 D1) and 5FU (1g/m^2 D1-4)

ECX: 4x 3w cycles of epirubicine (50mg/m^2 D1) , cisplatine (60mg/m^2 D1) and capecitabine (1250mg/m^2 daily)

Alderson D et al. *ASCO* 2015;#4002.

Epirubicin? – MRC OE5

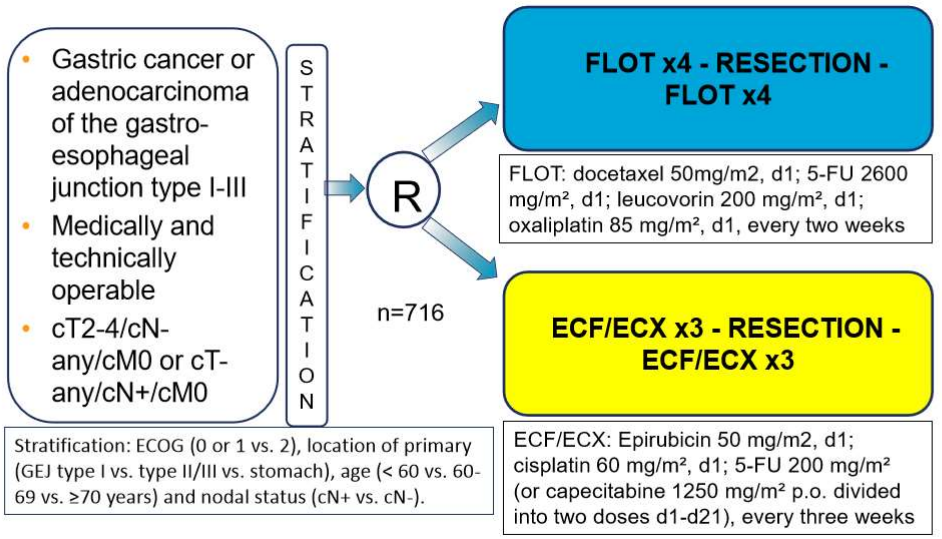


Median survival (95% CI)	
CF	2.02 (1.80, 2.38) ys
ECX	2.15 (1.93, 2.53) ys
HR	0.92 (0.79, 1.08)
P-value	0.8582
3-year survival (95% CI)	
CF	39% (35%, 44%)
ECX	42% (37%, 46%)

R0 resection	Yes	212	60%	223	67%	0.059
	No	144	40%	112	33%	
	Unavailable	31		29		

Alderson D et al. *ASCO* 2015;#4002.

FLOT4



al Batran et al, ASCO 2017

FLOT4

	ECF/ECX (n=360)	FLOT (n=356)	
Resection surgery	313/360(87%)	336/356 (94%)	0.001
R0 resection rate	276/360 (77%)	300/356 (84%)	0.011
Any surgical complication	188/341 (55%)	188/345 (55%)	
Median duration hospital stay	16 days	15 days	
Death 90 days	26 (8%)	16 (5%)	

✓ **VEČ R0 RESEKCIJ Z KT PO SHEMI FLOT VS . ECX/ECF**
✓ **ENAKA MORBIDITETA IN MORTALITETA MED KT PO SHEMI FLOT VS. ECX/ECF**

al Batran et al, ASCO 2017

Peri-operativna kemoterapija pri zdravljenju karcinoma želodca
TAXANI – FLOT4

	ECF/ECX (n=360)	FLOT (n=356)	
ypT stage			
≤T1	**53 (15%)**	**88(25%)**	**0.001**
T2	44 (12%)	44(12%)	
T3	175 (49%)	165(46%)	
T4	47(13%)	37(10%)	
NA	41(11%)	22(6%)	
ypN stage			
N0	**146(41%)**	**174(49%)**	**0.029**
N1	44(12%)	55(16%)	
N2	54(15%)	47(13%)	
N3	73(20%)	57(16%)	
NA	43(12%)	23(7%)	

✓ **VEČJI ODSTOTEK ZMANJŠANJA T STADIJA PRI KT PO SHEMI FLOT VS. ECX/ECF[1]**

PATOLOŠKI ODG.[2](%)	CR(kompletna remisija)	SR(sub-kompletna remisija)	CR+SR
FLOT	**12.8**	**16.7**	**29.5**
ECF	5.1	10.1	15.2

→ P=0.036

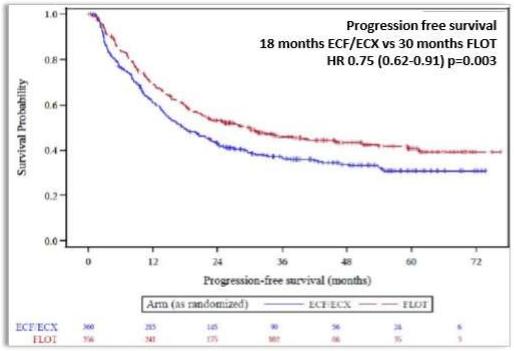
1. **al Batran et al**, ASCO 2017
2. **Pauligk C et al.** JCO 2015

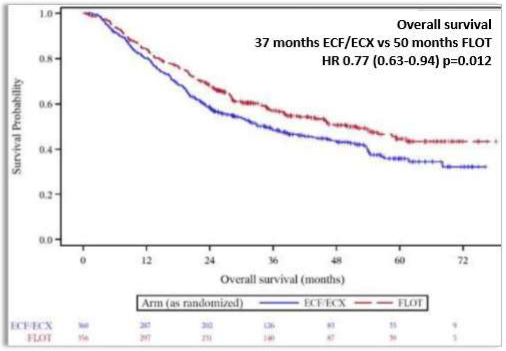
FLOT4

Grade 3-4 >5%	ECF/ECX (N=354)	FLOT (N=354)	P-value (Chi-Square)
Diarrhea	13 (4%)	34 (10%) ←	0.002
Vomiting	27 (8%) ←	7 (2%)	<0.001
Nausea	55 (16%) ←	26 (7%)	0.001
Fatigue	38 (11%)	25 (7%)	
Infections	30 (9%)	63 (18%) ←	<0.001
Leukopenia	75 (21%)	94 (27%)	
Neutropenia	139 (39%)	181 (51%) ←	0.002
Sensory	7 (2%)	24 (7%) ←	0.002
Thromboembolic	22 (6%) ←	9 (3%)	0.03
Anemia	20 (6%) ←	9 (3%)	0.04
Toxic event			
SEA any	220 (62%)	215 (61%)	
SEA w relation to tretment	137 (34%)	139 (35%)	
Toxic death	2 (<1%)	2 (<1%)	

al Batran et al, ASCO 2017

FLOT4





Projected PFS rates		
	ECF/X	FLOT
2 year	43%	53%
3 year	37%	46%
5 year	31%	41%

Projected OS rates		
	ECF/X	FLOT
2 year	59%	68%
3 year	48%	57%
5 year	36%	45%

✓ **PODALJŠANJE PREŽIVETJA BREZ PONOVITVE IN CELOKUPNEGA PREŽIVETJA PRI KT PO SHEMI FLOT vs. ECX/ECF**

al Batran et al, ASCO 2017

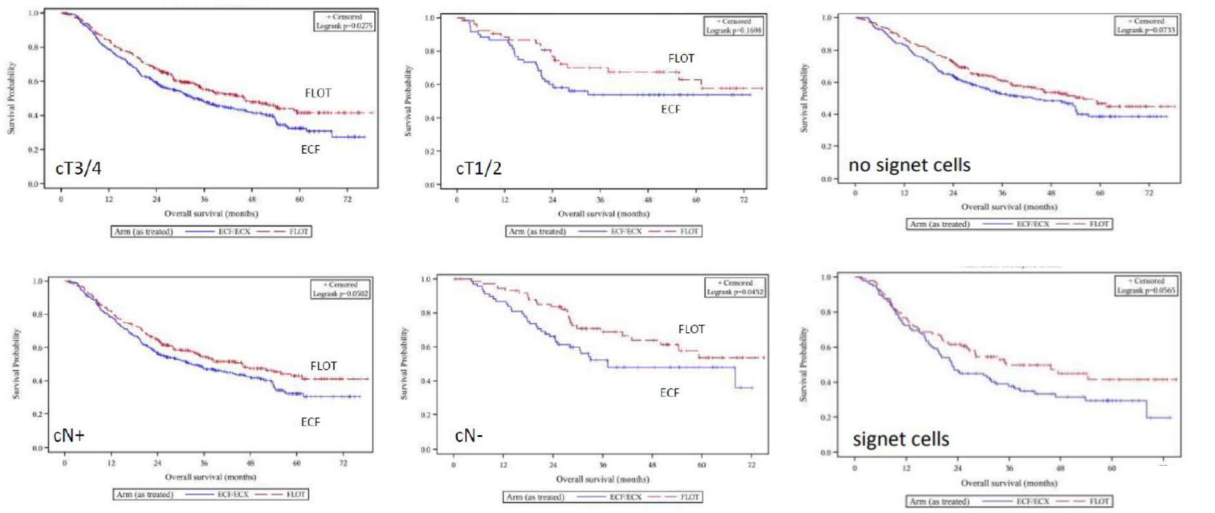
FLOT4

	ECF/ECX (n=360)	FLOT (n=356)
Completed pre-operative chemo	327 (91%)	320 (90%)
Surgery	340 (94%)	336 (94%)
Started post-operative chemo Completed protocol post-op chemo	187 (52%) 133 (37%)	213 (60%) 162 (46%)

✓ **VEČJI ODSTOTEK BOLNIKOV ZAČNE IN KONČA POOPERATIVNI DEL ZDRAVLJENJA PRI KT PO SHEMI FLOT vs. ECX/ECF**

al Batran et al, ASCO 2017

DOBROBIT SHEME FLOT PREKO VSEH PROGNOSTIČNIH SKUPIN



al Batran et al, ASCO 2017

DOPOLNILNA KEMOTERAPIJA- CLASSIC

Randomised fase III study
Stage II-IIIB gastric cancer

PostOP (D2 gastrectomy)

→ +CTX (6xXELOX)

→ SURGERY ONLY

	N	5-year disease-free survival			5-year overall survival		
		Adjuvant capecitabine and oxaliplatin	Observation alone	Hazard ratio	Adjuvant capecitabine and oxaliplatin	Observation alone	Hazard ratio
II	515	80% (74–85) ▲ 12%	68% (61–74)	0·55 (0·38–0·80)	88% (83–92) ▲ 9%	79% (73–84)	0·54 (0·34–0·87)
IIIA	377	58% (50–67) ▲ 14%	44% (35–53)	0·61 (0·44–0·84)	70% (62–77) ▲ 7%	63% (55–71)	0·75 (0·52–1·10)
IIIB	143	52% (40–65) ▲ 31%	21% (9–33)	0·52 (0·33–0·82)	66% (54–78) ▲ 21%	45% (31–58)	0·67 (0·39–1·13)

Data are % (95% CI) or hazard ratio (95% CI).

Table 3: Disease-free survival and overall survival by disease stage in the intention-to-treat population

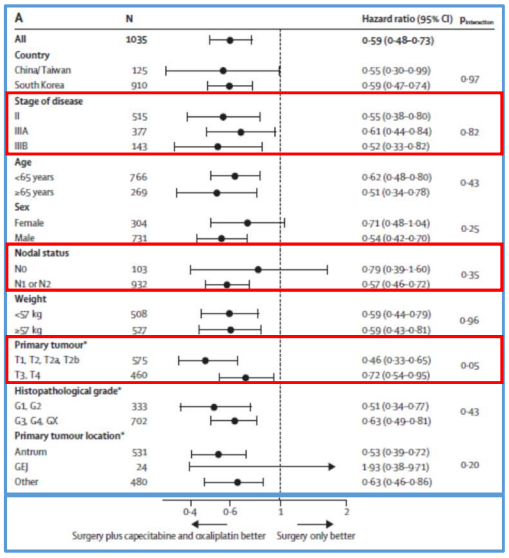
- SAMO **67%** BOLNIKOV PREJME VSEH 8 PREDVIDENIH CIKLUSOV
- PRILAGAJANJE ODMERKOV POTREBNO PRI **> 90%** BOLNIKOV
- **9x** VEČ TOKSIČNOSTI G3/4 V ROKI Z KEMOTERAPIJO

- LOKOREGIONALNA PONOVITEV 27% vs. 52%

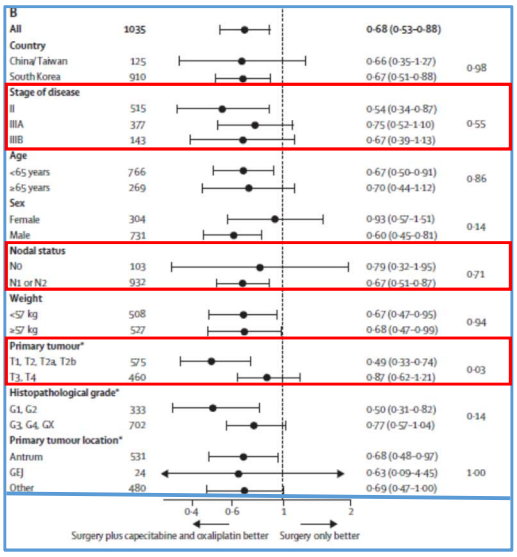
Noh HN et al. *Lancet oncol* 2014;1389-1396.
BangYJ et al. *Lancet* 2012;379:315-21.

DOPOLNILNA KEMOTERAPIJA- CLASSIC

DFS



OS

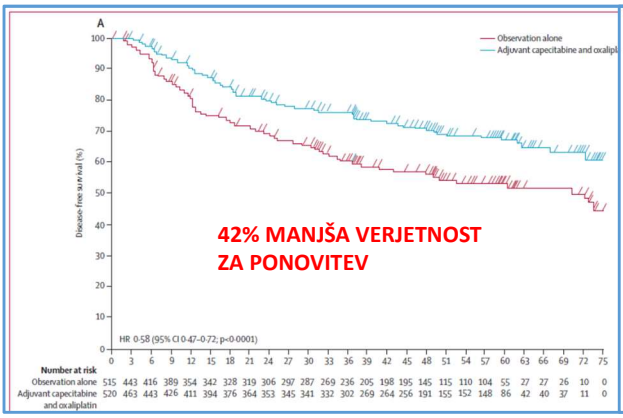


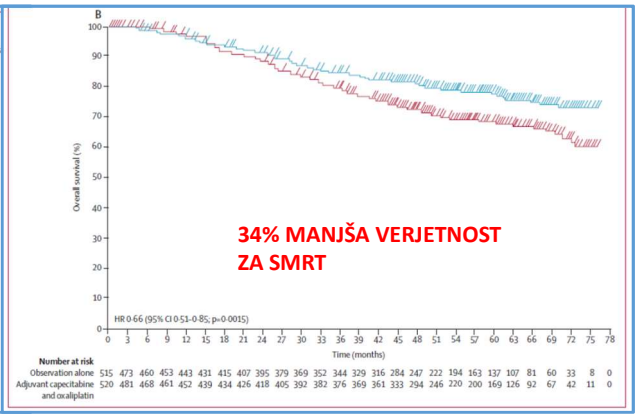
Noh HN et al. *Lancet oncol* 2014;1389-1396.

DOPOLNILNA KEMOTERAPIJA- CLASSIC

DFS

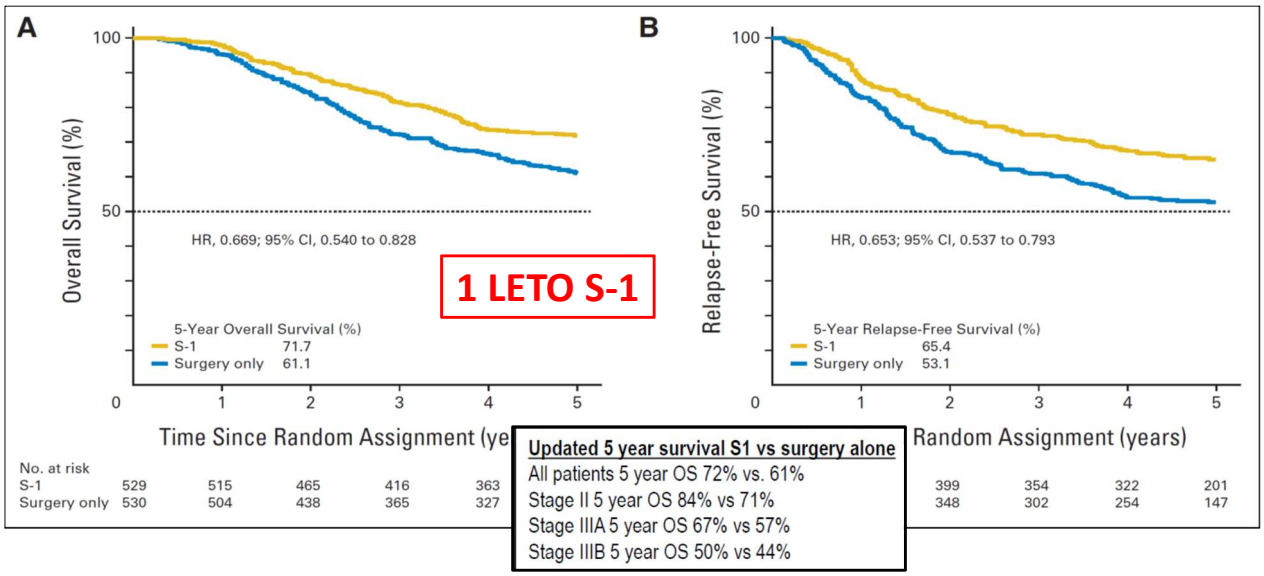
OS





Noh HN et al. *Lancet oncol* 2014;1389-1396.

DOPOLNILNA KEMOTERAPIJA– ACTS-GC 2007

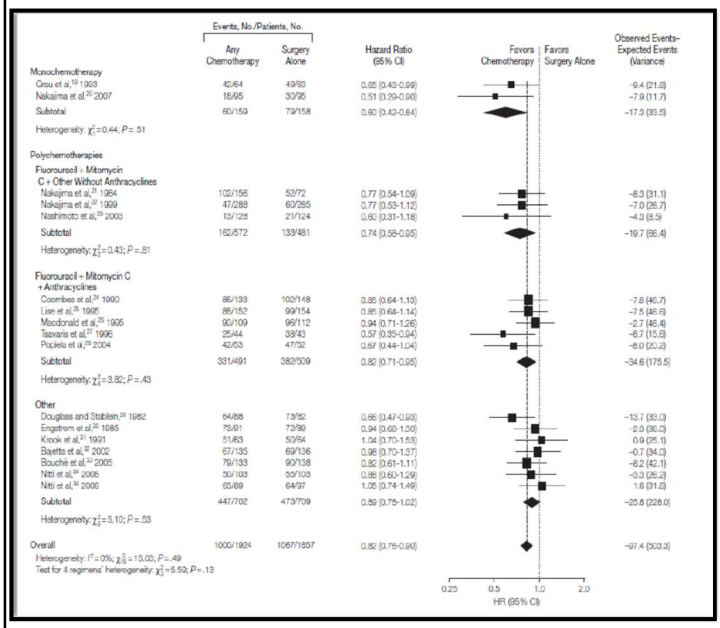


Updated 5 year survival S1 vs surgery alone
All patients 5 year OS 72% vs. 61%
Stage II 5 year OS 84% vs 71%
Stage IIIA 5 year OS 67% vs 57%
Stage IIIB 5 year OS 50% vs 44%

ESMO 2017 - OPAS-1 → 12m=6m

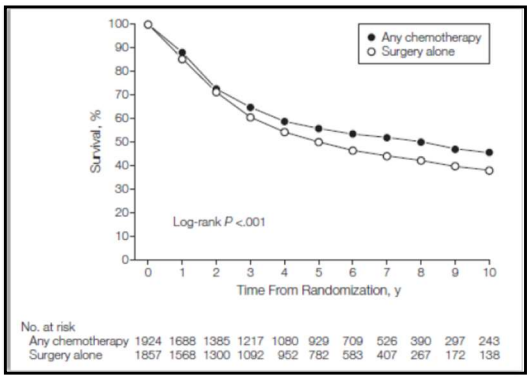
Sasako et al. *J Clin Oncol* 2011;29:4387.4393.
Sakuramoto S et al. *N Engl J Med* 2007;357:1810-1820.

DOPOLNILNA KEMOTERAPIJA PRI NE-AZIJSKI POPULACIJI



5L ABSOLUTNA DOBROBIT NA PREŽIVETJE 5.8% (55.3 vs. 49.6)
HR=0.82, P<.001

VEČJA DOBROBIT PRI N+



Paolettiet et al. JAMA. 2010 May 5;303(17):1729-37.

ADJUVANTNA KEMOTERAPIJA - ALI JE PRI INTENZIFIKACIJI KT DOBROBIT VEČJA

GISCAD

5FU (375mg/m²)/LV (20mg/m²) D1-5; q4w x 6

N=400

wPELF (weekly cisplatin, epirubicine, LV, 5FU) x 8

ITACA-S

5FU (400-600mg/m²)/LV (100mg/m²) D1-2; q2w x 9

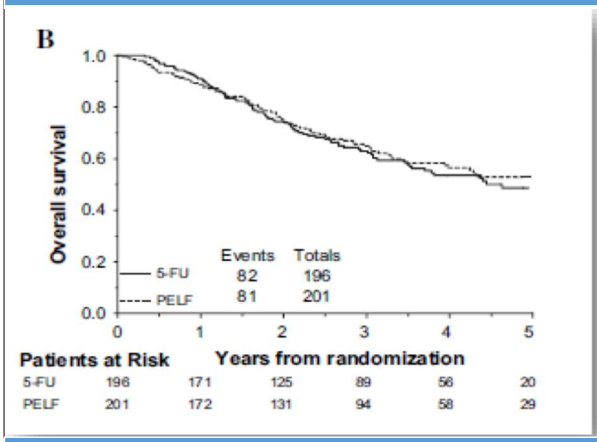
N=1106

FOLFIRI X 4 ➔ Docetaxel/Cisplatin x 3

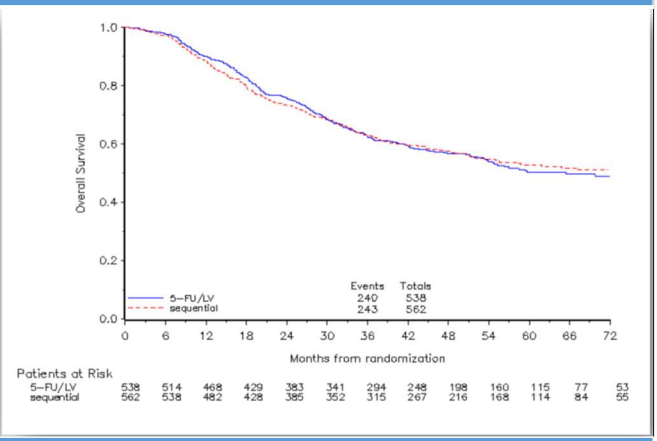
Cascinu et al. *J Nat Canc Inst* 2007; 99: 601-607.
Bajetta et al. *Ann Oncol* 2014;25:1373-8.

ADJUVANTNA KEMOTERAPIJA - ALI JE PRI INTENZIFIKACIJI KT DOBROBIT VEČJA

GISCAD[1]



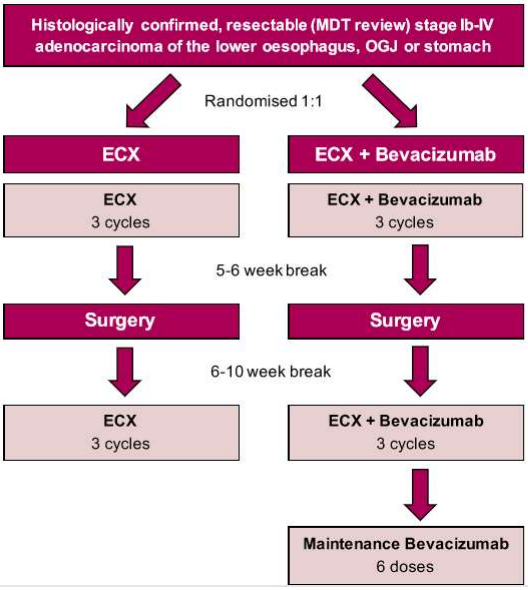
ITACA-S[2]



DOBROBIT OB INTENZIFIKACIJI KT NI VEČJA!

Cascinu et al. *J Nat Canc Inst* 2007; 99: 601-607.
Bajetta et al. *Ann Oncol* 2014;25:1373-8.

Peri-operativna kemoterapija pri zdravljenju karcinoma želodca
DODATEK BEVACIZUMABA – ST03 MAGIC



Chemotherapy regimens

21-day cycles

ECX

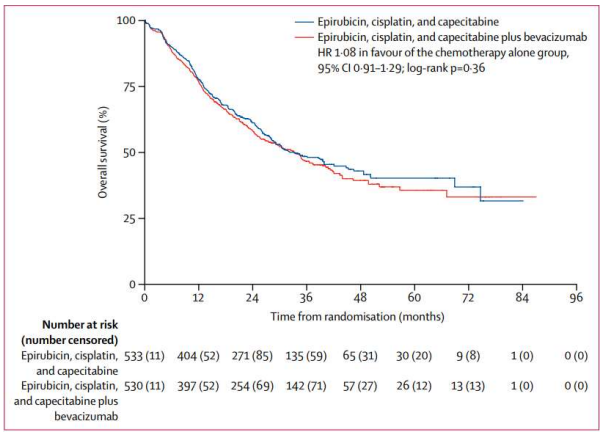
- Epirubicin 50mg/m² IV on day 1
- Cisplatin 60mg/m² IV on day 1
- Capecitabine 1250mg/m² PO daily

ECX + Bevacizumab

- Bevacizumab 7.5mg/kg IV on day 1 added to each ECX cycle

Lancet Oncol 2017; 18: 357–70

Peri-operativna kemoterapija pri zdravljenju karcinoma želodca
DODATEK BEVACIZUMABA – ST0-3/MAGIC-B



Overall survival		
Median OS	ECX	33.97 months
	ECX+B	34.46 months
Hazard Ratio		1.067
(95% CI)		(0.8911 to 1.279)
Log-rank p-value		0.4784

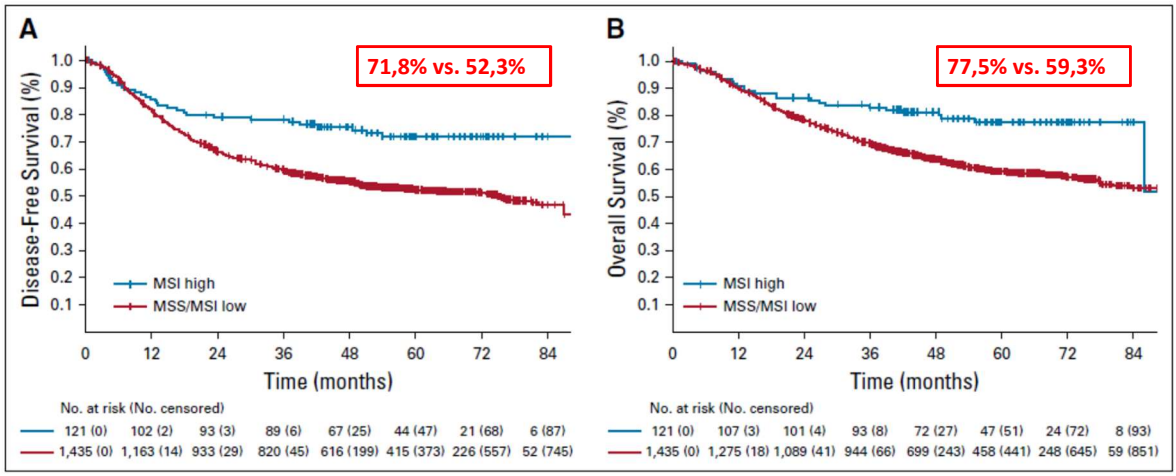
3-year overall survival (95% CI)	
ECX	48.9% (43.6% to 53.8%)
ECX+B	47.6% (42.3% to 52.7%)

- ✓ DODATEK BEVACIZUMABA SISTEMSKI KT V PERIOPERATIVNO NE DOPRINESE K UČINKOVITOSTI TERAPIJE, TAKO GLEDE PREŽIVETJA, KOT TUDI GLEDE ODGOVORA NA ZDRAVLJENJE IN ŠTEVILA R0 RESEKCIJ
- ✓ ENAKO ZAENKRAT VELJA TUDI ZA OSTALA PREIZKUŠENA TARČNA ZDRAVILA (TRASTUZUMAB, PERTUZUMAB, ITD.)

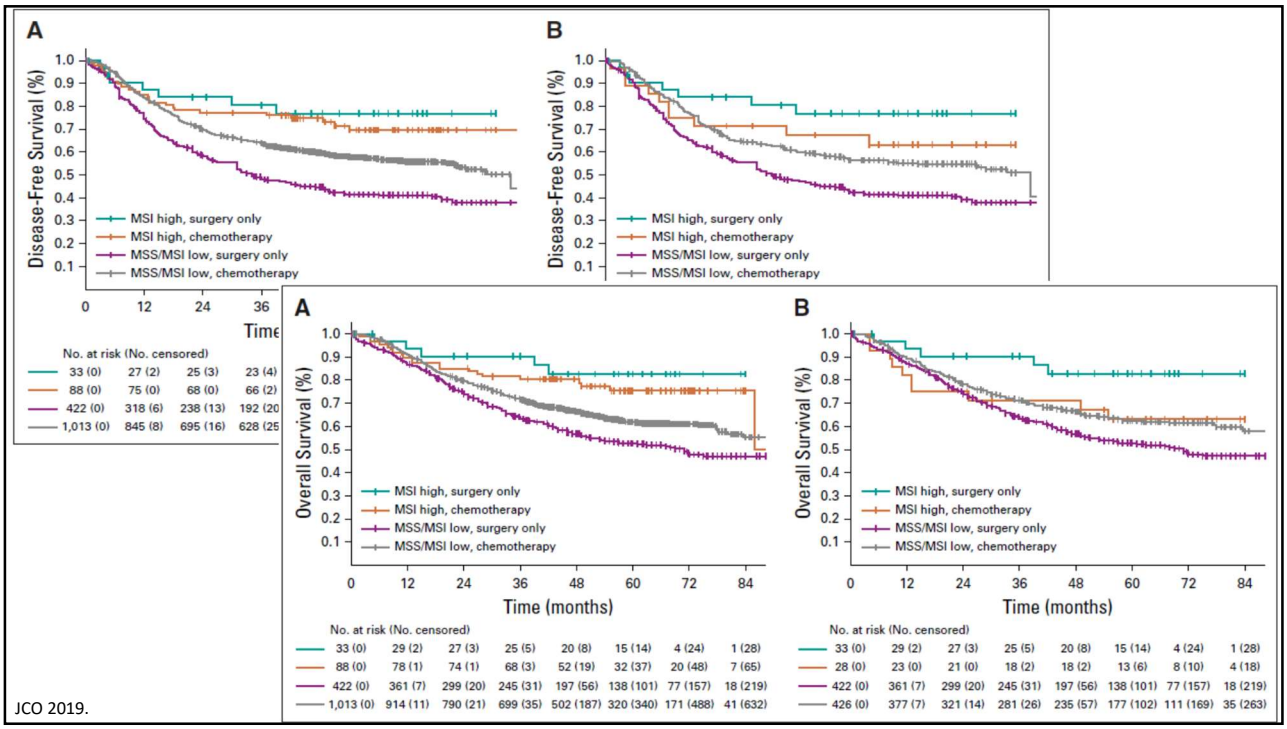
Lancet Oncol 2017; 18: 357–70.
Annals of Oncology 27 (Supplement 5): v38–v49, 2016 doi:10.1093/annonc/mdw350.

MAGIC
CLASSIC
ARTIST
ITACA-S

Individual Patient Data Meta-Analysis of the Value of Microsatellite Instability As a Biomarker in Gastric Cancer



JCO 2019.



JCO 2019.

TABLE 2. Analyses of MSI Predictive Role: Impact of Chemotherapy in MSI-High and MSS/MSI-Low Subgroups

Treatment Comparison by MSI Status and Survival Type	MAGIC + CLASSIC + ITACA-S + ARTIST: No. of Events	5-Year Survival, % (95% CI)	HR (95% CI)	P*	MAGIC + CLASSIC: No. of Events	5-Year Survival, % (95% CI)	HR (95% CI)	P*
DFS								
MSS/MSI low: CT + surgery *v* surgery only	431 *v* 247	56.9 (53.8 to 60.2) *v* 41.2 (36.6 to 46.4)	0.65 (0.53 to 0.79)	.133	190 *v* 247	55.3 (50.7 to 60.4) *v* 41.2 (36.6 to 46.4)	0.66 (0.53 to 0.81)	.147
MSI high: CT + surgery *v* surgery only	25 *v* 7	69.8 (60.4 to 80.7) *v* 76.9 (63.2 to 93.6) ▲ 7.1%	1.27 (0.53 to 3.04)		10 *v* 7	63.2 (47.4 to 84.4) *v* 76.9 (63.2 to 93.6) ▲ 13.7%	1.45 (0.51 to 4.17)	
OS								
MSS/MSI low: CT + surgery *v* surgery only	368 *v* 198	62.0 (58.9 to 65.3) *v* 52.8 (48.0 to 58.0)	0.75 (0.60 to 0.94)	.180	156 *v* 198	62.4 (57.8 to 67.4) *v* 52.8 (48.0 to 58.0)	0.74 (0.59 to 0.93)	.070
MSI high: CT + surgery *v* surgery only	21 *v* 5	75.4 (66.4 to 85.6) *v* 82.8 (70.1 to 97.8) ▲ 6.8%	1.50 (0.55 to 4.12)		10 *v* 5	63.1 (47.2 to 84.4) *v* 82.8 (70.1 to 97.8) ▲ 19.2%	2.18 (0.69 to 6.94)	

JCO 2019.

ZAKLJUČEK

- Perioperativna kemoterapija se svetuje pri vseh bolnikih z nemetastatskim resektabilnim karcinomom želodca ≥ stadij IB [ESMO I, A]:
  - perioperativna kemoterapija naj vključuje derivate platine in 5-FU,
  - dodatek epirubicina opcijski (toksičnost),
  - dodatek taksanov (FLOT) izboljša odgovor na zdravljenje, podaljša preživetje brez ponovitve bolezni in celokupno preživetje ➔ novi standard
- Bolniki ≥ stadij IB, operirani brez perioperativne kemoterapije, so kandidati za dopolnilno kemoradioterapijo ali dopolnilno kemoterapijo [ESMO I, A]
- Tarčna zdravila zaenkrat nimajo vloge v neoadjuvantnem sistemskem zdravljenju raka želodca
- MSI status – napovedni dejavnik perioperativnega zdravljenja

Lymphadenectomy and multivisceral resections in advanced gastric cancer

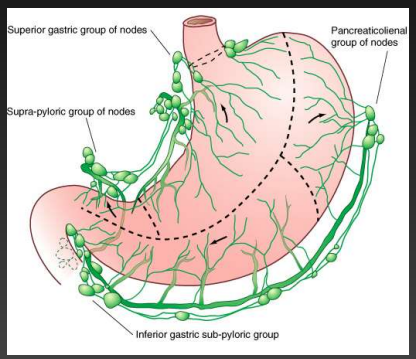
Omejc M

klinični center ljubljana
University Medical Centre Ljubljana

Department of Abdominal Surgery

Gastric cancer progression

↑ depth of gastric wall - ↑ lymph node involvement - ↓ survival



Goal of local control: lymph node metastasis

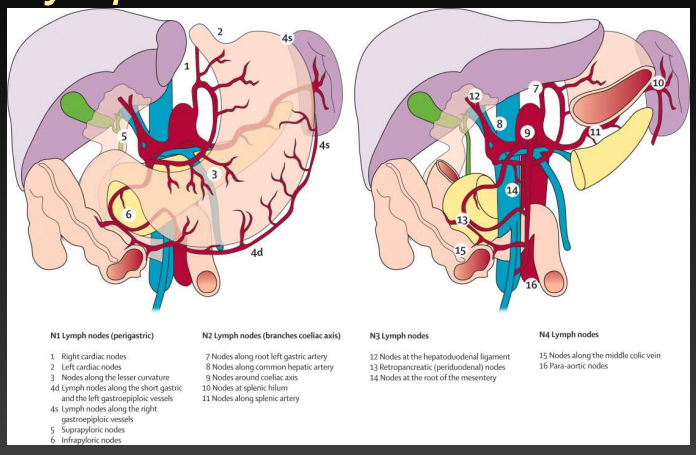
"The surgery of cancer is not the surgery of organs; it is the surgery of the lymphatic system".

Sir Berkeley Moynihan

Depth		(n)	LN	Liver	Perit.	5YSR
pT1	M	1063	3.3	0.0	0.0	93.3
	SM	881	17.4	0.1	0.0	88.9
pT2	MP	436	46.4	1.1	0.5	81.3
	SS	325	63.7	3.4	2.2	65.8
pT3	SE	1232	78.9	6.3	17.8	35.5
pT4	SI	724	89.8	15.5	41.6	10.1
Overall		4683	47.8	4.5	11.5	60.3

Incidence of metastasis and 5-YSR according to the depth of tumor invasion
Patients operated on between 1972 -91, NCCH

Lymph nodes



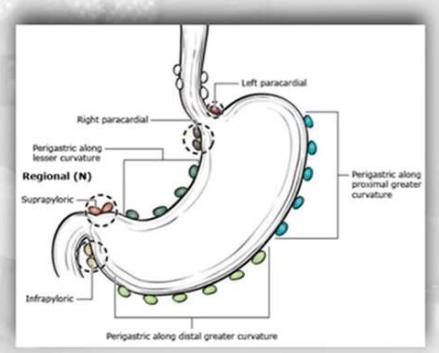
Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: Gastric Cancer 14, 101–112 (2011).

Stations 1-11: an average of 27 nodes (range 17-44 nodes)
Stations 1-16: an average of 43 nodes (range 25-64 nodes)

Wagner PK, Ramaswamy A, Rüschoff J, Schmitz-Moormann P, Rothmund M. Lymph node counts in the upper abdomen: anatomical basis for lymphadenectomy in gastric cancer. Br. J. Surg. 78(7), 825–827 (1991).

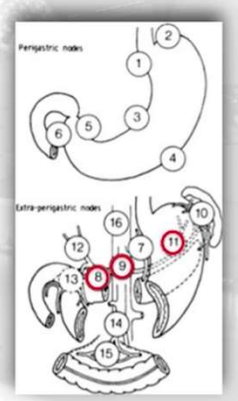
D1 lymphadenectomy

- D1 lymphadenectomy refers to a limited dissection of only the perigastric lymph nodes (stations 1 to 7)
- D1 indication:
  - –T1a without EMR / ESD criteria
  - –cT1bN0 Histologically distinct and 1.5 cm or less in diameter



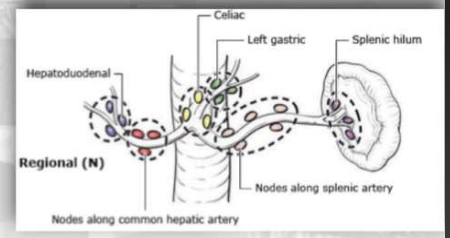
D1 + lymphadenectomy

- In the Japanese literature, a D1+ lymphadenectomy refers to a D1 lymphadenectomy plus stages 8a, 9, and 11p.
- D1 + lymphadenectomy is indicated for cT1N0 tumors other than the above criteria.



D2 lymphadenectomy

- D2 lymphadenectomy is a dissection that involves removal of the lymph nodes along the hepatic, left gastric, celiac and splenic arteries, as well as those of the splenic hilum (stations 1 to 12a).
- Indication:
  - Tumors T2-T4 and cT1N +
  - Complete clearance of 10 nodules by splenectomy should be considered for potentially curable T2-T4 tumors that invade the greater curvature of the upper part of the stomach



D3 lymphadenectomy

- The D3 dissection is a superextended lymphadenectomy.
- Some describe it for a D2 lymphadenectomy plus nodes within the hepatic portal and periaortic regions (stations 1 to 16) and others to designate a D2 lymphadenectomy plus periaortic lymph node dissection (PAND) alone
- Most Western surgeons classify the disease in these regions as distant metastases and do not remove nodes routinely in these areas during a potentially curative gastrectomy.

Lymphadenectomy

- to accurately stage gastric cancer (16 nodes)
- to reduce the risk of locoregional recurrence (24 nodes)
- to improve survival (up to 40 nodes)

  D3 (or D2 with para-aortic nodal dissection).

Does more extended lymphadenectomy lead to a survival advantage for patients undergoing surgery for gastric carcinoma?

Does the clinical evidence in literature support this?

"Stage migration"

"When the Okies left Oklahoma and moved to California, they raised the average intelligence level in both states."

Will Rogers

- ↑ extended lymphadenectomy = ↑ better staging
- "Upstaging"
- Improvement in "stage-specific" survival in extended lymphadenectomy (D2, D3)

Clinical evidence D1 vs D2

- The majority of multiple randomized trials have not shown a survival benefit of D2 versus D1
- However, recent studies support the concept that if D2 dissection can be performed with low operative mortality, survival will be positively affected

De Steur WO, Hartgrink HH, Dikken JL, Putter H, Van De Velde CJ. Quality control of lymph node dissection in the Dutch Gastric Cancer Trial. Br. J. Surg. 102(11), 1388–1393 (2015).

Dutch study: D2 vs D1 ?

"If postoperative death is excluded, the 11 year survival data favor the D2 dissection".

van de Velde CJH, 2004

Clinical evidence D2 vs D3

Cochrane Library

Cochrane Database of Systematic Reviews

Extent of lymph node dissection for adenocarcinoma of the stomach (Review)

Mocellin S, McCulloch P, Kazi H, Gama-Rodrigues JJ, Yuan Y, Nitti D

neither a significant difference in postoperative mortality, nor in disease-free and overall survival between D2 or D3 procedures.

WILEY

D2 lymphadenectomy in the era of neoadjuvant chemotherapy ?

- 129 pts. gastrectomy with D2 lymphadenectomy
- 22 pts. complete pathological response of primary tumor (17%)
- 12 pts. (55%) lymph node metastases

Shrikhande *et al. World Journal of Surgical Oncology* 2013, **11**:31
http://www.wjso.com/content/11/1/31

WORLD JOURNAL OF SURGICAL ONCOLOGY

RESEARCH Open Access

D2 lymphadenectomy is not only safe but necessary in the era of neoadjuvant chemotherapy

Shrikhandeet al. World Journal of Surgical Oncology 2013,11:31

5-year survival (UKC Ljubljana)

Digestive Surgery

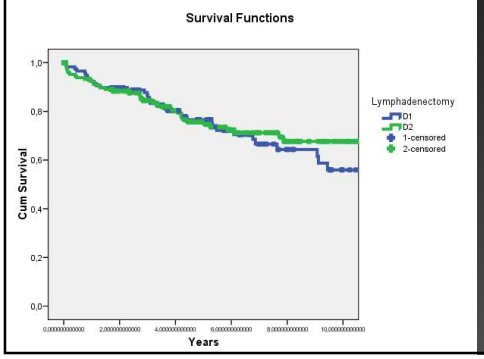
Preoperative Prediction of Lymph Node Status in Gastric Cancer Patients with the Help of Computer Analysis

Mekicar J. · Omejc M.

Dig Surg 2009;26:256–261
https://doi.org/10.1159/000227296

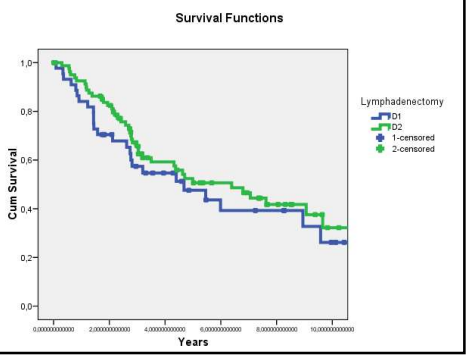
- Stage I+II (N0)
  - D1 : n = 122, 78%
  - D2 : n = 153, 77%

  p = ns



- Stage I+II (N1 in N2)
  - D1 : n = 47, 49%
  - D2 : n = 84, 51%

  p = ns



5-year survival (UKC Ljubljana)

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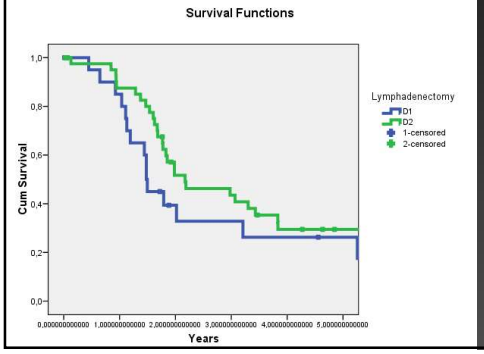
https://doi.org/10.1159/000227296

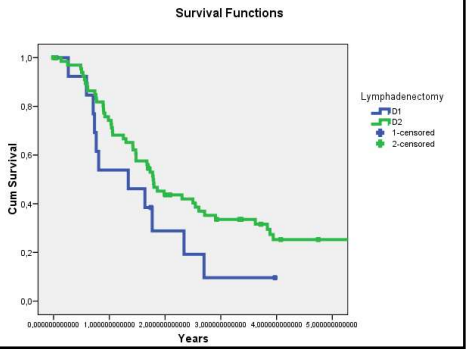
- Stage III (N0 in N1)
  - D1 : n = 20, 27%
  - D2 : n = 40, 33%

  p = 0.107



- Stage III (N2)
  - D1 : n = 13, 10%
  - D2 : n = 66, 30%

  p = 0.034



D2 lymphadenectomy

- D2 lymphadenectomy is a safe procedure for experienced surgical team.
- Better local control and staging.
- Potential benefit in subgroup with occult disease in D2 lymph nodes after D2 lymphadenectomy.

Conclusions

- Cancer specific mortality rate significantly lower in patients who undergo D2 rather than D1 lymphadenectomy.
- No evidence that D3 (paraaortic lymphadenectomy) confers a survival benefit on D2 dissection.
- D1 or D1+ lymphadenectomy is indicated for cT1N0.
- D2 for cN+ or cT2-T4 tumors.

Given that the pre and intraoperative diagnosis of lymph node metastasis remains unreliable, a D2 lymphadenectomy should be performed whenever nodal involvement is suspected.

Conclusions

- performance of a D2 lymphadenectomy provides the maximal benefit that can be achieved from a lymphadenectomy in gastric cancer for stages ≥IB
- D2 lymphadenectomy can improve disease specific survival in patients with resectable carcinoma, when increased incidence of postoperative mortality does not reduces its therapeutic benefit.

Multivisceral resections: pT4b tumor

UICC 8th ed. TNM classification:

Gastric cancer that invades adjacent structures (liver, colon, small intestine, adrenal, diaphragm, pancreas, spleen, kidney) is classified as pT4b.

- an important decrease in the patient's general condition and peritoneal (microscopic or macroscopic) dissemination.

Multivisceral resections: pT4b tumor

- not uncommon to interpret a CT scan as an invasion of adjacent organ (cT4b) and then confirm a desmoplastic reaction in the pathological specimen analysis.
- the challenge of evaluating tumor invasion is even greater when a tumor closely related to the pancreas
- accuracy of the radiological method: < 50%

Seevaratman R, Cardoso R, McGregor C et al. How useful is preoperative imaging for tumor, node, metastasis (TNM) staging for gastric cancer? A meta-analysis. Gastric Cancer. 2012;15 S3-18.

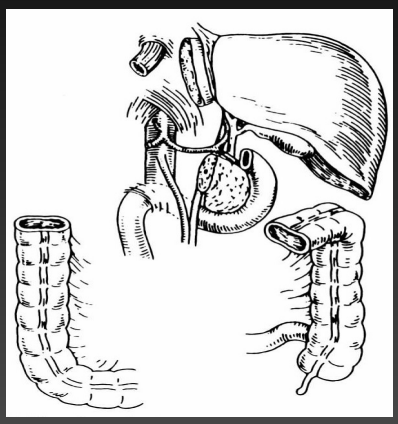
Cardoso R, Coburn N, Seevaratman R et al. A Systematic review and meta-analysis of the utility EUS for preoperative staging for gastric cancer. Gastric Cancer. 2012;15 Suppl 1:S19-26.

Multivisceral resections

- aggressiveness of the multiorganic surgery
- real benefit of multivisceral resection compared to palliative resections or derivative procedures ?
- multimodal treatment ?

Multivisceral resections

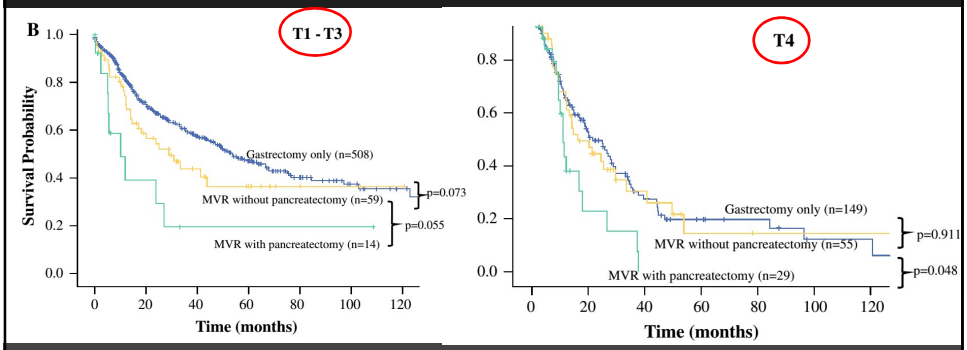
- **T4 tumor: R0 resection**
  - spleen, body and tail of pancreas, II and III. segment of the liver, transverse colon, right colon, duodenum with the had of pancreas.
  - LUAE (left upper abdominal exenteration).



Multivisceral Resection for Gastric Cancer: Results from the US Gastric Cancer Collaborative

Thuy B. Tran, MD[1], David J. Worhunsky, MD[1], Jeffrey A. Norton, MD[1], Malcolm Hart Squires III, MD[2],

Survival based on extent of resection: 159 pts

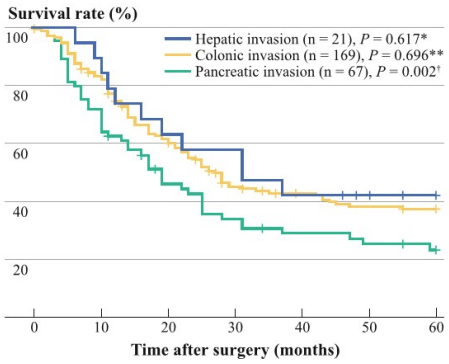


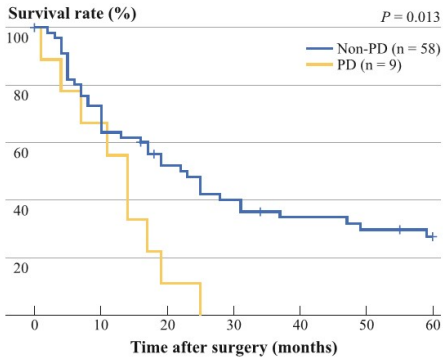
Ann Surg Oncol (2015) 22:S840–S847

Prognosis of Curatively Resected pT4b Gastric Cancer with Respect to Invaded Organ Type

Jae-Seok Min, MD[1], Sung-Ho Jin, MD[2], Sunhoo Park, MD[3], Sang-Bum Kim, MD[2], Ho-Yoon Bang, MD[4], and Jong-Inn Lee, MD[2]

Survival based on extent of resection: 243 pT4b pts.





Ann Surg Oncol (2012) 19:494–501

Conclusions

- Gastrectomy with MVR can be pursued in patients with locally advanced gastric cancer with the goal of R0 resection.
- Morbidity and mortality may be increased, but the benefit of attaining an R0 resection has a positive impact on overall patient survival.
- An attempt to identify true histological invasion before and during resection.
- In pT4b gastric cancer, pancreatic invasion the least favorable prognosis especially in cases requiring pancreaticoduodenectomy.
- Patient selection for MVR must take into account nodal status and the number of organs involved.
- More favorable after curative resection in patients without advanced lymph node stages (N2, N3a, and N3b)

VLOGA RADIOTERAPIJE PRI ZDRAVLJENJU RAKA ŽELODCA

Irena Oblak

Karcinom želodca

- Gre za bolezen s slabo prognozo;
- Bolezen je neresektabilna pri približno 50% bolnikih;
- Po radikalni operaciji se bolezen v 75% ponovi;
- 30 – 70% ponovitev je le lokalnih in/ali regionalnih.

1. Gunderson LL, Sosin H. Adenocarcinoma of the stomach: Areas of failure in a reoperation series (second or symptomatic look) clinicopathological correlation and implications for adjuvant therapy. Int J Radiat Oncol Biol Phys 1982.

2. Smalley SR, et al. Gastric surgical adjuvant radiotherapy consensus report: rationale and treatment implementation. Int J Radiat Oncol Biol Phys 2002.

3. Willett CG, Gunderson LL. Stomach. In: Perez CA, Brady LW, editors. Principles and practice of radiation oncology, 5th edition. Philadelphia: Lippincott-Raven Publishers; 2008.

Ponovitev bolezni po OP

Recurrences	Mean	Range
Locoregional - only	54%	(29-72%)
Locoregional - total	88%	(38-94%)
Distant - only	25%	(18-35%)

Gunderson et al. Int J Radiat Oncol Phys 1982; Smalley et al. Int J Radiat Oncol Phys 2002; Lim et al. Br J Cancer 2004

Zdravljenje

- Do leta 2000: le OP
- Leta 2001 smo uvedli adjuvantno RT+KT
- Leta 2006 smo uvedli predoperativno zdravljenje:

a). neresektabilni TU: KT+RT → OP

b). resektabilni TU: KT → OP → KT

Ni dokazov

- Katero kombinirano zdravljenje je najboljše?
- Ali je boljše poOP ali predOP zdravljenje?
- Ali je boljša predOP KT ali RT+KT?

Splošne usmeritve

- Za bolnike stadija ≥cT2N0: kombinirano zdravljenje;
- Raje predOP zdravljenje, predvsem pri:

1. Bulky T3-4
2. cN+
3. Linitis plastica

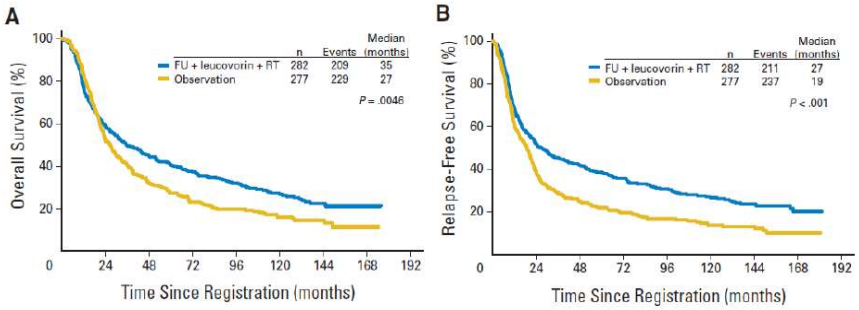
- OP→ ev. poOP zdravljenje za:

1. cT1-2
2. cN0
3. Non-bulky
4. Distalni TU

poOP RT+KT

SWOG 9008/INT 0116

	Surgery	CRT + surgery	p-value
Median DFS	19 months	30 months	0,001
3 year survival Median survival	40 % 27 months	50% 36 months	0,03



Macdonald et al. N Engl J Med 2001
Smalley et al. J Clin Oncol 2002

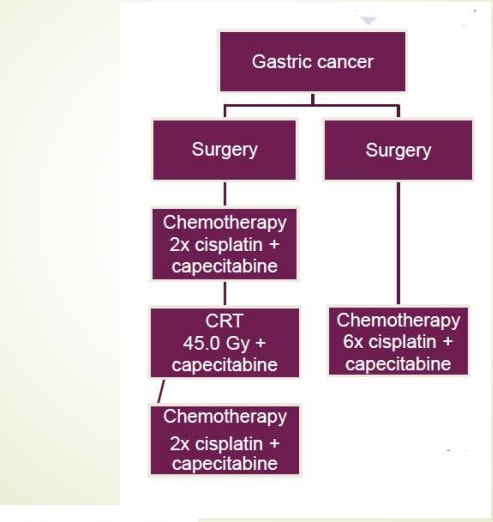
poOP zdravljenje

- **RT+KT** (FOLFOX, ECF, ECX ali derivati 5-FU)
- Lahko le KT (CAPOX 6 mesecev), če:

1. D2 limfadenektomija
2. ≥16 lgl
3. pN0
4. pT2-3

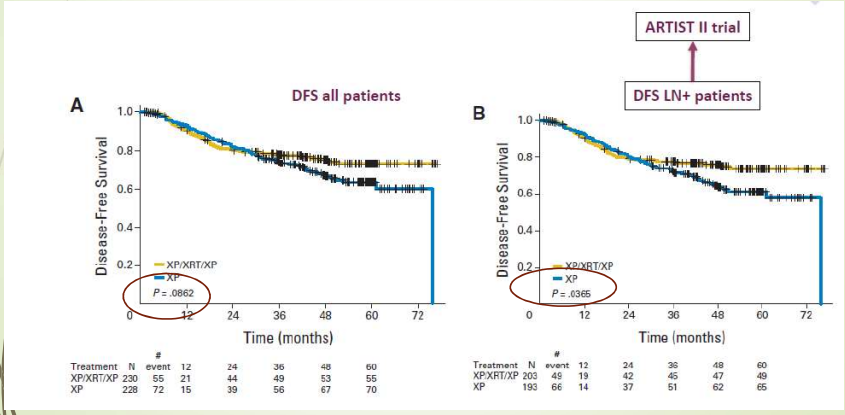
1. *Mcdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Eng J Med 2001; 345-725.*
2. *Kim S, Lim DH, Lee J, et al. An observation study suggesting clinical benefit for adjuvant postoperative chemoradioation in a population of over 500 cases after gastric resection with D2 nodal dissection for adenocarcinoma of the stomach. Int J Radiat Oncol Biol Phys 2005*
3. *Noh SH, Park SR, Yang HK, et al. Adjuvant capecitabin plus oxaliplatin for gastric cancer after D2 gastrectomy (CLASSSIC): a 5-year follow-up of an open-label, randomised phase 3 trial. Lancet Oncol 2014; 15:1389.*

ARTIST raziskava



Lee et al. J Clin Oncol 2012

ARTIST raziskava



Metaanaliza poOP KT vs. RT+KT

- poOP RT+KT:

1. ↑ DFS_5
2. ↓ LR
3. Trend ↑OS

Dai Q, Jiang L, Lin RJ, et al. Adjuvant chemoradiotherapy versus chemotherapy for gastric cancer: a meta-analysis of randomized controlled trials. J Surg Oncol 2015; 111:277.

Indikacija za poOP zdravljenje pri pT2pN0:

1. < D2 limfadenektomija
2. ≤ 16 lgl
3. G3
4. Limfovaskularna invazija ali
5. Perinevralna invazija

PreOP zdravljenje

PREDNOSTI:

- Downstaging : ↑R0 resekcij;
- Uničenje mikro-zasevkov;
- Izboljšanje sy in znakov, ki jih povzroča TU;
- ↓ toksično, kot poOP

PreOP zdravljenje

POMANJKLIVOSTI:

- Možen progres med preOP TH
- rizik poOP morbiditete?

PredOP zdravljenje s KT

- MAGIC trial (3xKT→OP→3xKT)
- FLOT4-AIO trial (4xKT→OP→4xKT):
- ↑pKR (16% vs 8%)
- ↑OS: 50 vs 35 mes. in S3: 57 vs 48%

1. *Cunningham, et al.Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. New England Journal of Medicine 2006.*
2. *Al Batran S-E, Homann N, Schmalenberg H, et al. Perioerative chemotherapy with docetaxel, oxaliplatin, and fluorouracil/leucovorin (FLOT) versus epirubicin, cisplatin, and fluorouracil or capecitabin (ECF/ECX) for resectable gastric cancer or gastroesophageal junction (GEJ) adenocarcinoma (FLOT4-AIO): A multicenter, randomized phase 3 trial (abstract). J Clin Oncol 35, 2017 (suppl; abstr 4004).*

Ali je boljša poOP RT+KT ali periOP KT?

Gastric Cancer Adjuvant Therapy
MAGIC and 0116

	S alone	CMT
5 yr survival		
0116	26%	44%
MAGIC	23%	36%
Local relapse		
0116	19%	7%
MAGIC*	21%	14%

*24% of patients who died had LR prior to death

CAN MAGIC BE COMPARED TO INT0116?

	MAGIC[1] (N=503)		INT116[2] (N=556)	
	Peri-op chemo + surgery N=250	Surgery only N=253	Post-op chemoRT + surgery N=282	Surgery only N=277
2 year survival	50%	41%	58%*	50%*
5 year survival	36%	23%	40%*	26%*
Median survival	24 months	20 months	35 months	27 months
Hazard ratio (95% CI)	0.75 (0.60-0.93) P=0.009		0.76 (0.62-0.93) P=0.006	

Direct comparison of results is difficult due to different inclusion criteria and different time of randomization.

[1] Cunningham NEJM 2006
[2] MacDonald NEJM 2001; 2004 GI Cancers Symposium

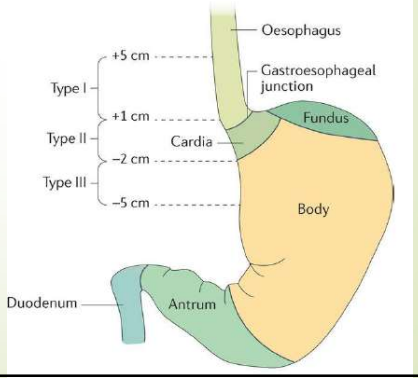
*Estimated from curve

Dutch Colorectal Cancer Group "CRITICS-study": primerjava poOP RT+KT in MAGIC raziskave

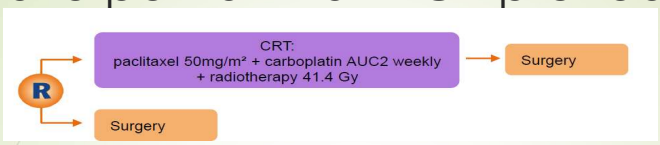
- Randomizacija
  - 3x ECC → OP → 3x ECC
  - 3x ECC → OP → poOP RT+KT
- ≥ 87% le D1 limfadenektomijo;
- ↓LR (11% vs 15%), ni razlik v DFS;
- Le 50% dokončalo zdravljenje po protokolu, vsi predOP KT, responder/ nonresponder?, ↑ delež bolnikov z nizkim stadijem, ki ima majhno korist od RT;
- Poteka CRITICS II trial

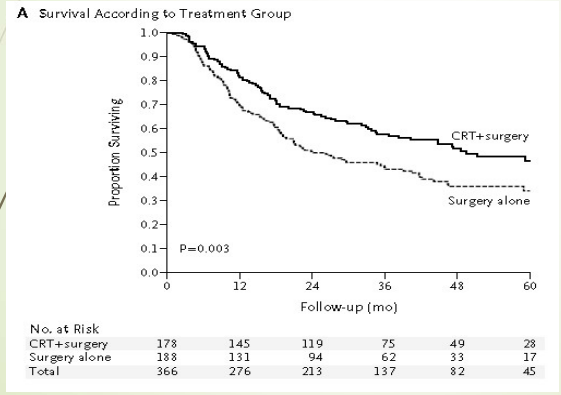
PredOP RT+KT

- Za zgornjo 1/3 želodca
- Za srednjo in spodnjo 1/3 želodca?



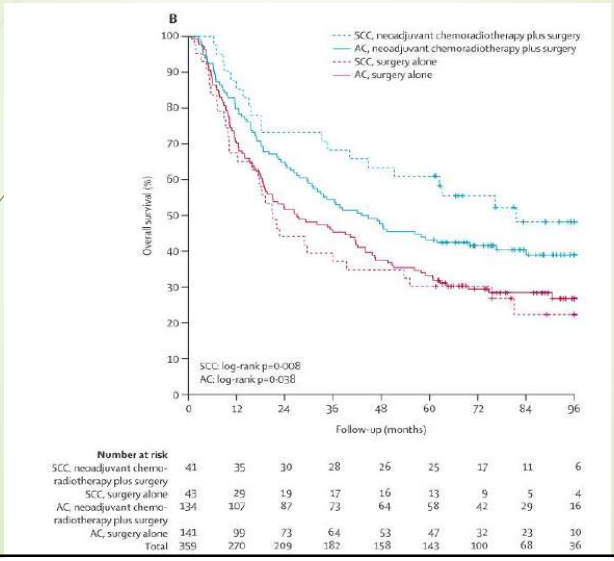
CROSS raziskava: PreOP RT+KT pri raku požiralnika in GE prehoda



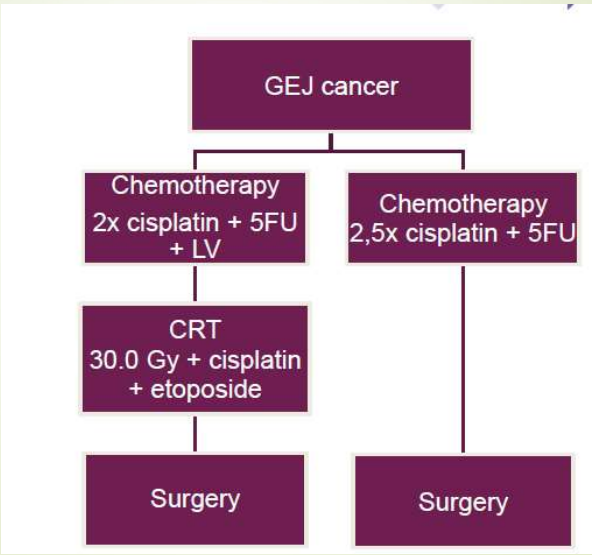


Shapiro , van Lanschot JJB, Hulshof MCCM, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol 2015; 16(9): 1090-8.

CROSS raziskava: PreOP RT+KT pri raku požiralnika in GE prehoda



POET raziskava



PredOP RT+KT > KT pri GEJ in kardiji

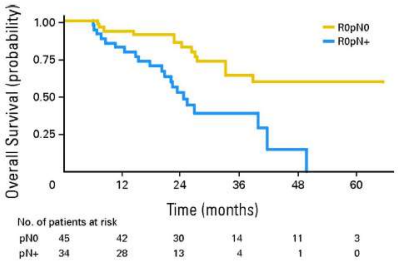
- ↑ R0 resekcijo;
- ↑ pN0;
- ↑ S;
- Ne ↑ poOP mortalitete

- Stahl M, Walz MK, Riera-Knorrenschild J, et al. Preoperative chemotherapy versus chemoradiotherapy in locally advanced adenocarcinomas of the oesophagogastric junction (POET): Long-term results of a controlled randomised trial. Eur J Cancer 2017; 81:183.

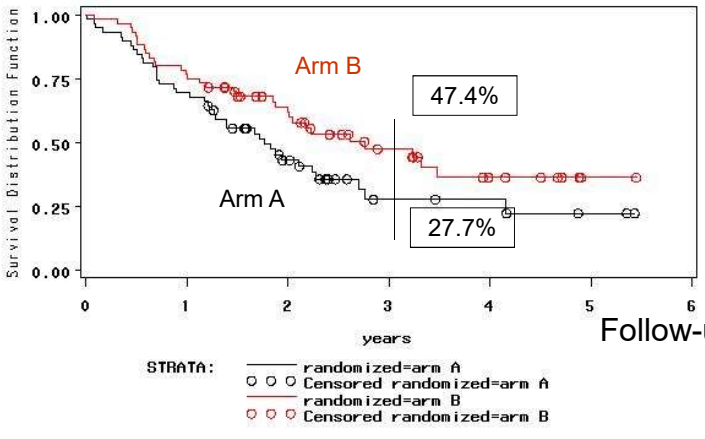
POET raziskava

	Arm A		Arm B		P-value
Treatment	No.	%	No.	%	P
Patients with resection	49	100.0	45	100.0	
pT0 N0 M0	1	2.0	7	15.6	.03*
pT1-4 N0 M0	17	34.7	22	48.9	
pT0-4 N0 M0†	18	36.7	29	64.4	.01*
pTall N M0	27	55.1	14	31.1	
pTall N M1	4	8.2	2	4.5	

Fisher's exact test.
† Bold text indicates data summarized from patients with pT0 N0 M0 and pT1-4 N0 M0.



POET raziskava-OS

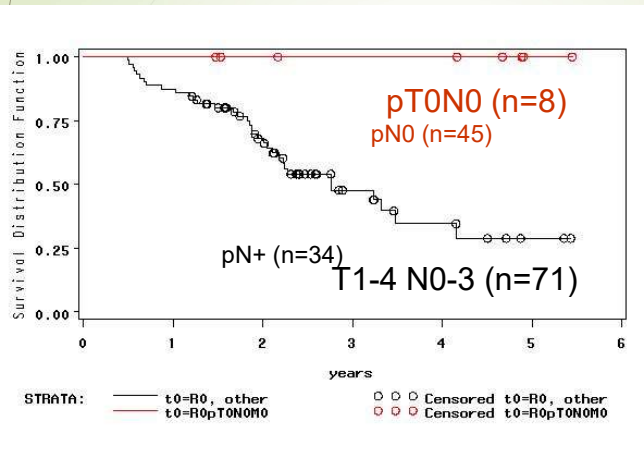


Logrank
p = 0.07

Follow-up 45.6 months

Stahl M, JCO 27:851, 2009

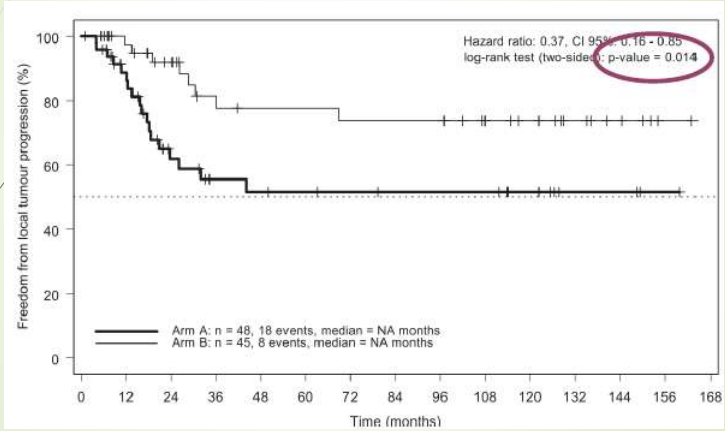
POET raziskava: OS
R0 pT0 pN0 vs. R0 T1-4 N0-3



Survival at
3 years:
T0N0 100%
other 47.7%
p = 0.01

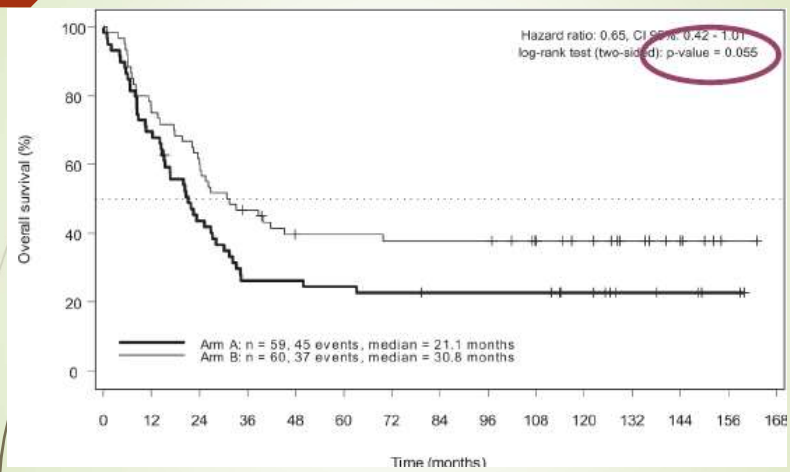
Stahl M, JCO 27:851, 2009

POET raziskava-LC



Stahl et al. Eur J Cancer 2017

POET raziskava - OS



Stahl et al. Eur J Cancer 2017

POET raziskava - patohistološki rezultati

	CT + S	CRT + S	Logrank p
T0-T4 **N0** M0	36.7%	64.4%	0.01
T0-T4 **N+** M0	55.1%	33.1%	ns
Tall Nall M1	8.2%	4.4%	ns

Stahl M, JCO 27:851, 2009

POET raziskava - patohistološki rezultati

	CT + S	CRT + S	Logrank p
T0 N0 M0	2.0%	15.6%	0.03
T0-T4 N0 M0	34.7%	48.9%	ns

Stahl M, JCO 27:851, 2009

Australasian faza II

	CT + S N=36	CRT + S N=39	Logrank p
R1-Resection	11%	0	0.04
Major Response	8%	31%	0.01
pT0N0	0	13%	0.02
Local recurrence	28%	18%	ns
5 year survival	36%	45%	ns

Burmeister BH, Eur J Cancer 47:345-60, 2011

Neradikalne resekcije

Raziskava	KT	KT+RT	P-value
German	8/52 (15,4%)	2/49 (4,1%)	0,01
Australasian	4/36 (11%)	0/39 (0%)	0,04

Stahl M, J Clin Oncol 2009
Burmeister BH, Eur J Cancer 2011

PredOP RT+KT pri raku želodca

- Resektabilni rak: 70% R0 resekcij, 30% pKR, sig. preživetje;
- Neresektabilni rak: 52% R0,14% pKR;
- Samo RT (brez KT): R0 resekcije (80%/62%), 10-letno preživetje: 20%/13%, 11% pKR
- Morbiditeta in mortaliteta nista

Ajani JA, et al.. Multi-institution trial of predoperative chemoradiotherapy in patients with potentially resectable gastric carcinoma. J Clin Oncol 2004.

Hazard L, et al.. Role of radiation therapy in gastric adenocarcinoma. World J Gastroenterol 2006.

Klautke G, et al.Neoadjuvant radiochemotharapy in locally advanced gastric carcinoma. Strahlenther Oncol, 2004.

Ajani JA, et al. Pacilitaxel-based chemoradiotherapy in localized gastric carcinoma.: degree of pathologic responce and not clinical parameters dictated patients outcome J Clin Oncol 2005.

Okawara GS, et al, A phase II trial of preoperative chemotherapy and chemoradiotherapy for potentially resectable adenocarcinoma of the stomach (RTOG 99-04). J Clin Oncol 2005.

Rivera F, et al. Phase II trial of preoperative irinotecan-cisplatin followed by concurrent irinotecan-cisplatin and radiotherapy for resectable locally advanced gastric and GE junction adenocarcinoma. Int J Radiat Oncol Biol Phys.2009.

Zhang Z.X., et al. Randomized clinical trial on the combination of preoperative irradiation and surgery in the treatment of adenocarcinoma of gastric cardia (AGC)--report on 370 patients. International Journal of Radiation Oncology, Biology, Physics.1998

Prednosti predoperativne RT+KT pred pooperativno RT+KT pri raku želodca

- Zdravimo ↑ delež bolnikov
- ↑ oksigeniranost tkiv → učinkovitost RT in KT
- ↓ možnost ostanka TU celic v OP polju
- ↓ razvoj M+(takojšna KT)
- vrisovanje RT volumnov natančnejše (lokacija TU znana)
- ↓ toksičnih pojavov (zdravimo delež bolnikov)
- ↓ bolnikove težave, PS in kvaliteto življenja
- ↑učinkovito?

Ajani JA, et al. Multi-institutional trial of preoperative chemoradiotherapy in patients with potentially resectable gastric carcinoma. J Clin Oncol. 2004

Hazard L, et al. Role of radiation therapy in gastric adenocarcinoma. World J Gastroenterol 2006.

Klautke G, Fortzik T, Kudwig K, Ketterer P, Klar E, Fiedkan R.Neoadjuvant radiochemotharapy in locally advanced gastric carcinoma. Strahlenther Oncol 2004

Neresektabilni rak želodca brez oddaljenih zasevkov: optimalno zdravljenje?

- predOP KT
- predOP RT+KT
- Kombinacija

- V okviru raziskav;
- Natančen restaging → KRG eksploracija (bulky N+, ascites)

Zaključki

- Tako predOP KT, kot RT+KT omogočata downstaging in ↑ R0 resekcij ter ↑ preživerje v primerjavi s samo OP;
- Raziskavi POET in avstral-azijska: predoperativna RT+KT boljše rezultate v primerjavi s predoperativno KT v smislu ↑ R0-resekcij, ↑ TU regresa in ↑ št. yN0-stadija;
- Rezultati metaanalize (Ronellenfitsch) kažejo, da predoperativna RT+KT ↓ smrtnost zaradi tumorja za 10 %, v primerjavi s preoperativno kemoterapijo;
- Nujna je randomizirana raziskava, ki bo primerjala obe vrsti zdravljenja: TOP GEAR raziskava.

ONKOLOŠKI INŠTITUT
INSTITUTE OF ONCOLOGY
LJUBLJANA

Zdravljenje metastatskega raka želodca

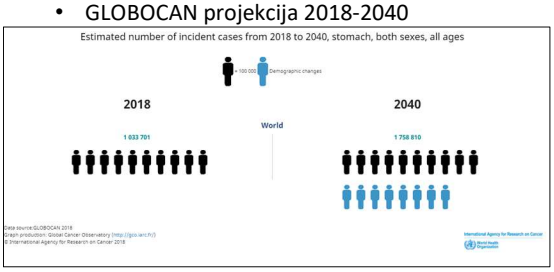
Dr. Neva Volk, dr. med.
Sektor za internistično onkologijo
Onkološki inštitut

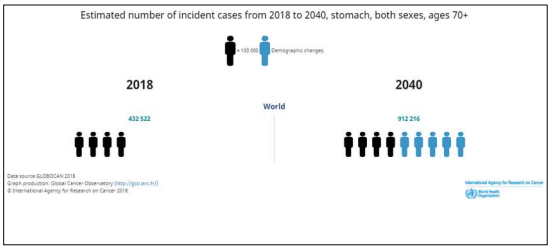
Šola tumorjev prebavil 2019, Ljubljana, 22.11.2019

Rak želodca

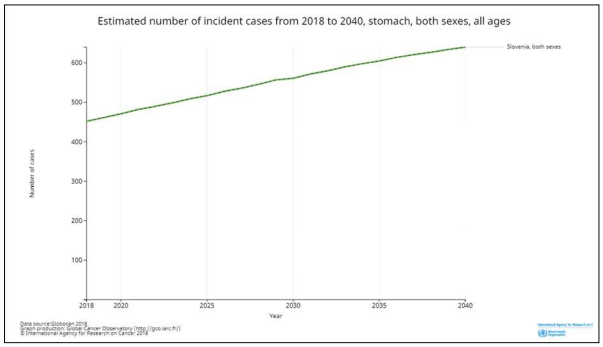
- 2018 : globalno > 1 milijon novozbolelih
- 5. najpogostejši rak
- 3. najpogostejši vzrok smrti zaradi raka
- >40% bolnikov z razsejano boleznijo ob postavitvi diagnoze (40-80%)
- Povprečna starost ~ 68 let

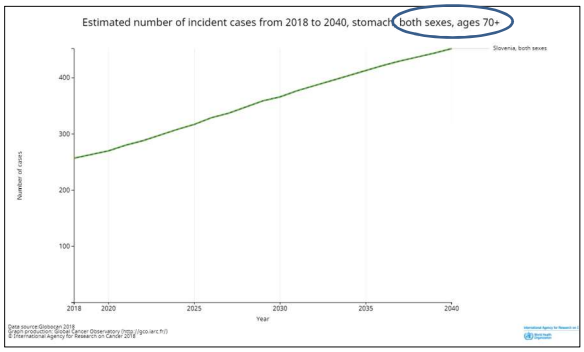
- GLOBOCAN projekcija 2018-2040





Želodčni rak v RS, *2018-2040 GLOBOCAN*





Cilji zdravljenja metastatskega raka želodca

Podaljšanje preživetja

Kvaliteta življenja

Zmanjšanje simptomov
Čim manj sopojavov zdravljenja

Oligometastatska bolezen – konverzija v kirurško zdravljenje –možnost ozdravitve?

Rak želodca – glavne raziskave f. III. citostatskega zdravljenja

Clinical trial	N	Treatment	OS		PFS		ORR	P value
(A) First-line chemotherapy treatment								
The V325 Trial *Van Cutsem* *J Clin Oncol 2006*	445	DPF PF	9.2 m 8.6 m	HR 1.29 p=0.02	5.6 m* 3.7 m	HR 1.47 p<0.01	37% 25%	0.01
The Randomized ECF for Advanced and Locally Advanced Esophagogastric Cancer 2 (REAL-2) Trial *Cunningham* *NEJM 2008*	1002	EPF EPC EOF EOC	9.9 m 9.9 m 9.3 m 11.2 m	Non-inferiority meet	6.2 m 6.7 m 6.5 m 7 m		40.7% 46.4% 42.4% 47.9%	
The ML17302 Trial *Kang* *Ann Oncol 2009*	316	CP FP	10.5 m 9.3 m	HR 0.85 p=0.008	5.6 m 5.0 m	HR 0.81 p<0.01	46% 32%	0.020
The FLAGS Trial *Ajani* *J Clin Oncol 2010*	1053	P-S1 P-F	8.6 m 7.9 m	HR 0.92 p=0.2	4.8 m 5.5 m	HR 0.99 p=0.92	29.1% 31.9%	0.40
The French Intergroup Trial *Guimbaud* *J Clin Oncol 2014*	416	EPC FOLFIRI	9.49 m 9.72 m	HR 1.01 p=0.95	5.29 m 5.75 m	HR 0.99 p=0.96	39.2% 37.8%	
(B) Second-line treatment and beyond								
The Arbeitsgemeinschaft Internistische Onkologie (AIO) Trial *Thuss-Patience* *Eur J Can 2011*	40	CPT-11 BSC	4.0 m 2.4 m	HR 0.48 p=0.012	2.6 m –		0% –	
The Salvage Chemo Trial *Kang* *J Clin Oncol 2012*	188	D/CPT-11 BSC	5.3 m 3.8 m	HR 0.65 p=0.007	–		13% –	
The COUGAR-02 Trial *Ford* *Lancet Oncol 2014*	168	D BSC	5.2 m 3.6 m	HR 0.67 p=0.01			7% –	
The West Japan Oncology Group (WJOG) Trial 4007 (WJOG 4007) *Hironaka* *J Clin Oncol 2013*	223	Pac CPT-11	9.5 m 8.4 m	HR 1.13 p=0.38	3.6 m 2.3 m	HR 1.14 p=0.33	20.9% 13.6%	0.24

Alsina M, et al. ESMO Open 2019;4:e000521. doi:10.1136/esmoopen-2019-000521

Metastatski rak želodca - prva linija zdravljenja

- KT podaljša preživetje[1]
- KT izboljša kontrolo simptomov napredovale bolezni[1]
- Starejši bolniki (>70 let) –korist od KT[2]
- Kombinacije so učinkovitejše kot monoterapija s 5FU[1]

Standard:
kombinacija derivat platine + fluoropirimidin[1]

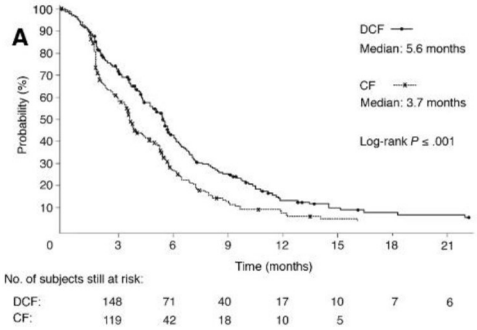
1. Wagner et al. Cochrane Database Syst Rev 2010 Mar 17;(3):CD004064
2. Trumper et al. Eur J Cancer 2006; 42: 827-34;3.

Metastatski rak želodca - prva linija zdravljenja

- Oxaliplatin enako učinkovit kot cisplatin [1,2]
  (prednost pri starejših)
- Kapecitabin in S-1 enako učinkovita kot 5-FU[3]
- Tretje zdravilo poveča učinkovitost in tudi toksičnost [1,4,5]

1. Al-Batran SE et al. J Clin Oncol 2008
2. Cunningam et al. N Engl J Med 2008; 258:36-46
3. Ajani JA et al. J Clin Oncol 2010; 28: 1547-1553
4. Van Cutsem et al. J Clin Oncol2006; 24: 4991-7
5. Kang YK et al. Ann Oncol 2009

Metastatski rak želodca – prva linija
Docetaksel kot 3. zdravilo : raziskava TAX325



Toksičnost gr. 3/4	DCF	CF
nevtropenija	82%	57%
Feb. nevtropenija	**29%**	**12%**
stomatitis	21%	27%
driska	19%	8%
letargičnost	19%	14%
Vsi	69%	59%

RR	**37% vs 25%**	P=0,01
TTP	**5,6 vs 3,7 *mes.***	p≤ 0,01
mOS	**9,2 vs 8,6 mes.**	p=0.02
2-letno preživetje	**18,4% vs 8,8%**	

Van Cutsem et al. J Clin Oncol 2006; 24:4991-7

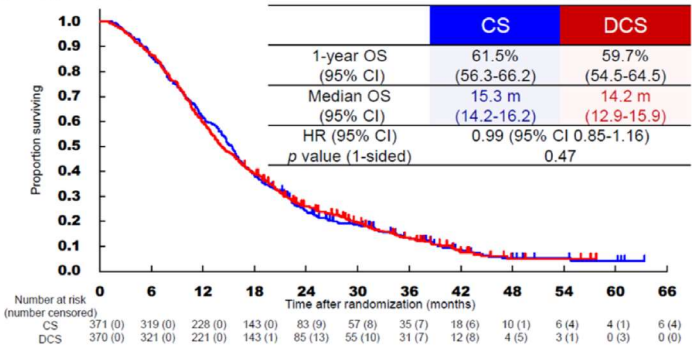
Metastatski rak želodca – prva linija

Dvojček ali trojček - DC vs. DCS Japonska

1ST-LINE - JAPAN

Doublet or Triplet?

Primary endpoint



Overall survival

	CS	DCS
1-year OS (95% CI)	61.5% (56.3-66.2)	59.7% (54.5-64.5)
Median OS (95% CI)	15.3 m (14.2-16.2)	14.2 m (12.9-15.9)
HR (95% CI)	0.99 (95% CI 0.85-1.16)	
p value (1-sided)	0.47	

Yamada Y et al. Lancet Gastroenterol 2019;4:501–510

Kombinacija z epirubicinom?

Ne!

„Whether the survival benefit for three-drug combinations including cisplatin, 5-FU, and epirubicin as compared to the same regimen without epirubicin is still valid when second-line therapy is routinely administered and when cisplatin is replaced by oxaliplatin and 5-FU by capecitabine is questionable.

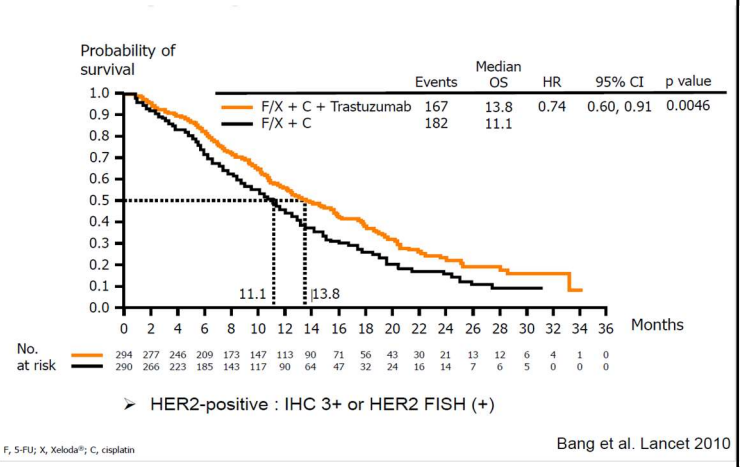
Furthermore, the magnitude of the observed survival benefits for the three-drug regimens is not large enough to be clinically meaningful as defined recently by the American Society for Clinical Oncology (Ellis 2014). „*

*Wagner AD et al. Cochrane Database Syst Rev. 2017;8:CD004064. Epub 2017 Aug 29

HER2-pozitivni rak želodca
TOGA - Trastuzumab + KT

- HER2 pozitivni: ~16%
- Proksimalni > distalni
- Intestinalni >> difuzni

- Samo za prvo linijo pri Her-2 pozitivnih tu.
- Problem: klonalna hete-rogenost mRŽ, razvoj rezistence



➢ HER2-positive : IHC 3+ or HER2 FISH (+)

F, 5-FU; X, Xeloda®; C, cisplatin

Bang et al. Lancet 2010

Kombinacija z irinotekanom?
Da!

- „In contrast to the comparisons in which a survival benefit was observed by adding a third drug to a two-drug regimen at the cost of increased toxicity, the comparison of regimens in which another chemotherapy was replaced by irinotecan was associated with a survival benefit (of borderline statistical significance), but without increased toxicity. For this reason irinotecan/5-FU-containing combinations are an attractive option for first-line treatment.“

*Wagner AD et al. Cochrane Database Syst Rev. 2017;8:CD004064. Epub 2017 Aug 29

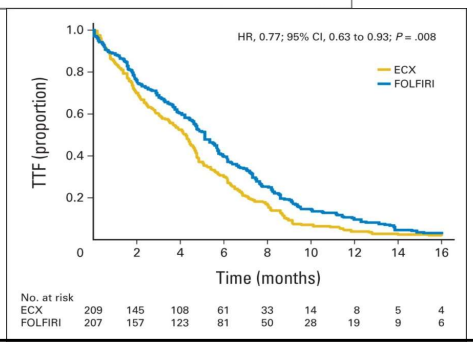
Metastatski rak želodca –irinotekan v prvi liniji
FFCD-GERCOR-FNCLCC 03-17; FOLFIRI vs ECF

Table 2. Efficacy Results for PFS and OS

Variable	ECX Arm (n = 209) No.	ECX Arm (n = 209) %	ECX Arm (n = 209) 95% CI	FOLFIRI Arm (n = 207) No.	FOLFIRI Arm (n = 207) %	FOLFIRI Arm (n = 207) 95% CI	P
PFS, months							.96*
Median	5.29			5.75			
Range	4.53-6.31			5.19-6.74			
24-month survival		5.03	2.46 to 8.97		2.76	1.01 to 6.03	
OS, months							.95*
Median	9.49			9.72			
Range	8.77-11.14			8.54-11.27			
24-month survival		11.17	7.03 to 16.36		10.71	6.51 to 16.09	

Abbreviations: ECX, epirubicin, cisplatin, and capecitabine; FOLFIRI, fluorouracil, leucovorin, and irinotecan; OS, overall survival; PFS, progression-free survival.
*Log-rank test.

Ni razlike v preživetju:
9.5 vs. 9.7 mes. (p=0.95)



Guimbaud R et al. J Clin Oncol 2014 32:31, 3520-3526

Raziskave s tarčnimi zdravili

Recent phase 3 of new agents for GC

Target	Trial/Author	Line	Screening	Agent	control	Endpoint	Results	difference mOS (HR)
HER2	ToGA	1st	HER2	Trastuzumab	(+chemo)	OS	Positive	+2.7 (HR 0.74)
HER2	Logic	1st	HER2(FISH)	Lapatinib	PBO (+chemo)	OS	Negative	+1.7 (HR 0.91)
HER2	JACOB	1st	HER2	Pertuzumab	PBO (+Chemo+T)	OS	Negative	+3.3 (0.84)
HER2	TyTAN	2nd	HER2(FISH)	Lapatinib	(+chemo)	OS	Negative	+3 (HR 0.84)
HER2	GATSBY	2nd	HER2	T-DM1	Taxanes	OS	Negative	-0.7 (HR 1.15)
EGFR	REAL-3	1st	-	Panitumumab	(+chemo)	OS	Negative	-2.5 (HR 1.37)
EGFR	EXPAND	1st	-	Cetuximab	PBO (+chemo)	PFS	Negative	-1.3 (HR 1.0)
EGFR	ENRICH	2nd	EGFR(IHC)	Nimotuzumab	(+chemo)	OS	Negative	
mTOR	GRANITE-1	2nd/3rd	-	Everolimus	PBO	OS	Negative	+1.05 (HR 0.9)
mTOR	GRANITE-2	2nd	-	Everolimus	PBO (+chemo)	OS	Negative	+1.0 (HR 0.92)
HGF	RILOMET1	1st	MET(IHC)	Rilotumumab	PBO (+chemo)	OS	Negative	-2.9 (HR 1.36)
MET	METgastric	1st	MET(IHC)	Onartuzumab	PBO (+chemo)	OS	Negative	-0.3 (HR 0.82)
VEGF-A	AVAGAST	1st	-	Bevacizumab	PBO (+chemo)	OS	Negative	+2 (HR 0.87)
VEGFR2	RAINFALL	1st	-	Ramucirumab	PBO (+chemo)	OS	Negative	+0.4 (HR 0.96)
VEGFR2	REGARD	2nd	-	Ramucirumab	PBO	OS	Positive	+1.4 (HR 0.776)
VEGFR2	RAINBOW	2nd	-	Ramucirumab	PBO (+chemo)	OS	Positive	+2.2 (HR 0.807)
VEGFR2	Li, et al	3rd	-	Apatinib	PBO	OS	Positive	+1.8 (HR 0.71)
PARP	GOLD	2nd	ATM(IHC)	Olaparib	PBO (+chemo)	OS	Negative	+1.9 (HR 0.79)
STAT3	BRIGHTER	2nd	-	Napabucasin	PBO(+chemo)	OS	Negative	+0.3 (HR 1.01)
PD1	Keynote061	2nd	PDL1 (IHC)	Pembrolizumab	Paclitaxel	OS	Negative	+0.8 (HR 0.82)
PD1	JAVELIN300	3rd	-	Avelumab	Iri/taxanes/BSC	OS	Negative	
PD1	ATTRACTION-2	3rd-	-	Nivolumab	PBO	OS	Positive	+1.2 (HR 0.63)

Only 5 / 22 positive trials
Difference in median survival: 1.2~2.7ms (vs. placebo)

Presented By Kohei Shitara at 2018 ASCO Annual Meeting

HER 2

	Study	Line	N	Treatment Arms	OS (m)	Hazard Ratio	
1st Line	TOGA[1]	1st	584	Cape-P/FP Cape-P/FP-trastuzumab	11.1 13.8	HR = 0.74 p < 0.01	✓
	LOGIC[2]	1st	545	XELOX XELOX + lapatinib	10.5 12.2	HR = 0.91 p = 0.34	✗
	JACOB[3]	1st	780	Cape-P/FP-trastuzumab-placebo Cape-P/FP-trastuzumaz- pertuzumab	14.2 17.5	HR = 0.84 p = 0.0565	✗
2nd Line	TyTAN[4]	2nd	261	Paclitaxel Paclitaxel + lapatinib	8.9 11.0	HR = 0.54 p = 0.21	✗
	GATSBY[5]	2nd	415	T-DM1 Taxane	7.9 8.6	HR = 1.14 p = 0.31	✗
	WJOG7112G [6] (Ph II)	2nd	91	Paclitaxel + trastuzumab Paclitaxel	10.20 9.95	HR= 1.230 p = 0.199	✗

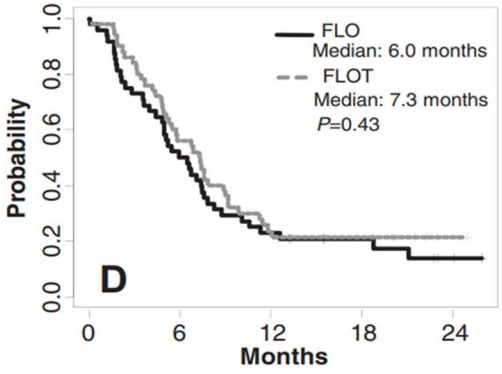
1. Bang Lancet 2010, 2. Hecht J Clin Oncol 2016, 3. Tabernero Lancet Oncol 2018, 4. Satoh J Clin Oncol 2014, 5. Thuss-Patience Lancet Oncol 2017, 6. Makiyama ASCO GI2018

Metastatski rak želodca – prva linija

Dvojček ali trojček pri starejših - FLOT 65+

FLOT65+ (N 143)

FLO/FLOT



FLOT več toksičnosti gr 3- 4

81.9% vs 38.6%; P < .001

Poslabšanje QoL > 10 točk

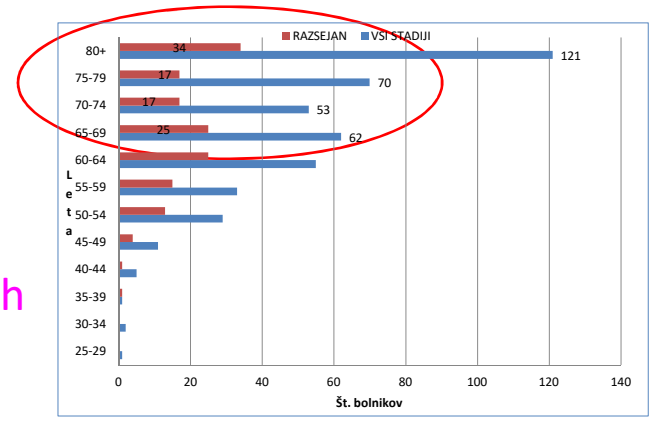
47,5% vs 20,5%

Al-Batran S et al., Eur J Cancer 2013; 49: 2823-2831

Incidenca raka želodca po starostnih skupinah in stadijih, RS 2016

Starejši od 65 let:

- 69% (306/443) vseh novih bolnikov z RŽ
- 61% (93/152) vseh novih bolnikov z metastatskim RŽ



mRŽ: 40-80% bolnikov ob postavitvi diagnoze

GO2 raziskava – KT v polnih ali reduciranih odmerkih?

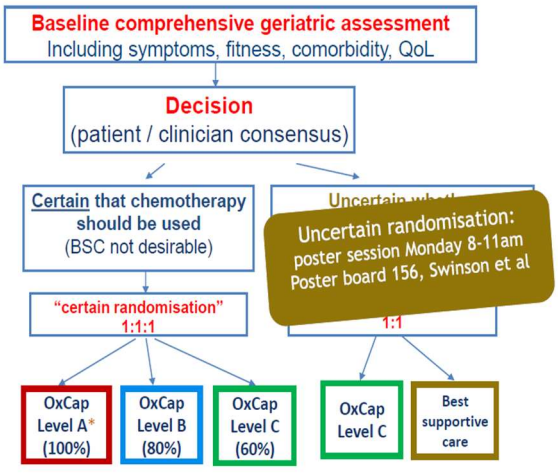
Recruitment
(certain randomisation)
- 512 patients
- 2014 – 2017
- 61 UK hospitals

Trial design

Phase III, randomised, multi-centre, prospective, controlled, open label, non-inferiority trial

Eligibility
Not fit for full-dose 3-drug chemotherapy, but suitable for reduced intensity chemotherapy.

Follow-up
Total 1 year; 9 weekly imaging and PROMs



*Oxaliplatin 130mg/m^2 day 1 of a 21 day cycle Capecitabine 625mg/m^2 bd continuously - given until progression

Hall P et al., ASCO 2019; #4006

GO2 raziskava – značilnosti bolnikov

		OxCap Level A* (100%)	OxCap Level B (80%)	OxCap Level C (60%)	
		Level A (n=170)	Level B (n=171)	Level C (n=173)	Total (n=512)
Median age (range)		76	76	77	76 (51 - 96)
Male gender		77%	75%	72%	75%
Site of primary	Oesophagus	32%	42%	39%	38%
	GO junction	29%	19%	22%	23%
	Gastric	38%	37%	37%	37%
Squamous histology		12%	11%	12%	11%
Trastuzumab treated		4%	6%	6%	5%
Distant metastases		68%	69%	70%	69%
Performance Status ≥2		31%	32%	31%	31%
Severely frail (≥3 domains)		61%	56%	58%	58%

Hall P et al., ASCO 2019; #4006

GO2 raziskava - rezultati PFS

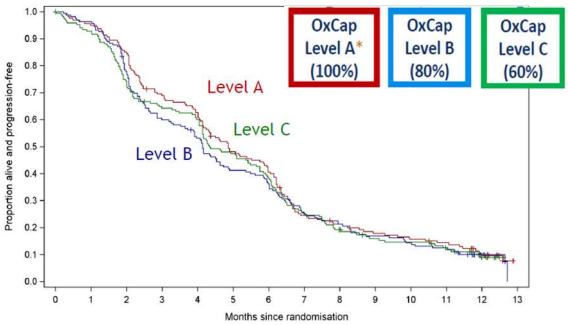
Results: step 1 - non-inferiority is confirmed

Primary endpoint
Progression Free Survival

Adjusted hazard ratios

Level B vs A 1.09 [95% CI 0.89 - 1.32]

Level C vs A 1.10 [95% CI 0.90 - 1.33]



The non-inferiority boundary of 1.34 is excluded, so non-inferiority is confirmed

Hall P et al., ASCO 2019; #4006

Preživetje

Results: step 1 - non-inferiority

Overall survival

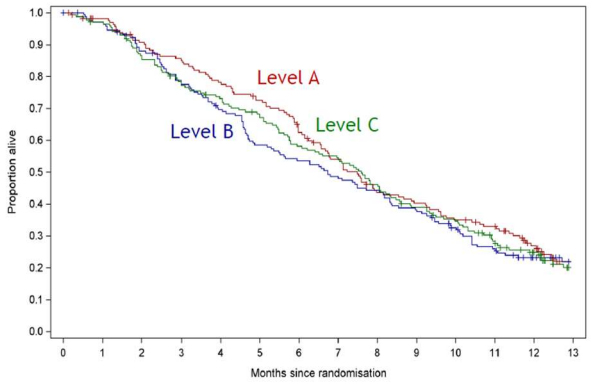
Median survival

Level A 7.5 months

Level B 6.7 months

Level C 7.6 months

OxCap Level A* (100%) | OxCap Level B (80%) | OxCap Level C (60%)



Hall P et al., ASCO 2019; #4006

Zadovoljstvo bolnikov

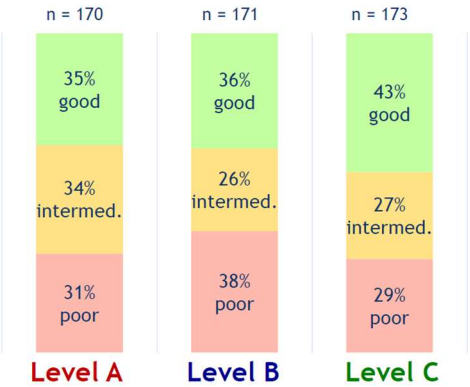
Overall Treatment Utility

Overall treatment utility favours **Level C**, which had the highest percentage of Good and lowest percentage of Poor OTU scores

Adjusted odds ratios (trend for better OTU)

Level B vs A 0.87 [95% CI 0.59 - 1.29]

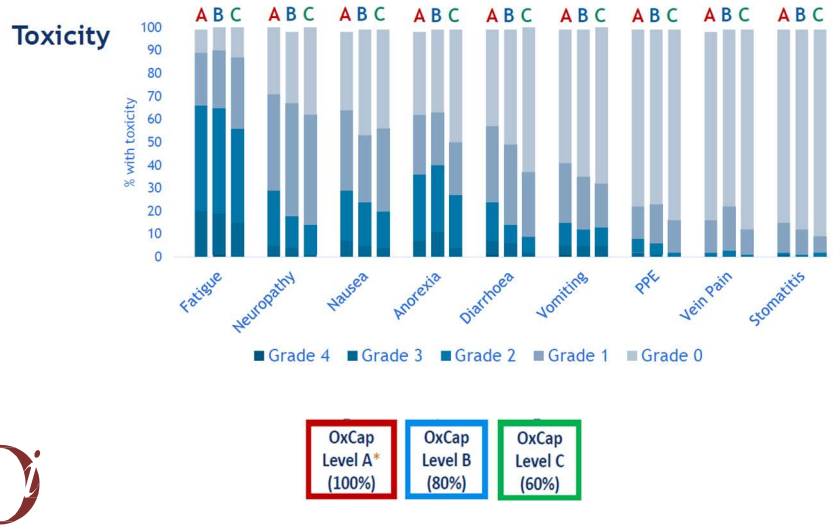
Level C vs A 1.24 [95% CI 0.84 - 1.84]



OxCap Level A* (100%) | OxCap Level B (80%) | OxCap Level C (60%)

Hall P et al., ASCO 2019; #4006

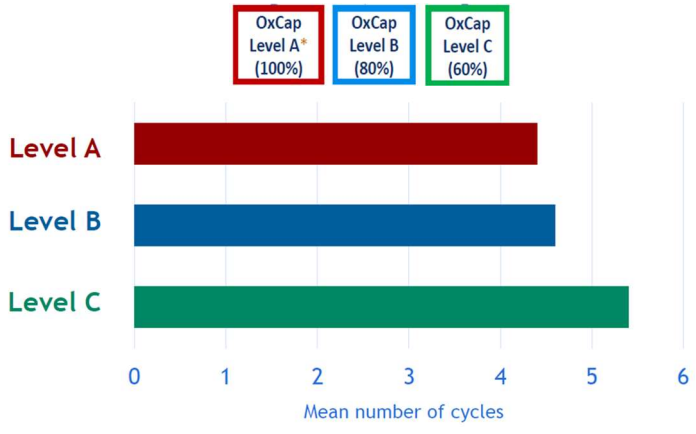
Neželeni učinki



OxCap Level A* (100%) | OxCap Level B (80%) | OxCap Level C (60%)

Hall P et al., ASCO 2019; #4006

Trajanje zdravljenja



Hall P et al., ASCO 2019; #4006

GO2 raziskava - zaključki

- Doslej največja raziskava starejših in krhkih bolnikov z rakom želodca in požiralnika
- Najnižji odmerki zdravil

➢ zagotavljajo enakovredno kontrolo bolezni kot višji

XELOX 60%=80%=100%

➢ najugodnejši za bolnika glede NUZ in kvalitete življenja

- Nobena od podskupin ni imela koristi od višjih odmerkov zdravil
- Raziskave personaliziranega odmerjanja potekajo

Oligometastatska bolezen

Vloga MDK

	Locally advanced resectable	Oligometastatic	Metastatic
Clinical definition	T3-T4 and/or N+	M1 with retroperitoneal lymph nodes and/or one potentially resectable incurable site	M1 patients other than oligometastatic
Prevalence	30-40%	Unknown	40-50%
Treatment strategy	Perioperative FLOT	Neoadjuvant FLOT followed by surgery ± adjuvant FLOT	Platinum-fluoropyrimidine-based doublet or triplet
Median OS	50 months	31.3 months	9-11 months
3-year OS	57%	NA	< 10%

Neoadjuvantna KT!

ESMO: eksperimentalno

Salati M et al. Eur J Surg Oncol. 2018 Nov 10. pii: S0748-7983(18)31997-8. doi: 10.1016/j.ejso.2018.11.006. [Epub ahead of print]

Metastatski rak želodca – prva linija
Zaključki

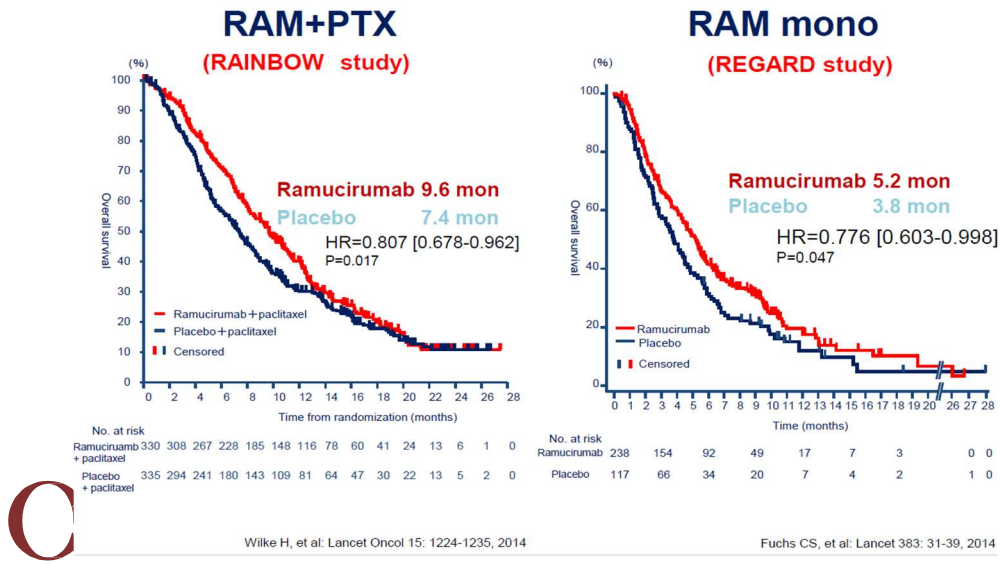
- Standard: kombinacija dveh zdravil: d. platine + fluoropirimdin
- Ni znanstvene utemeljitve za kombinacijo z epirubicinom
- Kombinacija treh zdravil z docetakselom za posebne primere: nujno hitro zmanjšanje tumorskega bremena, ali možnost sekundarne resekcije (DCF, FLOT), pri mlajših izbranih bolnikih
- FOLFIRI – enakovredna alternativa
- Starejši in krhki bolniki – redukcija odmerkov zdravil
- Her2 + tumorji: trastuzumab + KT

Metastatski rak želodca –druga linija
Randomizirane kontrolirane KR

	Št. bolnikov	Zdravilo	Preživetje Celokupno (meseci)	Izboljšanje (meseci)
Thuss-Patience[1] AIO Study	40	Irinotekan vs BSC	4,0 vs. 2,4 (p=0,012)	HR 0,48 Δ 1,6
Kang[2] Koreja	202	irinotekan ali docetaksel vs BSC	5,3 vs. 3,8 (p=0,01)	HR 0,657 Δ 1,5
Ford[3] COUGAR-2	168	Docetaksel vs BSC	5,2 vs 3,6 (0,01)	HR 0,67 Δ 1,6
Hironaka[4] WJOG	219	Paklitaksel vs irinotekan	9,5 vs. 8,4 (p=0,38)	HR 1,13 Ni razlike
Fuchs [5] REGARD	335	Ramucirumab vs BSC	5,2 vs 3,8 (p=0,38)	HR 0,776 Δ 1,4
Wilke[6] RAINBOW	665	Ramucirumab + paklitaksel vs placebo+paklitaksel	9,6 vs 7,4 (p=0,017)	HR 1,13 Δ 2,2

BSC- podporna terpija. 1. Thuss-Patience PC et al. Eur J cancer 2011;47:2306-14; 2. Kang JH et al.J Clin Oncol 2012;30:1513-18; 3. Ford HE et al. Lancet Oncol 2014; 15:78-86; 4. Hironaka S, et al. J Clin Oncol 2013;31:4438-44. 5. Fuchs C et al Lancet 2014;383:31-9; 6. Wilke H et al. Lancet Oncol 2014 ;1224-35

Metastatski rak želodca – druga linija: ramucirumab



Wilke H, et al: Lancet Oncol 15: 1224-1235, 2014

Fuchs CS, et al: Lancet 383: 31-39, 2014

Metastatski rak želodca –druga linija

Zaključki

- Motivirani bolniki, dobro stanje zmogljivsti PS 0-1
- Izboljšanje preživetja in kvalitete življenja (IA)
- Zaenkrat: najboljša opcija ramucirumab + paklitaksel
- Lahko tudi kombinacije (FOLFIRI)
- Rechallenge (PD > 3 mesece po zaključku KT)

Metastatski rak želodca –tretja linija
Trifluridin-tipiracil

EMA
Nova indikacija

Rak želodca Zdravilo Lonsurf je indicirano v monoterapiji za zdravljenje odraslih bolnikov z metastatskim rakom želodca vključno z adenokarcinomom gastro-ezofagealnega prehoda, ki so bili predhodno že zdravljeni z najmanj dvema sistemskima režimoma zdravljenja za napredovalo bolezen.*

*SPC Lonsurf

eUpdate – Gastric Cancer Treatment Recommendations

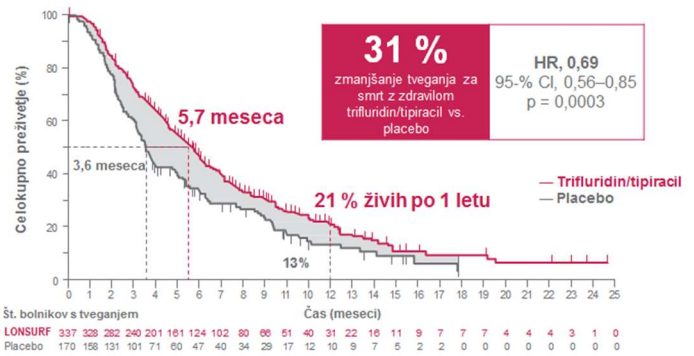
Published: 4 November 2019. Authors: ESMO Guidelines Committee
Clinical Practice Guidelines
This update refers to the Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Smyth EC, Verheij M, Allum W et al. Ann Oncol 2016; 27 (Suppl 5): v38–v49.
Section
Management of advanced/metastatic disease, second- and further-line treatment
Text update
This sentence:
"Treatment options may be used sequentially in second and third line, but there is no clear evidence for a benefit beyond second line treatment."
Is replaced with:
In a phase III randomised trial of patients with chemorefractory gastric cancer (patient treated with at least two prior lines of chemotherapy), trifluridine/tipiracil improved overall survival (OS) compared to placebo {OS 5.7 versus 3.6 months hazard ratio (HR) 0.69 [95% confidence interval (CI) 0.56–0.85], two-sided *P*=0.00058}.
Recommendation:
Third-line chemotherapy with trifluridine/tipiracil is recommended for patients who are of PS 0–1 [I, A].

TAGS - randomizirana, dvojno slepa raziskava f.3: TAS-102 vs placebo pri bolnikih z refraktornim mRŽ

Trifluridin/tipiracil pomembno podaljša celokupno preživetje[1] | Primarni izid

Za 2,1 meseca izboljšana mediana OS v primerjavi s placebom[1]

Celokupno preživetje (populacija bolnikov z namenom zdravljenja – ITT)[1]



31 % zmanjšanje tveganja za smrt z zdravilom trifluridin/tipiracil vs. placebo

HR, 0,69
95-% CI, 0,56–0,85
p = 0,0003

21 % bolnikov, zdravljenih z zdravilom trifluridin/tipiracil, je bilo še vedno živih po 12 mesecih napram 13 % bolnikov na placebu[1]

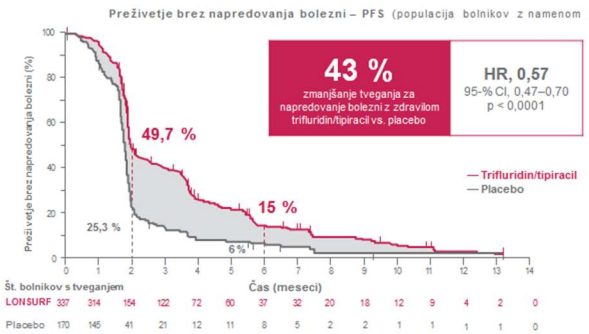
GEJC: rak gastroezofagealnega prehoda; CI: interval zaupanja; HR: razmerje tveganja; OS: celokupno preživetje. Obe skupini sta prejemali najboljšo podporno oskrbo.
1. Shitara K et al; TAGS Study Group. *Lancet Oncol.* 2018;19(11):1437-1448. 2. Mansoor W, et al. Predstavljeno na 55. konferenci ASCO 2019. 3. Ilson DH, et al. Predstavljeno na simpoziju ASCO GI 2019.

TAGS - randomizirana, dvojno slepa raziskava f.3: TAS-102 vs placebo pri bolnikih z refraktornim mRŽ

PFS

- **Po 6 mesecih bolezen ni napredovala pri 15 % bolnikov, ki so se zdravili z zdravilom trifluridin/tipiracil, vs. 6 % na placebu[1]**
- **Mediana PFS je bila 2,0 meseca z zdravilom trifluridin/tipiracil vs. 1,8 meseca s placebom[1]**

Preživetje brez napredovanja bolezni – PFS (populacija bolnikov z namenom zdravljenja – ITT)[1]



43 % zmanjšanje tveganja za napredovanje bolezni z zdravilom trifluridin/tipiracil vs. placebo

HR, 0,57
95-% CI, 0,47–0,70
p < 0,0001

Po 2 mesecih bolezen ni napredovala pri **49,7 %** bolnikov, ki so prejemali trifluridin/tipiracil, vs. **25,3 %** bolnikov na placebu[2*]

CI: interval zaupanja; HR: razmerje tveganja; PFS: preživetje brez napredovanja bolezni. *Povzetek glavnih značilnosti zdravila LONSURF, julij 2019.
1. Shitara K et al; TAGS Study Group. *Lancet Oncol.* 2018;19(11):1437-1448. 2. Mansoor W, et al. Predstavljeno na 55. konferenci ASCO 2019. 3. Ilson DH, et al. Predstavljeno na simpoziju ASCO GI 2019.

TAGS: Neželeni učinki

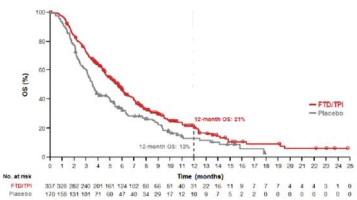
	TFD/TPI	placebo
NUZ:	**81%**	**57%**
Gradus ≥3:	**53%**	**13%**

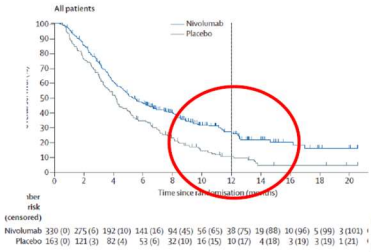
Najpogostejši NU gr. ≥3, pri >10% bolnikov z TFD/TPI:

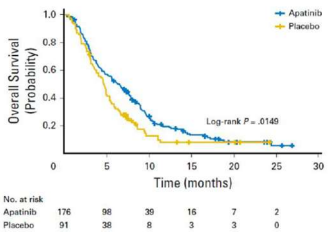
neutropenija (34%)

anemija (19%)

Preživetje: trifluridin/tipiracil vs nivolumab vs apatinib

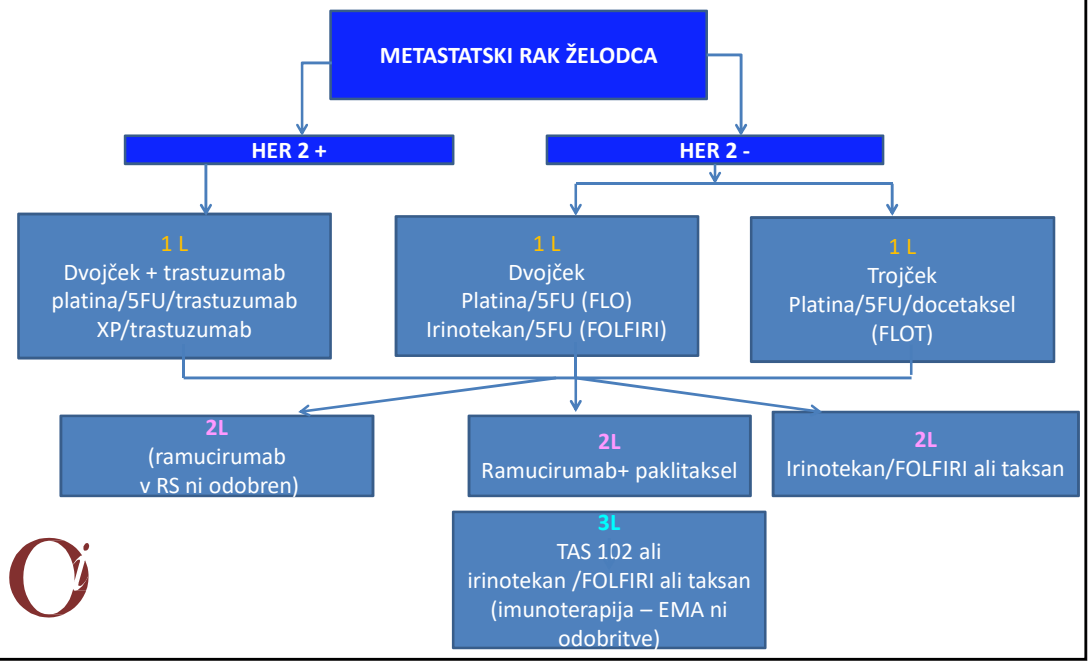






Median OS			
	5.7 mo vs 3.6 mo	5.3 mo vs 4.1 mo	6.5 mo vs 4.7 mo
HR	0.69	0.63	0.71

Algoritem zdravljenja metastatskega raka želodca 2019



NOVOSTI V SISTEMSKEM ZDRAVLJENJU RAKA ŽELODCA/GEP
Prikaz primera

Hribernik Nežka, dr.med.
9. ŠOLA TUMORJEV PREBAVIL

22.11.2019
ONKOLOŠKI INŠTITUT LJUBLJANA

PREDSTAVITEV BOLNIKA

- 68. letni nekadilec
- Poročen, zaposlen v šolstvu
- Brez družinske obremenitve za rakave bolezni

- PB: SB tipa 2 na dieti, hiperlipidemija (atorvastatin), osa (CPAP), obesitas III. stopnje (BMI 43)
- Alergija na sulfanamide
- PS WHO 1

DIAGNOSTIČNI POSTOPKI

- Januar 2018: disfagija, levkocitoza
- EGDS: delno obstruktivna lezija GEP
- Histologija: slabo diferenciran adenokarcinom, HER2 neg (IHC)
- PET/CT, MRI glave: 8 cm velika lezija GEP, N+ M0
- EUS: T3 N2

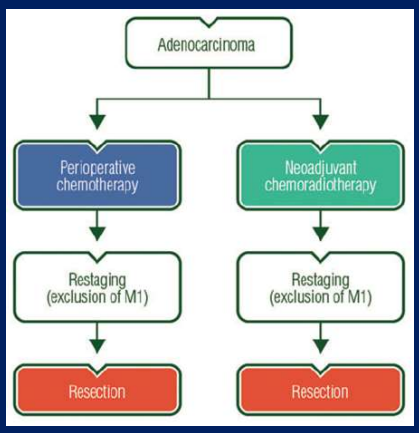
- **HER2 neg adenokarcinom GEP, cT3 N2 M0**

RADIKALNO ZDRAVLJENJE

- Konzilij (Virginia): svetovana periop. KT + kirurška resekcija
  FLOT x 4 (brez resnih NU)
  PET/CT: dosežen delni odgovor

- Drugo mnenje (Mayo clinic): svetovana predop. KT-RT + ev. kirurška resekcija
  Protonska RT (TD 50 Gy, #25) + **tedenski karbo/pakli**
  PET/CT ob koncu KT-RT: **progres** bolezni s številnimi patološkimi perigastričnimi bezgavkami in bezgavkami ob trunkus celiakusu
  → histološka verifikacija bezgavk z EUS: N3+, kirurška resekcija ni bila več možna

LOKALNO NAPREDOVAL ADENOKARCINOM GEP (cT3-4 ali cN1-3 M0)



Primerjava obeh režimov

Potekata randomizirani študiji faze 3:

1. ESOPEC (NCT02509286)
2. TOPGEAR (NCT01924819)

ESMO UPPER GI CANCER 2019

ZDRAVLJENJE NAPREDOVALE BOLEZNI

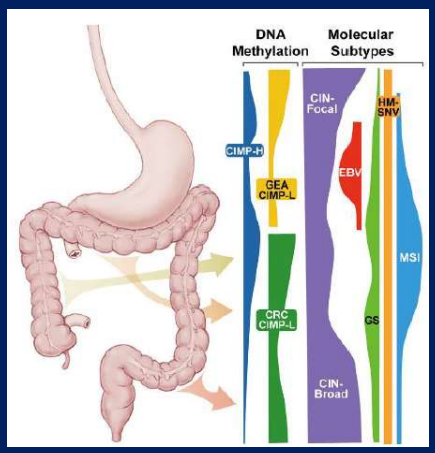
- NGS testiranje: **MSI-H**
- Avgust 2018: uvedba zdravljenja s PD-1 zaviralcem **pembrolizumabom**
- Dosežen popolni odgovor
- Neželeni učinki zdravljenja:
  - Hipotiroidizem st. 2 (levotiroksin)
  - Ledvično popuščanje st. 1
  - Občasne artralgije st. 1

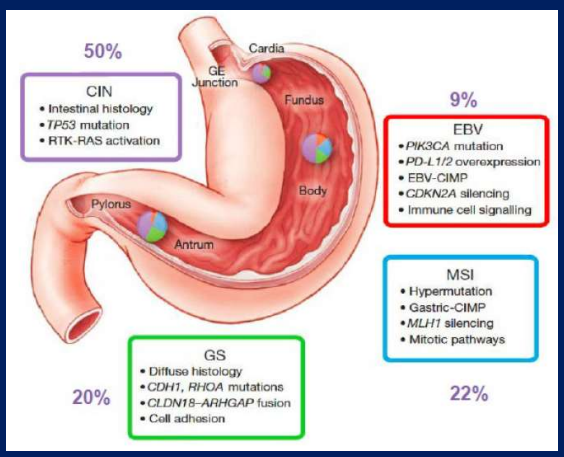
ZDRAVLJENJE V SLOVENIJI

- Od julija 2019 do danes je zdravljen v Sloveniji:

  Nadaljuje s pembrolizumabom
  PS WHO 1, dela za polni delovni čas
  Brez novih toksičnih sopojavov
  Vztrajanje popolnega odgovora (PET/CT november 2019)

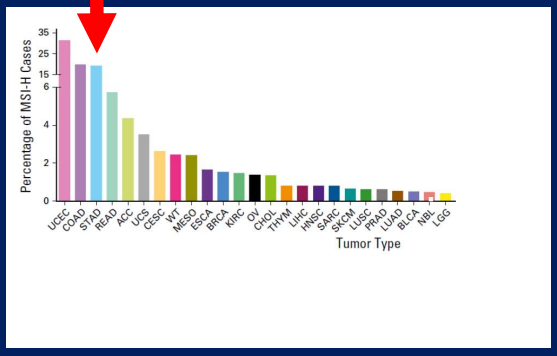
MOLEKULARNA KLASIFIKACIJA ADENOKARCINOMA ŽELODCA/GEP





Cancer Cell 2018, TCGA Nature 2014

INCIDENCA MSI-H/dMMR PRI RAKU ŽELODCA



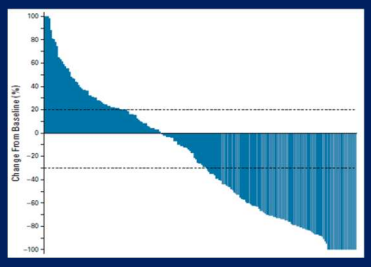
- Med pogostejšimi med vsemi raki (poleg endometrijskega raka in RDČD)
- Omejena oblika: 8-22% (dobra prognoza)
- Razsejana oblika: 7% (slaba prognoza ob standardnem citostatskem zdravljenju)

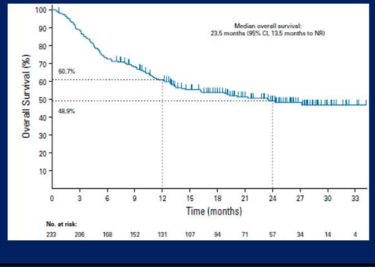
Bonneville et al. JCO 2017

UČINKOVITOST PEMBROLIZUMABA PRI MSI-H/dMMR

- Tumor-agnostično zdravljenje
- Visok ORR
- Dolgotrajni odgovori
- Dober toksični profil

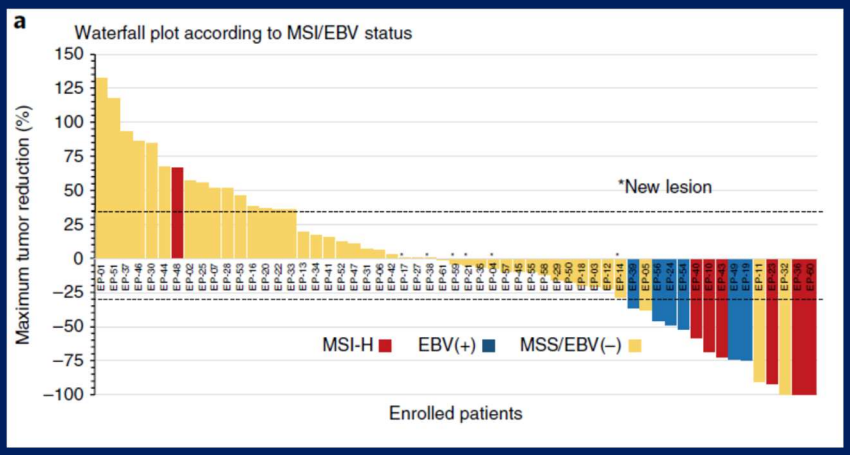
Tumor Type	No.	CR, No.	PR, No.	ORR, % (95% CI)	Median PFS, Months (95% CI)	Median OS, Months (95% CI)
Gastric	24	4	7	45.8 (25.6 to 67.2)	11.0 (2.1 to NR)	NR (7.2 to NR)
Pancreatic	22	1	3	18.2 (5.2 to 40.3)	2.1 (1.9 to 3.4)	4.0 (2.1 to 9.8)
Small intestine	19	3	5	42.1 (20.3 to 66.5)	9.2 (2.3 to NR)	NR (10.6 to NR)
Ovarian	15	3	2	33.3 (11.8 to 61.6)	2.3 (1.9 to 6.2)	NR (3.8 to NR)
Brain	13	0	0	0.0 (0.0 to 24.7)	1.1 (0.7 to 2.1)	5.6 (1.5 to 16.2)





Marabelle et al. JCO 2019

MSI-H/dMMR PRI ZDRAVLJENJU RAZSEJANE OBLIKE RAKA ŽELODCA/GEP S PD-1 ZAVIRALCI



Tae Kim et al. Nat Med 2018

MSI-H/dMMR PRI RADIKALNEM ZDRAVLJENJU RAKA ŽELODCA/GEP

- Pri RDČD stadij II: negativni prediktivni faktor za korist dopolnilne KT (v Sloveniji presejanje ob diagnozi/resekciji)

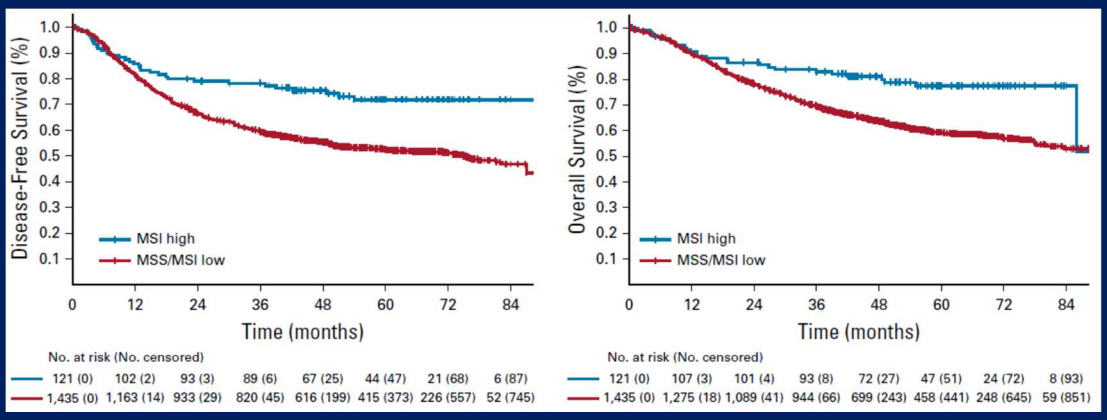
- Pri raku želodca do sedaj neznan pomen za dopolnilno zdravljenje
- Meta-analiza štirih mednarodnih randomiziranih študij (MAGIC, CLASSIC, ARTIST, ITACA-s)

  Vključenih 1556 bolnikov, 121 (7.8%) MSI-H

Individual Patient Data Meta-Analysis of the Value of Microsatellite Instability As a Biomarker in Gastric Cancer

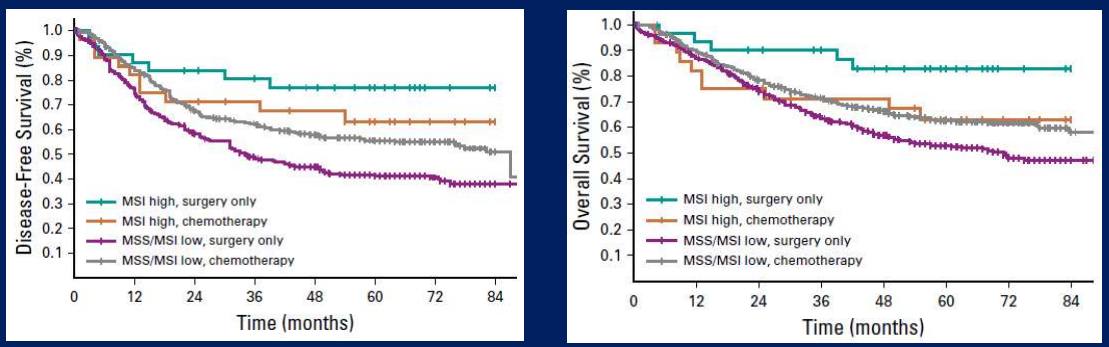
Petrantonio et al. JCO 2019

MSI-H bolniki imajo značilno boljše preživetje napram MSS bolnikom (HR 1.88 za DFS, HR 1.78 za OS)



Petrantonio et al. JCO 2019

MSI-H bolniki nimajo koristi od dodatka KT ob kirurški resekciji (-/+ KT: HR 1.45 za 5-letno DFS, HR 2.18 za 5-letni OS)



Petrantonio et al. JCO 2019

ZAKLJUČKI

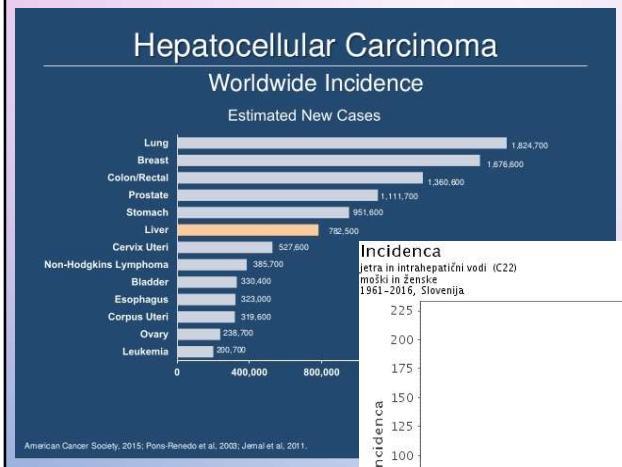
- Zdravljenje adenokarcinoma želodca/GEP se nadalje razvija.
- Molekularna klasifikacija postaja pomembna za načrtovanje zdravljenja.
- Optimalno perioperativno zdravljenje še ni dokončno definirano. Studije so v teku, potrebno bi bilo vključiti robustne prognostične markerje (MSI-H/dMMR).
- Imunoterapija je učinkovita za podskupino bolnikov (MSI-H/dMMR, EBV+).

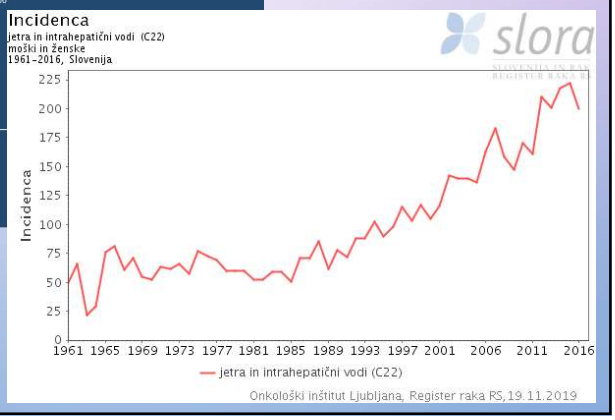
SISTEMSKO ZDRAVLJENJE PRIMARNEGA RAKA JETER

ASIST.DR.TANJA MESTI, DR.MED.

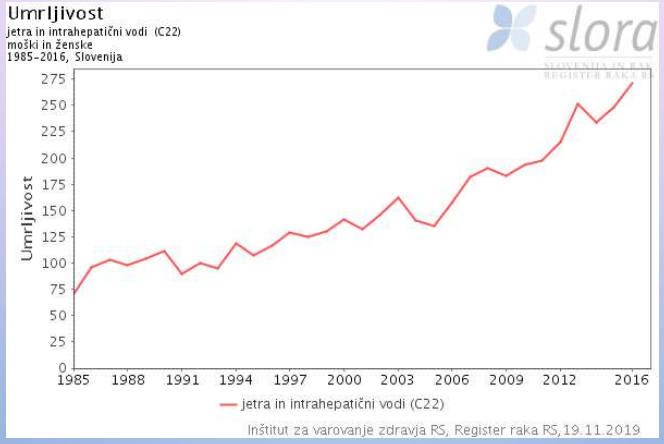
ONKOLOŠKI INŠTITUT LJUBLJANA

INCIDENCA

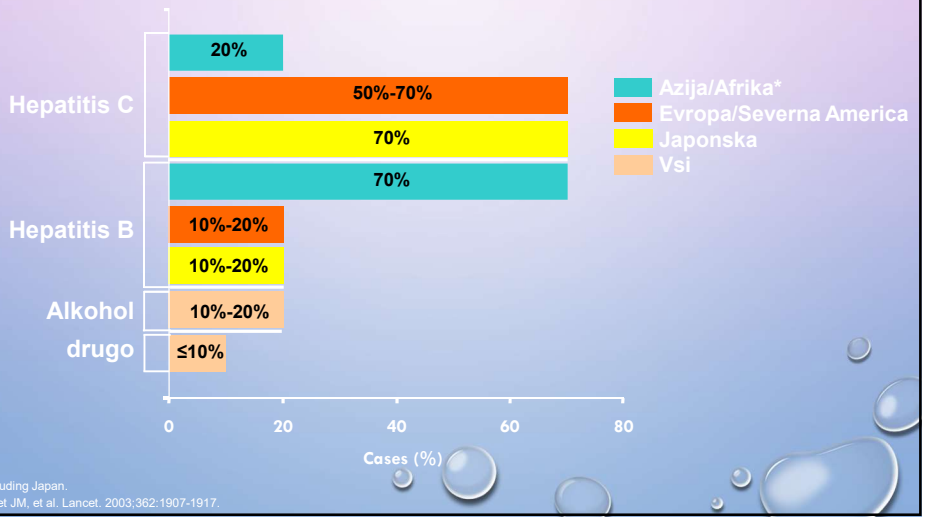




UMRLJIVOST



DEJAVNIKI TVEGANJA ZA HCC – PO REGIJAH



*Excluding Japan.
Llovet JM, et al. Lancet. 2003;362:1907-1917.

BCLC STAGING SYSTEM

BCLC Staging

BCLC Stage		ECOG PS	Tumor Size/Number, Vascular Involvement, Etc	Child-Pugh Score
0	Very early	0	Solitary <2 cm nodule	A
A	Early	0	Solitary <5 cm nodule or up to 3 nodules each ≤3 cm	A - B
B	Intermediate	0	Large/multinodular	A - B
C	Advanced	1-2	Portal venous invasion and/or extrahepatic spread (N+ or M+)	A - B
D	Terminal	>2	Any of the above	C

BCLC – Barcelona Clinic Liver Cancer; ECOG PS – Eastern Cooperative Oncology Group performance status.
Llovet et al, 1999.

Table 2. Child Pugh Turcotte (CTP) Score

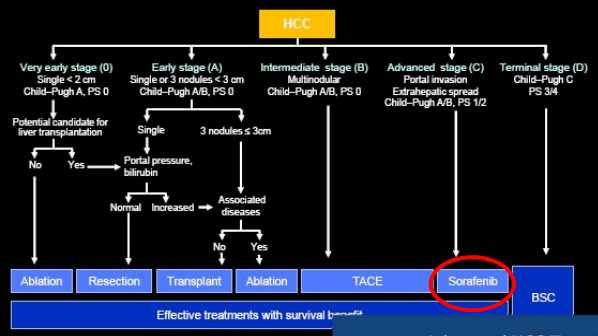
Parameters	Points		
	1	2	3
Serum Bilirubin(mg/dl)	2.0	2-3	>3.0
Serum Albumin(g/dl)	>3.515	2.8-3.5	<2.8
Prothrombin Time (Prolongation (s))	1-4	5-6	>6
Hepatic encephalopathy	None	Minimal	Advanced
Ascites	None	Slight	Moderate

One and two year survival based on CTP Score

Class	1 yr	2 yr
A (5-6 points)	100 %	85 %
B (7-9 points)	80%	60%
C (10-15 points)	45%	35%

Data from Child CG, Turcotte JG.Surgery and portal hypertension. In: Child CG. The liver and portal hypertension. Philadelphia: Saunders; 1964.p.50-64

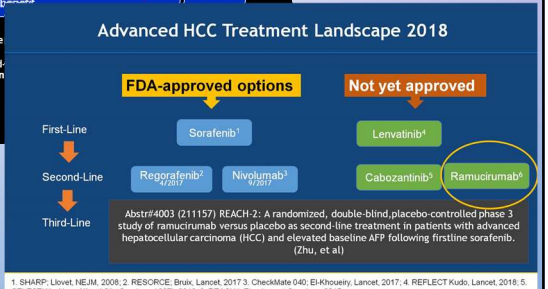
BCLC Staging and Treatment Strategy



*Note that Child-Pugh classification is not sensitive to accurately identify those liver transplant consideration.
**Patients with end stage cirrhosis due to heavily impaired liver function (Child- prognosis high MELD score) should be considered for liver transplantation. In the enlistment criteria.

Bruix J, et al. *Gastroenterol*. 2016;150:835–853.

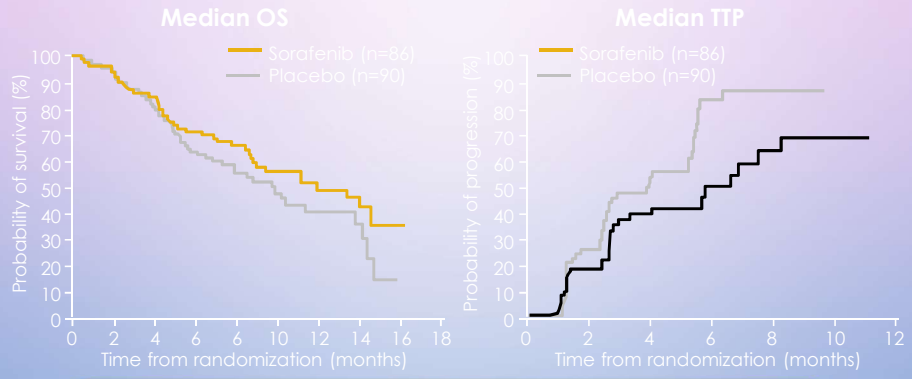
Advanced HCC Treatment Landscape 2018



Abstr#4003 (211157) REACH-2: A randomized, double-blind,placebo-controlled phase 3 study of ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma (HCC) and elevated baseline AFP following firstline sorafenib. (Zhu, et al)

1. SHARP; Llovet, NEJM, 2008; 2. RESORCE; Bruix, Lancet, 2017 3. CheckMate 040; El-Khoueiry, Lancet, 2017; 4. REFLECT Kudo; Lancet, 2018; 5. CELESTIAL; Abou-Alfa, J Clin Onc (suppl 207), 2018; 6. REACH1; Zhu, Lancet Oncology, 2015

UČINKOVITOST SORAFENIBA PRI BOLNIKIH PO TACE



Sorafenib: n=86; placebo: n=90
Median OS: 11.9 vs 9.9 months (HR: 0.75; CI: 0.49–1.14)
Median TTP: 5.8 vs 4.0 months (HR: 0.57; CI: 0.36–0.91)

HR, HAZARD RATIO; OS, OVERALL SURVIVAL; TTP, TIME TO PROGRESSION; TACE, TRANSARTERIAL CHEMOEMBOLIZATION
BRUIX J ET AL. J HEPATOL. 2012;57:821–9.

SORAFENIB PRI BOLNIKIH NEPRIMERNIH ZA TACE OZ REFRAKTORNIH NA TACE

Intermediaren HCC je zelo raznolika skupina bolnikov

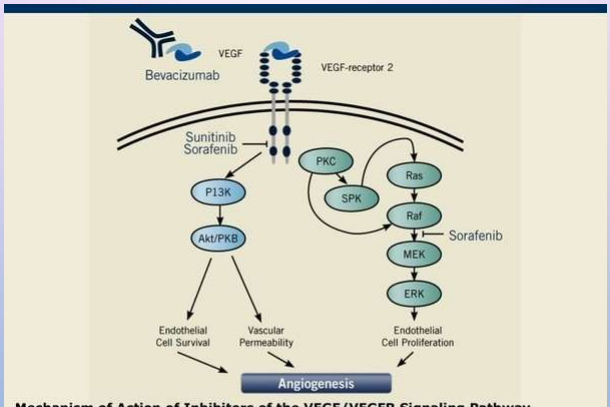
Že izhodiščno niso vsi bolniki primerni za TACE

SORAFENIB PRI BOLNIKIH NEPRIMERNIH ZA TACE OZ REFRAKTORNIH NA TACE

Učinkovitost sorafenib pri BCLC-B bolnikih, ki so neprimerni za TACE ali TACE refraktorni (brez odgovora po 2 TACE)

bolnike z poslabšanjem jetrne funkcije ali pomembnimi NU po 1. TACE

Sorafenib – mehanizem delovanja



Mechanism of Action of Inhibitors of the VEGF/VEGFR Signaling Pathway
Reprinted with permission from Rini BJ. *Clin Cancer Res* 2007;13(4):1098-106. Figure 1.

SHARP FAZA III: SORAFENIB VS PLACEBO PRI NAPREDOVALEM HCC

Vključitveni kriteriji
- napredoval HCC
- Child–Pugh A status
- ECOG PS 0–2
- Pričakovano preživetje ≥12 mesecev
- Neprimerni ali odpoved lokoregionalnega zdravljenja

Stratifikacija po
- ECOG PS
- Obsežnost tumourja
- Geografska regija

Randomizacija
- 1:1 (n~602)

Sorafenib 400 mg b.i.d.

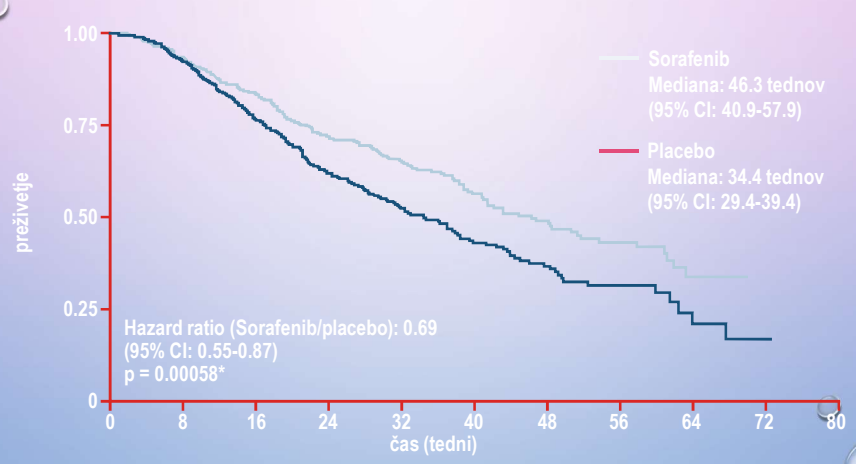
Placebo

Primarni cilj
- OS
- TTSP

Sekundarni cilj
- TTP
- Nadzor bolezni (OR + SD)

- Zdravljenje do radiografskega ali simptomatskega progresa ali neželenih učinkov, ki so vodili v prekinitev zdravljenja
- Cikel zdravljenja – 6 tednov

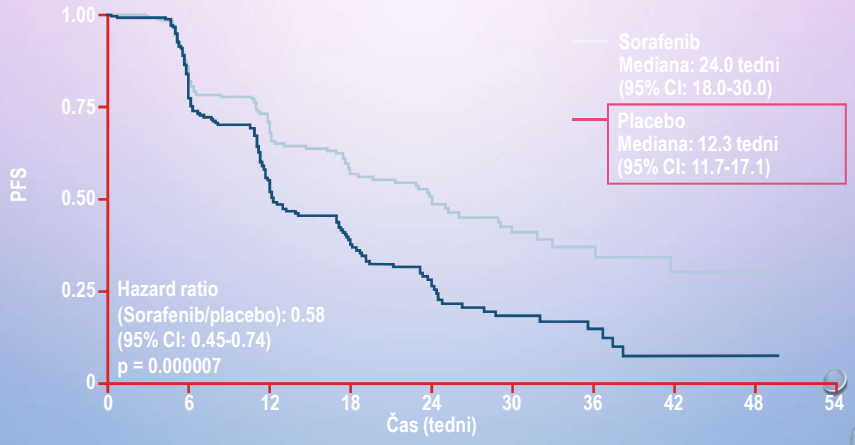
SHARP: VPLIV NA CELOKUPNO PREŽIVETJE



*O'Brien–Fleming statistično signifikanten p = 0.0077

Llovet JM. Proc Am Soc Clin Oncol 2007

SHARP – VPLIV NA PFS



Llovet JM. Proc Am Soc Clin Oncol 2007

SHARP - ODGOVOR NA ZDRAVLJENJE

	Sorafenib N = 299	Placebo N = 303
	n (%)	n (%)
Celokupni odgovor		
popoln odg. (CR)	0	0
delni odg. (PR)	7 (2.3)	2 (0.7)
Mirovanje bolezni (SD)	211 (71)	204 (67)
Progres (PD)	54 (18)	73 (24)
Ni bilo določeno	27 (9)	24 (8)
Kontrola bolezni (DCR)**	130 (44)	96 (32)

**DCR = CR + PR + SD vsaj 28 dni od prve evidence

Llovet JM. Proc Am Soc Clin Oncol 2007

SHARP - VARNOST

	Sorafenib N = 297	Placebo N = 302
Resni neželeni učinki (%)	52	54
Resni neželeni učinki zaradi zdravila (%)	13	9
Neželeni učinki, ki so vodili v ukinitev zdravljenja (%)	32	35

Llovet JM. Proc Am Soc Clin Oncol 2007

SHARP – NEŽELENI UČINKI

	Sorafenib N = 297		Placebo N = 302	
Neželeni učinki	Vsi (%)	3/4 (%)	vsi (%)	3/4 (%)
Kateri koli	98	39/6	94	24/8
Diareja	55	10/<1	25	2
Bolečina (abdomen)	31	9	26	5/1
Izguba teže	30	2	10	1
Anoreksija	29	3	18	3/<1
Bruhanje	24	1	20	3
Sindrom roka - noga	21	8	3	<1
Izpuščaj	19	1	14	0
Slabost	15	2	11	2
Alopecija	14	0	2	0
Srbečica	14	<1	11	<1
Zaprtje	14	0	10	0
Suha koža	10	0	6	0

Llovet JM. Proc Am Soc Clin Oncol 2007

SORAFENIB PRI HCC

- DO SORAFENIBA JE BILO SISTEMSKO ZDRAVLJENJE HCC SKORAJ NEUČINKOVITO.
- REZULTATI SHARP KAŽEJO, DA SORAFENIB VPLIVA NA PREŽIVETJE NAPREDOVALEGA, NERESEKTABILNEGA HCC.
- SORAFENIB JE PRVO UČINKOVITO SISTEMSKO ZDRAVLJENJE, NAPREDOVALEGA NERESEKTABILNEGA HCC
- ADJUVANTO (POST-RESEKCIJSKO ALI POST-ABLATIVNO ZDR.) V FAZI RAZISKOVANJA

REZULTATI SHARP IN VSAKODNEVNE UPORABE SORAFENIBA PRI INTERMEDIARNEM HCC

SHARP[1] BCLC-B subgroup	• **Increased OS and TTP with sorafenib (n=54) vs placebo (n=51)** – Median OS: 14.5 vs 11.4 months (HR: 0.72; 95% CI: 0.38–1.38) – Median TTP: 6.9 vs 4.4 months (HR: 0.47; 95% CI: 0.23–0.96)
SHARP[1] previous TACE subgroup	• **Increased OS and TTP with sorafenib (n=86) vs placebo (n=90)** – Median OS: 11.9 vs 9.9 months (HR: 0.75; 95% CI: 0.49–1.14) – Median TTP: 5.8 vs 4.0 months (HR: 0.57; 95% CI: 0.36–0.91)
SOFIA[2]	• **Good efficacy demonstrated in BCLC-B HCC** – Longer survival in BCLC-B vs BCLC-C patients: 20.6 vs 8.4 months
INSIGHT[3]	• **Good efficacy demonstrated in BCLC-B HCC** – Longer survival in BCLC-B vs BCLC-C patients: 19.6 vs 14.5 months
GIDEON interim analysis[4]	• **Similar safety profile for sorafenib across BCLC stages**

BCLC, BARCELONA CLINIC LIVER CANCER; HCC, HEPATOCELLULAR CARCINOMA; HR, HAZARD RATIO; OS, OVERALL SURVIVAL; TTP, TIME TO PROGRESSION

1. BRUIX J ET AL. J HEPATOL. 2012;57:821–9; 2. IAVARONE M ET AL. HEPATOLOGY 2011;54:2055–63; 3. GANTEN TM ET AL. EMSO 2012;POSTER 77; 4. LENCIONI R ET AL. EUR J CANCER 2011;47 (SUPPL 1):ABSTRACT 6500

TACE – NOVOSTI: SORAFENIB + TACE

STUDY OBJECTIVE (TACTICS: ABSTRACT 4017 – KUDO M, ET AL)

- **PRIMERJAVA UČINKOVITOSTI IN VARNOSTI SORAFENIB + TACE PRI BOLNIKIH S HCC**

STUDY DESIGN

- PATIENTS (N=156) WERE RANDOMISED (1:1) TO RECEIVE SORAFENIB 400 MG/DAY WITH TACE (N=80) OR TACE ALONE (N=76)

KEY RESULTS

- THE MATURITY OF OS RESULTS WAS 73.6%

	Sorafenib + TACE (n=80)	TACE (n=76)	HR (95%CI)	p-value
Median PFS, months	25.2	13.5	0.59 (0.41, 0.87)	0.006

KUDO M, ET AL. J CLIN ONCOL 2018;36(SUPPL):ABSTR 4017
PECK-RADOSAVLJEVIC M, ET AL. J CLIN ONCOL 2018;36(SUPPL):ABSTR 4018
ABOU-ALFA GK, ET AL. J CLIN ONCOL 2018;36(SUPPL):ABSTR 4019
ZHU AX, ET AL. J CLIN ONCOL 2018;36(SUPPL):ABSTR 4020

RESORCE Trial Design

Clinicaltrials.gov NCT01774344

- HCC patients with documented radiological progression during sorafenib treatment
- Stratified by:
  - Geographic region (Asia vs ROW)
  - Macrovascular invasion
  - Extrahepatic disease
  - ECOG PS (0 vs 1)
  - AFP (<400 ng/mL vs ≥400 ng/mL)

R 2:1

Regorafenib
160 mg po once daily
3 weeks on / 1 week off
(4-week cycle)
(n=379)

N= 573

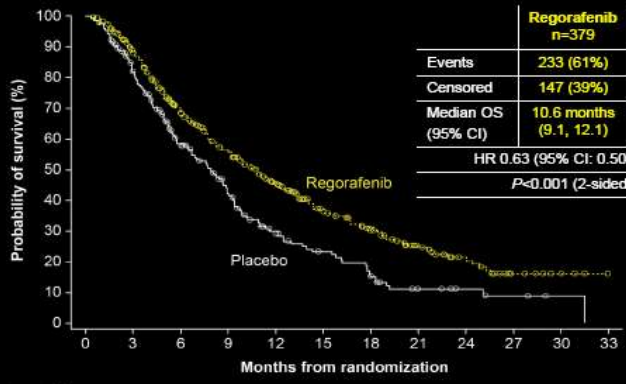
Placebo
(n=194)

- 152 centers in 21 countries in North and South America, Europe, Australia, Asia
- All patients received best supportive care
- Treat until progression, unacceptable toxicity, or withdrawal

ROW, rest of the world; ECOG PS, Eastern Cooperative Oncology Group performance status; AFP, alpha-fetoprotein

Presented at: 2016 World Congress on GI Cancer; June 28 - July 2, 2016; Barcelona, Spain. Abstracts LBA03.

Regorafenib vs Placebo in Second Line Overall Survival (OS)



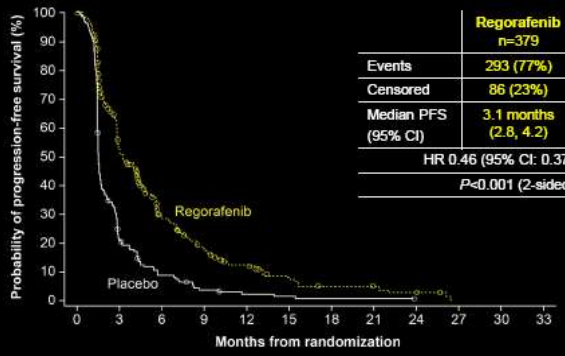
	Regorafenib n=379	Placebo n=194
Events	233 (61%)	140 (72%)
Censored	147 (39%)	54 (28%)
Median OS (95% CI)	10.6 months (9.1, 12.1)	7.8 months (6.3, 8.8)
HR 0.63 (95% CI: 0.50, 0.79)		
P<0.001 (2-sided)		

Number at risk

Regorafenib	379	316	224	170	122	78	54	34	21	10	4	0
Placebo	194	149	95	62	37	26	16	8	5	3	1	0

Presented at: 2016 World Congress on GI Cancer; June 28 – July 2, 2016; Barcelona, Spain. Abstracts LBA03.

Progression-free Survival (PFS)



	Regorafenib n=379	Placebo n=194
Events	293 (77%)	181 (93%)
Censored	86 (23%)	13 (7%)
Median PFS (95% CI)	3.1 months (2.8, 4.2)	1.5 months (1.4, 1.6)
HR 0.46 (95% CI: 0.37, 0.56)		
P<0.001 (2-sided)		

Number at risk

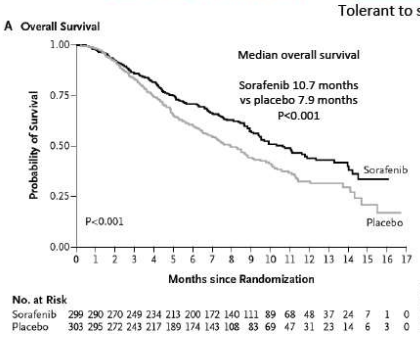
Regorafenib	379	166	76	43	27	14	8	7	4	0	0	0
Placebo	194	37	15	6	3	2	1	1	0	0	0	0

Based on mRECIST

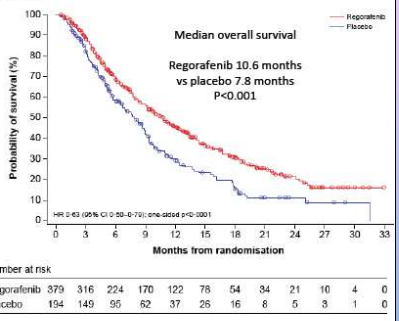
Presented at: 2016 World Congress on GI Cancer; June 28 – July 2, 2016; Barcelona, Spain. Abstracts LBA03.

Sorafenib and regorafenib in advanved HCC

Sorafenib in first line → Progression → Tolerant to sorafenib → Regorafenib in second line



Llovet J, et al. NEJM 2008



Bruix J, et al. Lancet 2016

LENVATINIB – MULTIKINAZNI ZAVIRALEC

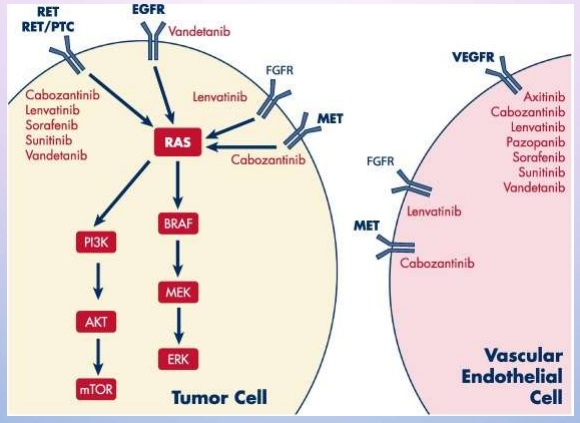
Lenvatinib: A New Option in HCC

- Oral, multitargeted inhibitor of:
  - VEGF receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4)
  - FGFR1, 2, 3, and 4
  - PDGFRα, KIT, and RET
- Approved for recurrent or metastatic iodine-refractory thyroid cancer and in renal cell carcinoma in combination with everolimus following prior antiangiogenic therapy

i3Health

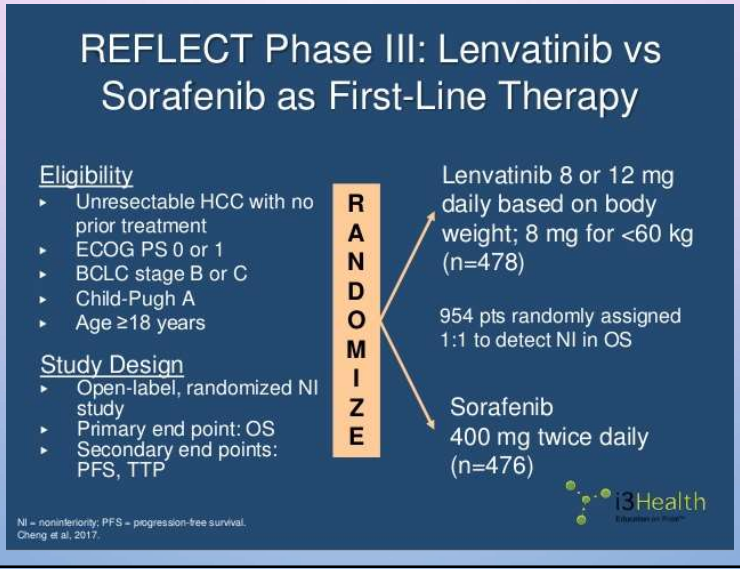
Lenvima® prescribing information, 2017.

LENVATINIB – MEHANIZEM DELOVANJA



LENVATINIB: ROLE IN THYROID CANCER AND OTHER SOLID TUMORS; MARIA E.CABANILLASMOUHAMMED AMIRHABRA. CANCER TREATMENT REVIEWS. VOLUME 42, JANUARY 2016, PAGES 47-55

REFLECT ŠTUDIJA



REFLECT - REZULTATI

REFLECT: Outcomes

Outcomes	Lenvatinib	Sorafenib	HR
Median OS, mo (95% CI)	13.6 (12.1-14.9)	12.3 (10.4-13.9)	0.92 (0.79-1.06)
Median PFS, mo (95% CI)	7.4 (6.9-8.8)	3.7 (3.6-4.6)	0.66 (0.57-0.77)
Median TTP, mo (95% CI)	8.9 (7.4-9.2)	3.7 (3.6-5.4)	0.63 (0.53-0.73)
ORR, n (%)	115 (24%)	44 (9%)	

ORR = overall response rate.
Cheng et al, 2017.

REFLECT - AEF

REFLECT: Treatment-Emergent AEs

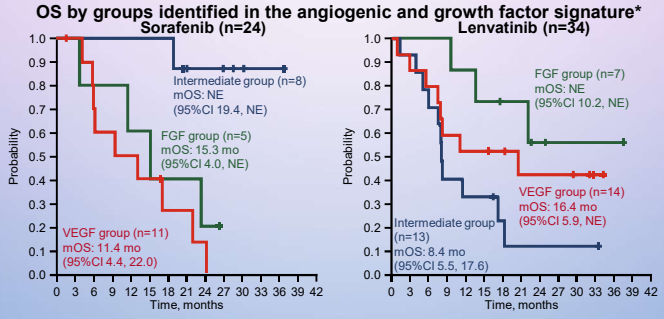
- Grade 3 and higher events were more common in the lenvatinib arm (57% vs 49%)
- Most common AEs in the lenvatinib arm:
  - Hypertension (42% overall with 23% grade ≥3)
  - Diarrhea (39%)
  - Decreased appetite (34%)
  - Weight loss (31% with 8% grade ≥3)
  - Fatigue (30%)
- Grade 3 HFSR was more common in the sorafenib arm (11% vs 3%)

Cheng et al, 2017.

ANALIZA SERUMSKIH BIOMARKERJEV - LENVATINIB (LEN) VS SORAFENIB (SOR) V PRVEM REDU ZDRAVLJENJA NERESEKTABILNEGA HCC

ITT population	Lenvatinib	Sorafenib	HR (95%CI)
mOS, months (95%CI)	13.6 (12.1, 14.9)	12.3 (10.4, 13.9)	0.92 (0.79, 1.06)

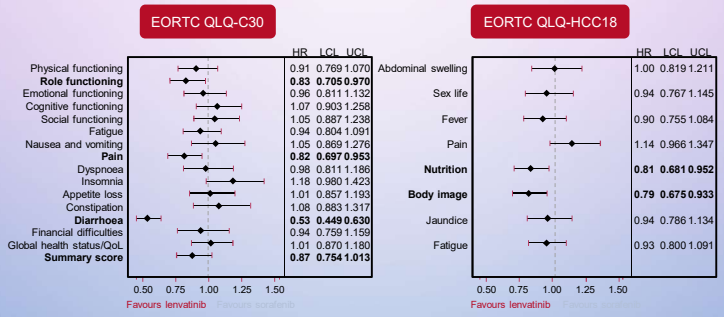
OS by groups identified in the angiogenic and growth factor signature*



*A cluster analysis using expression levels of 36 genes involved in VEGF, FGF and angiopoietin signalling identified 3 groups: (1) VEGF enriched, (2) FGF enriched , (3) FGF/VEGF intermediate

FINN RS, ET AL. ANN ONCOL 2017;28(SUPPL 5):ABSTR LBA30

KVALITETA ŽIVLJENJA (HRQOL) IN KONTROLA SIMPTOMOV BOLEZNI - LENVATINIB (LEN) VS SORAFENIB (SOR) V PRVEM REDU ZDRAVLJENJA NERESEKTABILNEGA HCC



VOGEL A, ET AL. ANN ONCOL 2017;28(SUPPL 5):ABSTR 6180

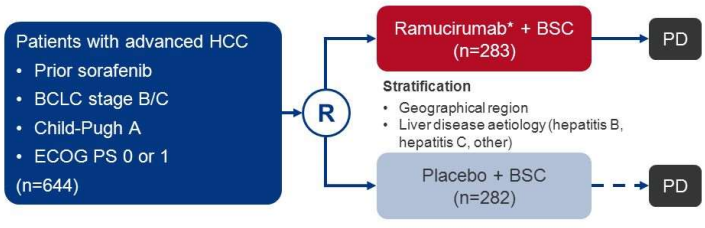
ZAKLJUČKI

- PRVA USPEŠNA ŠTUDIJA PO SHARP
- LENVATINIB NI INFERIOREN VS SORAFENIB
- LENVATINIB - VEGF IN FGF GROUP > OS
- LENVATINIB > ČAS DO UPADA FUNKCIJ VITALNIH ORGANOV, NUTRICIJE, DIAREJE IN BOLEČINE

REACH – RAMUCIRUMAB V DRUGEM REDU ZDRAVLJENJA HCC

LBA16: Ramucirumab (RAM) as second-line treatment in patients (pts) with advanced hepatocellular carcinoma (HCC) following first-line therapy with sorafenib: Results from the randomized phase III REACH study – Zhu A et al.

- **Study objective**
  - To assess the efficacy and safety of ramucirumab after first-line treatment with sorafenib in patients with advanced HCC



Primary endpoint
- OS

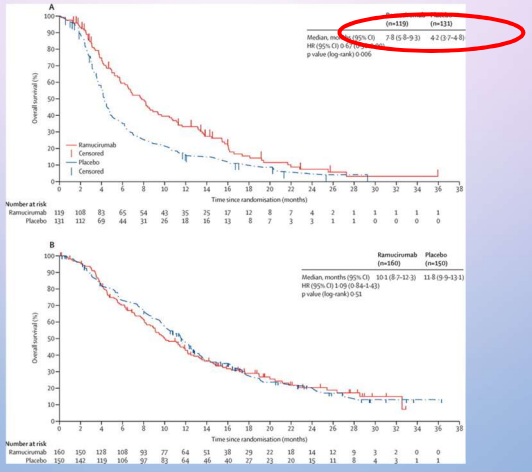
Secondary endpoints
- PFS, TTP, ORR
- Safety, patient-reported outcomes

*8mg/kg, q2w per cycle

Zhu et al. Ann Oncol 2014; 25 (suppl 4): abstr LBA16

REZULTATI

- RAMUCIRUMAB V DRUGEM REDU ZDRAVLJENJA HCC NI IZKAZAL IZBOLJŠANJA OS. OPAZEN JE BIL UČINEK NA PFS, TTP IN ORR.
- RAZEN:



RAMUCIRUMAB VERSUS PLACEBO AS SECOND-LINE TREATMENT IN PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA FOLLOWING FI RST-LINE THERAPY WITH SORAFENIB (REACH): A RANDOMISED, DOUBLE-BLIND, MULTICENTRE, PHASE 3 TRIAL ANDREW X ZHU, JOON OH PARK, BAEK-YEOL RYOO, CHIA-JUI YEN, RONNIE POON, DAVIDE PASTORELLI,ET AL. LANCET ONCOL 2015; 16: 859–70.

REACH-2: RANDOMIZIRANA, DVOJNO SLEPA PLACEBO – KONTROLIRANA ŠTUDIJA FAZE 3 RAMUCIRUMAB VERSUS PLACEBO V DRUGEM REDU ZDRAVLJENJA NAPREDOVALEGA HCC IN POVIŠANIM ALFA-FETOPROTEINOM (AFP) PO PRVEM REDU ZDRAVLJENJA S SORAFENIBOM

STUDY OBJECTIVE

- TO ASSESS THE BENEFIT OF RAMUCIRUMAB IN PATIENTS WITH HCC AND BASELINE AFP ≥400 NG/ML IN THE REACH-2 STUDY

Key patient inclusion criteria
- HCC with BCLC stage C or B, refractory or unamenable to locoregional therapy
- Prior sorafenib
- Child-Pugh A
- Baseline AFP ≥400 ng/mL
- ECOG PS 0–1

(n=292)

R 2:1

Ramucirumab 8 mg/kg iv q2w + BSC (n=197)

Placebo + BSC (n=95)

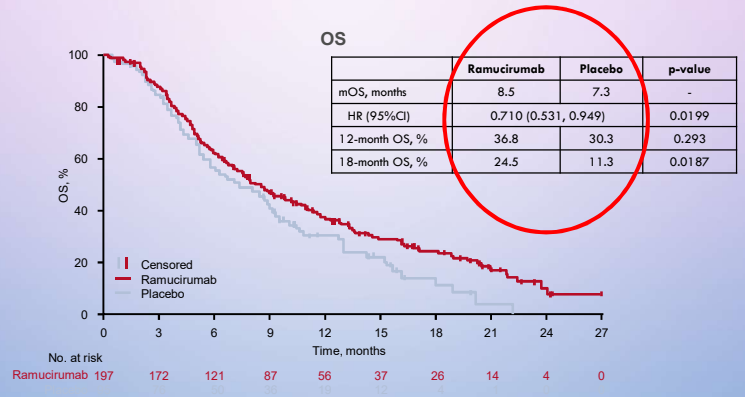
Stratification
- Macrovascular invasion (yes vs. no)
- ECOG PS (0 vs. 1)
- Geographic region (Americas, Europe, Australia vs. Asia [except Japan] vs. Japan)

PRIMARY ENDPOINT
- OS

SECONDARY ENDPOINTS
- PFS, TTP, ORR, safety

ZHU AX, ET AL. J CLIN ONCOL 2018;36(SUPPL):ABSTR 4003

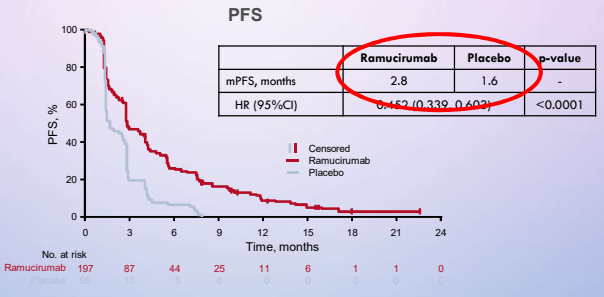
REACH-2: RANDOMIZIRANA, DVOJNO SLEPA PLACEBO – KONTROLIRANA ŠTUDIJA FAZE 3 RAMUCIRUMAB VERSUS PLACEBO V DRUGEM REDU ZDRAVLJENJA NAPREDOVALEGA HCC IN POVIŠANIM ALFA-FETOPROTEINOM (AFP) PO PRVEM REDU ZDRAVLJENJA S SORAFENIBOM



	Ramucirumab	Placebo	p-value
mOS, months	8.5	7.3	-
HR (95%CI)	0.710 (0.531, 0.949)		0.0199
12-month OS, %	36.8	30.3	0.293
18-month OS, %	24.5	11.3	0.0187

ZHU AX, ET AL. J CLIN ONCOL 2018;36(SUPPL):ABSTR 4003

REACH-2: RANDOMIZIRANA, DVOJNO SLEPA PLACEBO – KONTROLIRANA ŠTUDIJA FAZE 3 RAMUCIRUMAB VERSUS PLACEBO V DRUGEM REDU ZDRAVLJENJA NAPREDOVALEGA HCC IN POVIŠANIM ALFA-FETOPROTEINOM (AFP) PO PRVEM REDU ZDRAVLJENJA S SORAFENIBOM

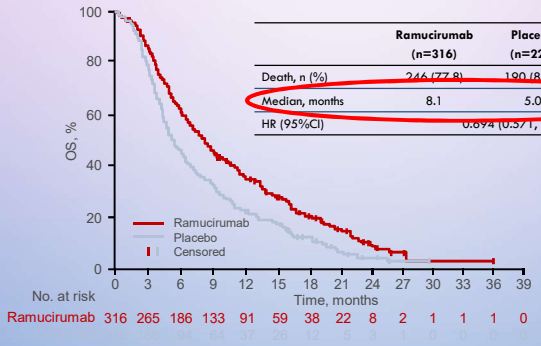


	Ramucirumab	Placebo	p-value
mPFS, months	2.8	1.6	-
HR (95%CI)	0.452 (0.339, 0.602)		<0.0001

	Ramucirumab (n=197)	Placebo (n=95)	p-value
ORR, n (%) [95%CI]	9 (4.6) [1.7, 7.5]	1 (1.1) [0.0, 3.1]	0.1697
DCR	118 (59.9) [53.1, 66.7]	37 (38.9) [29.1, 48.8]	0.0006

ZHU AX, ET AL. J CLIN ONCOL 2018;36(SUPPL):ABSTR 4003

IZPELJANA ANALIZA - REACH-2 IN REACH
UČINKOVITOST



	Ramucirumab (n=316)	Placebo (n=226)	Difference	p-value
Death, n (%)	246 (77.8)	190 (84.1)		
Median, months	8.1	5.0	3.1	
HR (95%CI)		0.694 (0.571, 0.842)		0.0002

No heterogeneity in treatment effect observed across both studies

A random effect frailty model after adjusting for study (as random effect) produced a similar treatment result (HR 0.689; p=0.0002)

ZHU A, ET AL. ANN ONCOL 2018;29(SUPPL 5):ABSTR LBA-001

IZPELJANA ANALIZA - REACH-2 IN REACH
UČINKOVITOST

	Ramucirumab (n=316)	Placebo (n=226)	p-value
PFS			
Median, months	2.8	1.5	
HR (95%CI)	0.572 (0.472, 0.694)		<0.0001
ORR, n (%) [95%CI]	17 (5.4) [2.9, 7.9]	2 (0.9) [0.0, 2.1]	0.0064
DCR, n (%) [95%CI]	178 (56.3) [50.9, 61.8]	84 (37.2) [30.9, 43.5]	<0.001

ZHU A, ET AL. ANN ONCOL 2018;29(SUPPL 5):ABSTR LBA-001

IZPELJANA ANALIZA - REACH-2 IN REACH VARNOST

Grade >3 AEs of special interest occurring in ≥3% of patients, n (%)	Ramucirumab (n=316)	Placebo (n=223)
Liver injury/failure	63 (19.9)	59 (26.5)
Ascites	15 (4.7)	9 (4.0)
Bleeding/haemorrhage events	15 (4.7)	15 (6.7)
GI haemorrhage events	11 (3.5)	12 (5.4)
Hypertension	40 (12.7)	8 (3.6)

ZAKLJUČKI

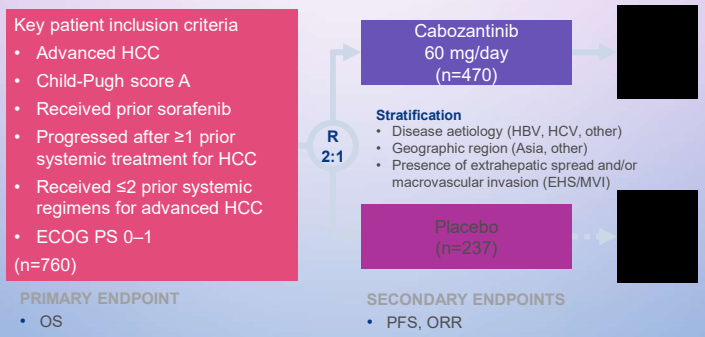
- **BOLNIKI Z NAPREDOVALIM HCC IN AFP ≥400 NG/ML, RAMUCIRUMAB PODALJŠA OS VS. PLACEBO**
- **RAMUCIRUMAB IMA VARNOSNI PROFIL V KONZISTENCI Z OSTALIMI ŠTUDIJAMI Z RAMUCIRUMABOM IN GA BOLNIKI DOBRO PRENAŠAJO**
- **PRI BOLNIKIH S HCC IN POVIŠANIM AFP PO SORAFENIBU V PRVEM REDU ZDRAVLJENJA, JE RAMUCIRUMAB NOVA POTENCIJALNO UČINKOVITA OPCIJA ZDRAVLJENJA**

ZHU A, ET AL. ANN ONCOL 2018;29(SUPPL 5):ABSTR LBA-001

CABOZANTINIB (C) VERSUS PLACEBO (P) PRI BOLNIKIH Z NAPREDOVALIM HCC PO SORAFENIBU: RANDOMIZIRANA ŠTUDIJA FAZE 3 - CELESTIAL ŠTUDIJA

STUDY OBJECTIVE

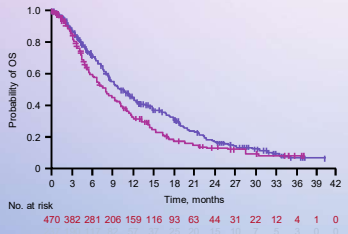
- TO ASSESS THE EFFICACY AND SAFETY OF CABOZANTINIB VS. PLACEBO IN PATIENTS WITH ADVANCED HCC AFTER PRIOR SYSTEMIC THERAPY



ABOU-ALFA G, ET AL. J CLIN ONCOL 2018;36(SUPPL 4S):ABSTR 207

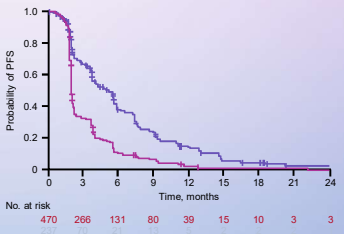
ODGOVOR NA ZDRAVLJENJE - CELESTIAL ŠTUDIJA

OS and PFS



	mOS, months (95%CI)	No. of deaths
Cabozantinib (n=470)	10.2 (9.1, 12.0)	317
Placebo (n=237)	8.0 (6.8, 9.4)	167

HR 0.76 (95%CI 0.63, 0.92); p=0.0049*



	mPFS, months (95%CI)	No. of deaths
Cabozantinib (n=470)	5.2 (4.0, 5.5)	349
Placebo (n=237)	1.9 (1.9, 1.9)	205

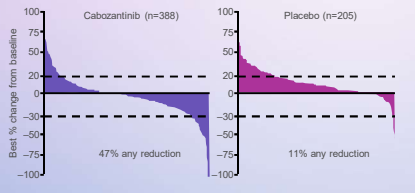
HR 0.44 (95%CI 0.36, 0.52); p<0.0001

*CRITICAL P-VALUE ≤0.021 FOR SECOND INTERIM ANALYSIS

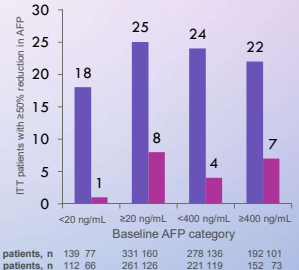
ABOU-ALFA G, ET AL. J CLIN ONCOL 2018;36(SUPPL 4S):ABSTR 207

EVALUACIJA TUMORSKEGA ODGOVORA, AFP TER TTP – CELESTIAL ŠTUDIJA

Best % change from baseline in sum of diameters



AFP response

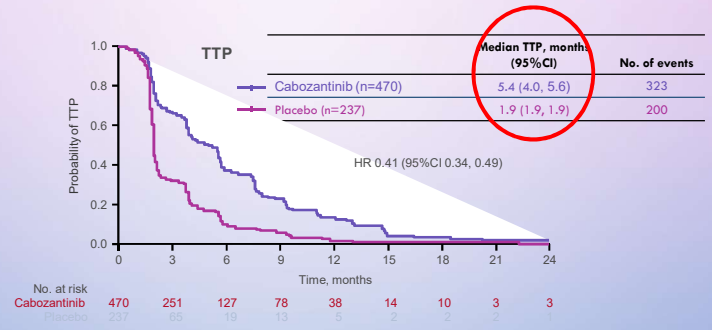


Cabozantinib
Placebo

ITT patients, n	139 77	331 160	278 136	192 101
AFP-evaluable patients, n	112 66	261 126	221 119	152 73

MERLE P, ET AL. ANN ONCOL 2018;29(SUPPL 5):ABSTR O-011

EVALUACIJA TUMORSKEGA ODGOVORA, AFP TER TTP – CELESTIAL ŠTUDIJA



- ZMANJŠANJE ODMERKA - 62% IN 13% (CABOZANTINIB VS PLACEBO)
- PREKINITEV ZARADI TRAES -16% IN 3% (CABOZANTINIB VS PLACEBO)

MERLE P, ET AL. ANN ONCOL 2018;29(SUPPL 5):ABSTR O-011

STRANSKI UČINKI - CELESTIAL ŠTUDIJA

	Cabozantinib (n=467)	Placebo (n=237)
Median duration of exposure, months (range)	3.8 (0.1–37.3)	2.0 (0–27.2)
Median average daily dose, mg	35.8	58.9
Any dose reduction, %	62	13
Discontinuation due to TRAEs, %	16	3
Grade 3/4 AEs, %	**Cabozantinib (n=467)**	**Placebo (n=237)**
Any	68	36
Palmar-plantar erythrodysesthesia	17	0
Hypertension	16	2
AST increased	12	37
Fatigue	10	4
Diarrhoea	10	2
Asthenia	7	2
Decreased appetite	6	<1
Anaemia	4	5

ABOU-ALFA G, ET AL. J CLIN ONCOL 2018;36(SUPPL 4S):ABSTR 207

ZAKLJUČKI – CELESTIAL ŠTUDIJA

- **PRI BOLNIKIH Z NAPREDOVALIM HCC, CABOZANTINIB ZNAČILNO PODALJŠA OS, PFS AND ORR PO PRVEM REDU ZDRAVLJENJA S SORAFENIBOM**
- **VARNOSTNI PROFIL CABOZANTINIBA JE BIL SPREJEMLJIV, STOPNJA PREKINITVE JE BILA NIZKA**
- **CABOZANTINIB JE LAHKO NOVA OPCIJA ZDRAVLJENJA NAPREDOVALEGA HCC PO PRVEM REDU ZDRAVLJENJA**

ABOU-ALFA G, ET AL. J CLIN ONCOL 2018;36(SUPPL 4S):ABSTR 207

IMUNOTERAPIJA

Nivolumab in sorafenib-experienced patients with advanced hepatocellular carcinoma with or without chronic hepatitis: CheckMate 040 study

- Phase 1 / 2 using nivolumab 3 mg/kg every 2 weeks in patients with advanced HCC progressor or intolerant to sorafenib
- Primary endpoint: objective response rate

Inclusion criteria
Child Pugh A patient
Advanced HCC
Progression after 1 prior line of systemic therapy or intolerant to sorafenib

Exclusion criteria
Any history of hepatic encephalopathy
Prior or current clinically significant ascites

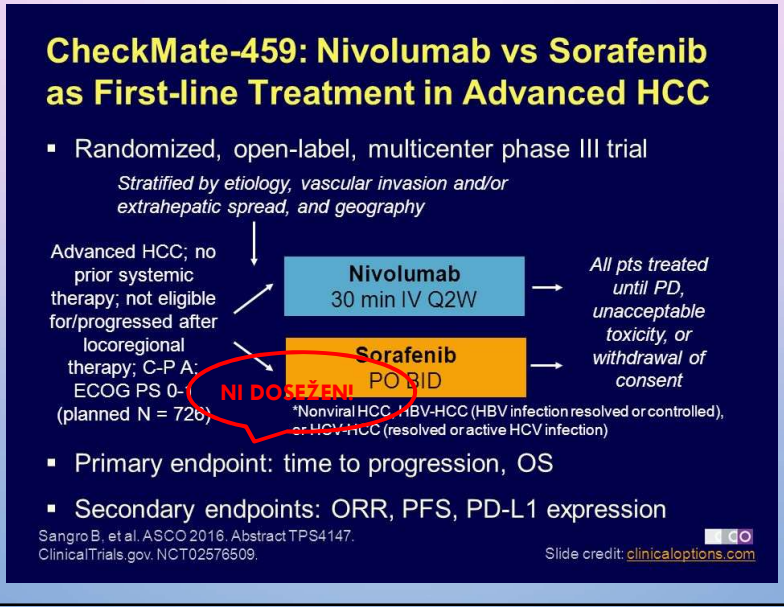
El Khoueiry AB, et al. Lancet 2017

CHECKMATE 040 : NIVOLUMAB PRI NAPREDOVALEM HCC ZAKLJUČKI

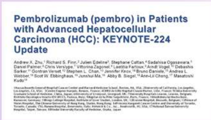
- NIVOLUMAB 3 MG/KG VODI V OBJEKTIVNE ODGOVORE PRI 16% BOLNIKOV PO RECIST 1.1 (15% OF PR AND 1% OF CR)
- NADZOR BOLEZNI -68%
- SREDNJE PREŽIVETJE 15 MESECEV
- SPREJEMLJIV VARNOSTNI PROFIL
- RANDOMIZIRANE RAZISKAVE FAZE III – PRIMERJAVA SORAFENIBA IN NIVOLUMABA PRI NAPREDOVALEM HCC (CHECKMATE 459)

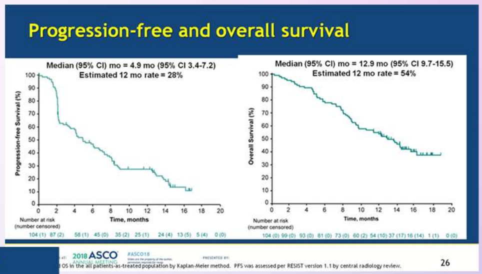
El Khoueiry AB, et al. Lancet 2017

NIVOLUMAB VS SORAFENIB



PEMBROLIZUMAB


Pembrolizumab (pembro) in Patients with Advanced Hepatocellular Carcinoma (HCC): KEYNOTE-224 Update



Response per RECIST version 1.1 by independent central review

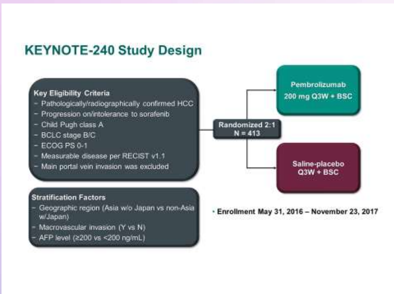
	Total N=104
ORR, n (%, 95%CI)*	18 (17, 11-26)
BOR, n (%)†	
CR	1 (1)
PR	17 (16)
SD	46 (44)
PD	34 (33)
No assessment‡	6 (6)
DCR, n (%, 95%CI)§	64 (62, 52-71)
Median time to response, mo (IQR)¶	2.1 (2.1-4.1)
Median DOR, mo (range)¶ǁ	Not reached (3.1-14.6+)
Response duration ≥9 mo, n (%)¶ǁ	12 (77)

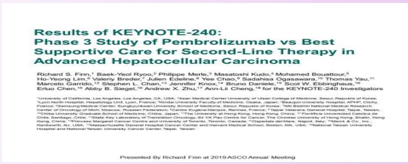
PDL-1 overexpressers may do better, but so may older women from the US

2018 ASCO ANNUAL MEETING 25

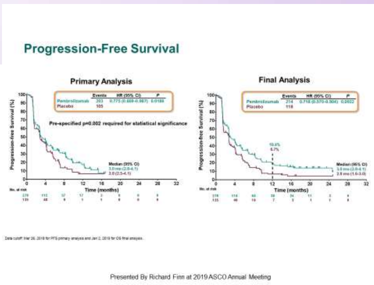
	Pembrolizumab (n=104)
Median OS, months (95%CI)	12.9 (9.7, 15.5)
Median PFS, months (95%CI)	4.9 (3.4, 7.2)
ORR, n (%)	18/104 (17)

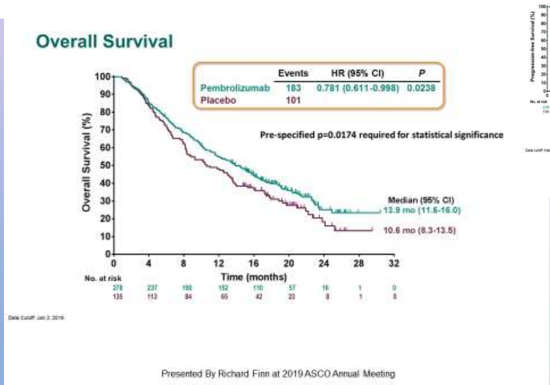
KUDO M, ET AL. J CLIN ONCOL 2018;36(SUPPL):ABSTR 4017
PECK-RADOSAVLJEVIC M, ET AL. J CLIN ONCOL 2018;36(SUPPL):ABSTR 4018
ABOU-ALFA GK, ET AL. J CLIN ONCOL 2018;36(SUPPL):ABSTR 4019
ZHU AX, ET AL. J CLIN ONCOL 2018;36(SUPPL):ABSTR 4020




Results of KEYNOTE-240: Phase 3 Study of Pembrolizumab vs Best Supportive Care for Second-Line Therapy in Advanced Hepatocellular Carcinoma

Presented By Richard Finn at 2019 ASCO Annual Meeting





Key Takeaways

- Sorafenib and regorafenib are the only agents approved for advanced HCC
  - Both are multikinase inhibitors with prominent antiangiogenic effects
  - Sorafenib is approved for first-line treatment
  - Regorafenib is approved for second-line treatment after sorafenib failure or intolerance
- In a head-to-head phase III trial, lenvatinib was shown to be noninferior to sorafenib and may be considered an alternative to sorafenib, particularly in patients with intolerance
- Important to recognize the class-wide side effects of these agents (eg, hand-foot skin reaction, hypertension, diarrhea, weight loss) and employ timely interventions to optimize treatment outcomes

i3Health

HCC - DRUGI RED ZDRAVLJENJA

Landscape-Second line therapy for HCC

		Total N	PFS benefit	OS benefit	RR
CHECKMATE040 (SINGLE ARM)	Nivolumab*	154	NA	NA median OS =15 mo*	14%
RESOURCE	Regorafenib* v placebo	573 (2:1)	+1.6 mo HR 0·46 (0.37-0.56); p<0·0001	+2.8 mo HR 0.63 (0.50-0.79) p<0.0001)	11%
CELESTIAL**	Cabozantinib v placebo	707 (2:1)	+3.3 mo HR=0.44 [0.36-0.52]; *P* < 0.001	+2.2 mo HR=0.76 (0.63-0.92) P = 0.0049	4%
REACH1	Ramucirumab v placebo	565	+0.7mo HR 0.63 [0.52-0.75]; p<0.0001	NO	7%
REACH 2 (AFP≥400)	**Ramucirumab v placebo**	**292 (2:1)**	**+1.2 mo HR 0.452 (0.339, 0.603) p< 0.0001**	**+1.2 mo HR 0.71 (0.531, 0.949); p=0.0199**	**4.6%**
Pooled REACH 1 / 2 (AFP≥400 subgroup)	*Ramucirumab v placebo*	*542*	*NA*	*+3.1 mo HR 0.694 (0.571, 0.842) P=0.0002*	*NA*

PRESENTED AT: 2018 ASCO ANNUAL MEETING

*FDA approved
** included 2nd and 3rd line; 2nd line update: Kelley, et al. Abstr #4088 ASCO 2018

7

VLOGA KIRURGA PRI ZDRAVLJENJU BOLNIKOV s HCC

J Cancer Res Clin Oncol (2009) 135:1067–1072
DOI 10.1007/s00432-009-0546-z

ORIGINAL PAPER

Twenty-year survivors after resection for hepatocellular carcinoma-analysis of 53 cases

Xin-Da Zhou · Zhao-You Tang · Zeng-Chen Ma ·

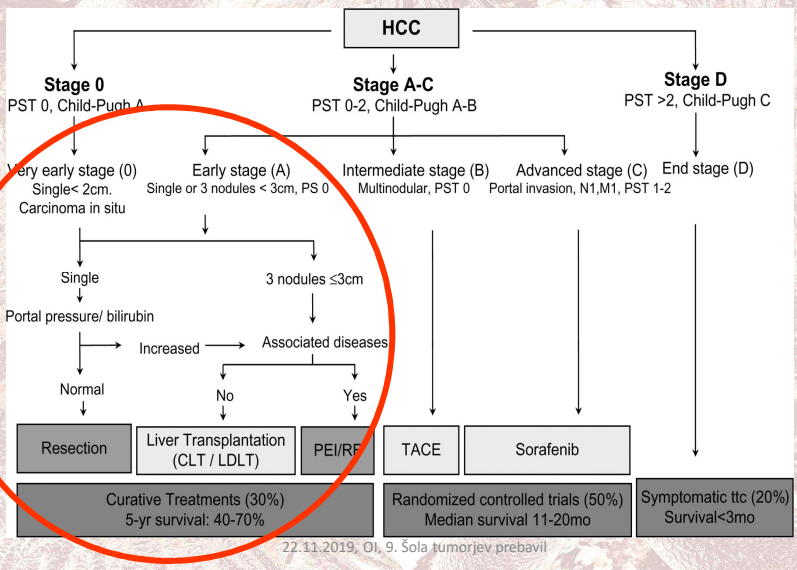
"These results may indicate that early detection and curative resection are the principal factors influencing long-term survival;

Reresection for subclinical recurrence and solitary metastasis remains an important approach towards further survival prolongation after curative resection."

In summary, our data showed that for patients with early stage HCC and underwent curative resection, long-term survival after resection could be expected. However, because tumor recurrence is common, postoperative follow-up is important and should continue for the remainder of the patient's life. Finally, aggressive therapy for recurrence, including reresection when necessary, is recommended.

BCLC-klasifikacija (99) + algoritem zdravljenja

Llovet et al., J Natl Cancer Inst 2008; 100: 698

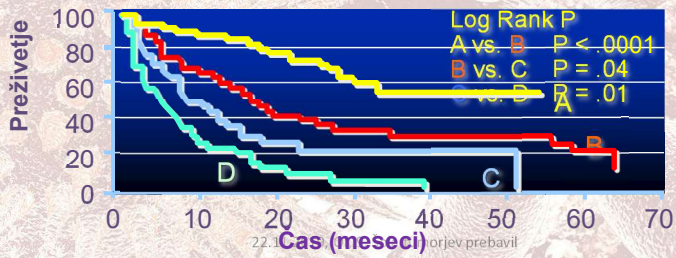


BCLC klasifikacija – "thin red surgical line"

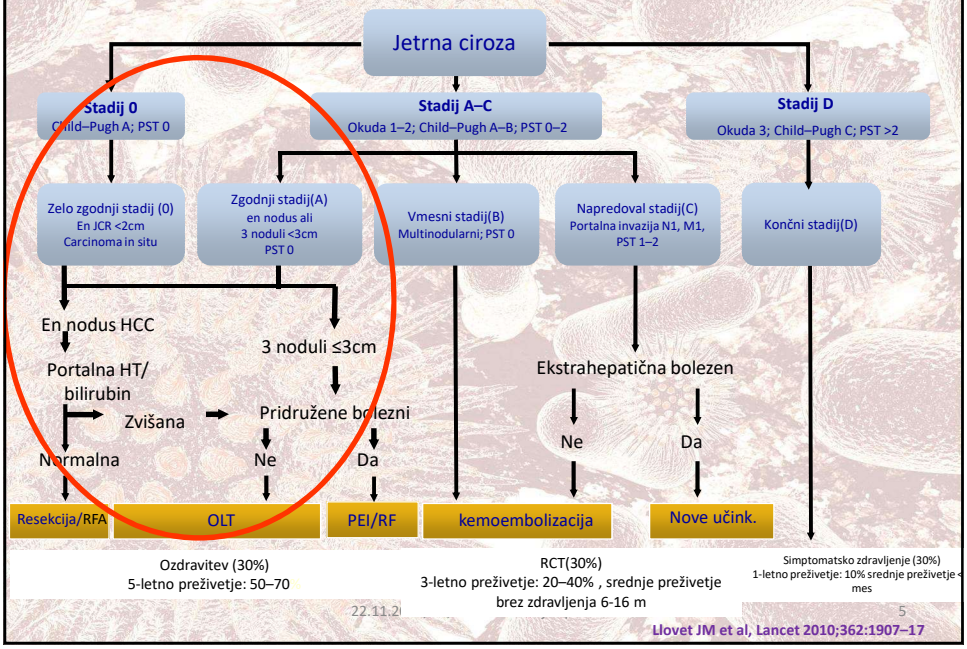
Table 1. Barcelona Clinic Liver Cancer Staging System

Stage	Tumor burden	Child–Pugh class	Performance status[a]	Median survival
Very early (0)	Single lesion <2 cm	A	0	*
Early (A)	Single lesion <5 cm or three lesions <3 cm each	A–B	0–2	53 months
Intermediate (B)	Single lesion >5 cm or multiple lesions, with largest >3 cm	A–B	0–2	16 months
Advanced (C)	Any tumor burden	A–B	1–2	7 months
Terminal (D)	Any tumor burden	C	>2	3 months

Adapted from [11].



BCLC - sistem in strategija zdravljenja



Uvod

- R0 Resekcija (≈50%) in OPJ (≈75%) omogočata 5- letno preživetje bolnikom s HCC.

- Samo 20-40% bolnikov je kandidatov za kurativno zdravljenje.
  - Obseg in število tumorjev
  - Širjenje izven jeter
  - Obseg osnovne jetrne bolezni (90% HCC).

RESEKCIJE

- Število resekcij narašča:
  - Izboljšanje slikovnih tehnik
  - Napredek v kirurških tehnikah
  - Izboljšanje pred in pooperativne oskrbe

Okvirni kriteriji za resekcijo ob kronični okvari jeter

Resekcija	Dejavniki
Manjša	C-P A
	Bilirubin < 35 µmol/L
	Ø ascitesa
	Trombociti >100x10^3/mm^3
Večja	Bilirubin < 17 µmol/L (Ø↑)
	Ø portalne hipertenzije
	FLR > 40% sicer PE
	C-P A, Ø ascitesa, Tr >100x10^3/mm^3

Izbor bolnikov

- Pomemben za optimalne rezultate po resekciji:
  - Obolevnost
  - Umrljivost
  - Dolgoročno preživetje
- Ocena:
  - Splošno stanje
  - Obseg tumorja
  - Stadij tumorja
  - Jetrna funkcija
  - V_{FLR}

Izbor bolnikov

- Spremljajoče bolezni so NND umrljivosti ob večjih resekcijah, neodvisno od starosti.
- ASA>1 – tvegani posegi
- Tveganje ni opravičljivo ob:
  - Srčnem popuščanju
  - KOPB
  - KLO

Wei AC, Tung-Ping Poon R, Fan ST, Wong J (2003) Risk factors for perioperative morbidity and mortality after extended hepatectomy for hepatocellular carcinoma. Br J Surg 90:33–41

Belghiti J, Hiramatsu K, Benoist S, Massault P, Sauvanet A, Farges O (2000) Seven hundred forty-seven hepatectomies in the 1990s: an update to evaluate the actual risk of liver resection. J Am Coll Surg 191:38–46

Ocena tumorja

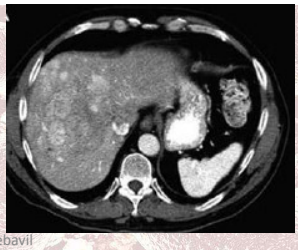
- MS-CT, MRI…. Na osnovi slikovnih metod
- Resekcija DA:
  - Možna R0 resekcija
  - Zadosten FLR
- Resekcija NE:
  - Širjenje izven jeter
  - Obsežni tumorski trombi v VCI
  - Zajetost AHC ali debla VP
  - **Invazivna rast v okolico npr. prepono, NI kontrindikacija če dosežemo R0**

Velikost tumorja

- Brez presejalnih programov >50% HCC na Zahodu v napredovalih stadijih.
  - (T>10 cm, multipli, ↑↑αFP, ruptura, trombi)
- Tudi take resekcije so varne!
  - 300, MR 5% - 30d

Pawlik TM, Poon RT, Abdalla EK et al (2005) Critical appraisal of the clinical and pathologic predictors of survival after resection of large hepatocellular carcinoma. Arch Surg 140:450–457

  – 5-letno preživetje 27-73%.
- Resekcija je edina možnost!
  - OPJ in RFA ne
  - TACE + EPV- downsize/downstage



Multinodularnost tumorja

- Med seboj neodvisni
- Napredoval stadij z jetrnimi zasevki
- Resekcija močno??
- 380/ B-BCLC/ MR 2,4%/ 5-l 39%

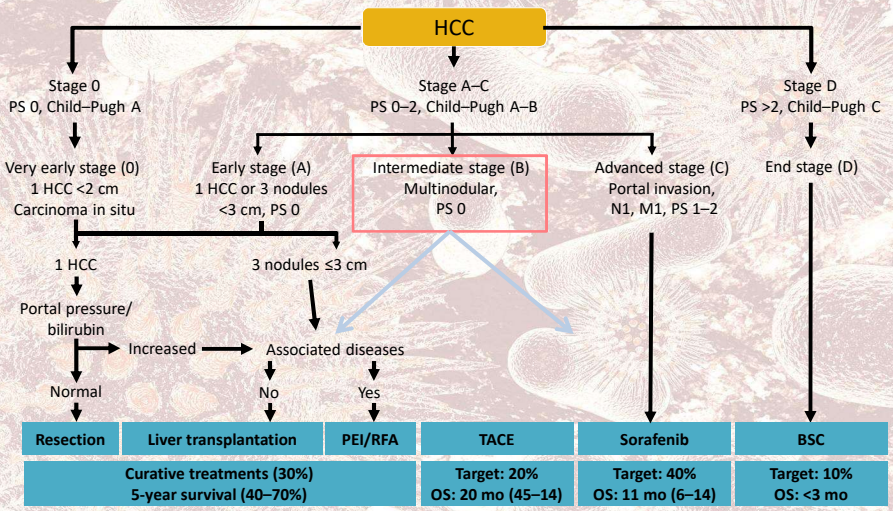
Ng KK, Vauthey JN, Pawlik TM et al (2005) Is hepatic resection for large or multinodular hepatocellular carcinoma justified? Results from a multi-institutional database. Ann Surg Oncol 12:364–373

- 15/63, bilobarno, R+LAT (RFA,PEI,TACE,R) - ↑preživetja

Liu CL, Fan ST, Lo CM, Ng IO, Poon RT, Wong J (2003) Hepatic resection for bilobar hepatocellular carcinoma: is it justified? Arch Surg 138:100–104

- R0 možna ob V_{FLR} – ena od možnosti

Downstaging



BSC, best supportive care; EASL, European Association for the Study of the Liver; EORTC, European Organisation for Research and Treatment of Cancer; mo, months; PEI, percutaneous ethanol injection; OLT, orthotopic liver transplantion; OS, overall survival; PS, performance status; RFA, radiofrequency ablation; TACE, transarterial chemoembolization

EASL–EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 2012;56:908–43; Available at: http://www.easl.eu/assets/application/files/d38c7689f123edf_file.pdf.

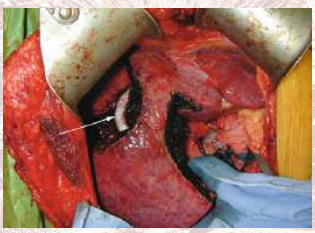
Zajetje PV in HV

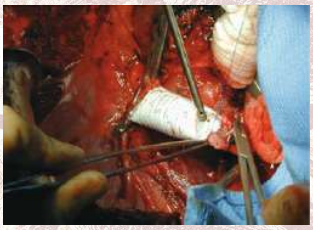
- Kirurški in onkološki izziv
- Resekcija izboljša preživetje
- HV in PV 102/ 5-l 23%

Pawlik TM, Poon RT, Abdalla EK et al (2005) Hepatectomy for hepatocellular carcinoma with major portal or hepatic vein invasion: results of a multicenter study. Surgery 137: 403–410

- PV 23/42%

Minagawa M, Makuuchi M, Takayama T, Ohtomo K (2001) Selection criteria for hepatectomy in patients with hepatocellular carcinoma and portal vein tumor thrombus. Ann Surg 233:379–384





Neuspeh resekcijskega zdravljenja recidiv

- 70-100% po 5 l
- 80-90% zgodnji
  - Vaskularna invazija – microsateliti
- 10-20% pozni
  - Novi primarni v cirozi
- Reresekcija smiselna, ko je možna, odvisna od:
  - F jeter, vzorca ponovitve, obsega 1. resekcije

– MR 0-8%, 5-l/50-70%.

Ocena jetrne funkcije

- C-P MR A-10%, B-32%, C-82%.
- PH > 10mm Hg NND dekompenzacije po op
  - Pooperativno: krvavitve iz varic, sepsa, jetrna odpoved
  - Splenomegalija, IA in esofagealne varice, Tr <100x10^3/mm^3 so kontraindikacija za op.

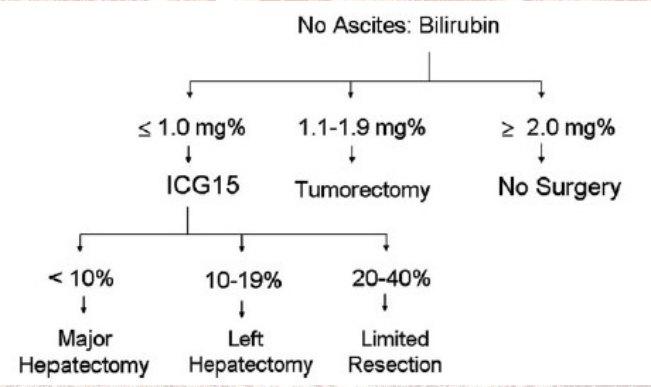
Bruix J, Castells A, Bosch J et al (1996) Surgical resection of hepatocellular carcinoma in cirrhotic patients: prognostic value of preoperative portal pressure. Gastroenterology 111:1018–1122

- Ciroza + aktivni hepatitis ↑MR 6x
  - 2x↑[ALT], [bilirubin] > 35 µmol/L ≠ OP

Noun R, Jagot P, Farges O, Sauvanet A, Belghiti J (1997) High preoperative serum alanine transferase levels: effect on the risk of liver resection in Child grade A cirrhotic patients. World J Surg 21:390–394

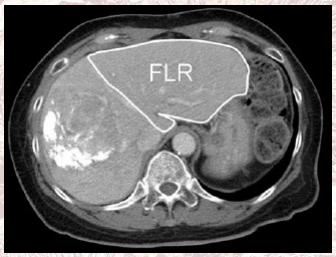
Ocena jetrne funkcije

- LIMON – očistek indocyanine zelene (ICG)
  - Japonski algoritem – MR 0%



OCENA V_{FLR}

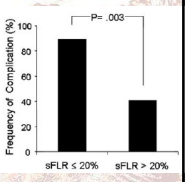
- CT- 3D volumetrija
- V_{FLR} 20% = min necirotična jetra
- V_{FLR} 40% = min ciroza ali hepatitis

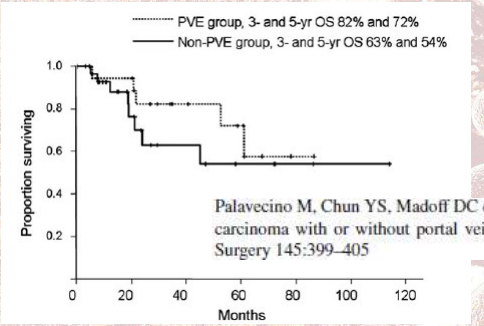


- %TLV = IzmerjenV_{FLR} / TLV (BSAx Konst)

Predoperativna priprava

- EPV - ↑V_{FLR}
  - malo zapletov < 5%, ↑V, ↑očistek ICG
  - Manj postop. zapletov in krajša hospitalizacija

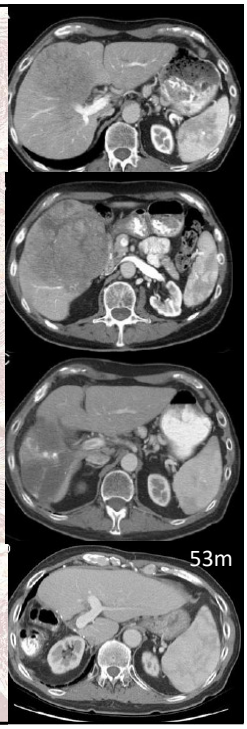




Palavecino M, Chun YS, Madoff DC et al (2009) Major hepatic resection for hepatocellular carcinoma with or without portal vein embolization: Perioperative outcome and survival. Surgery 145:399–405

Predoperativna priprava

- EPV ↑pretok po HA, ki prehranjuje HCC
- EPV + TACE
  - Podaljša interval brez bolezni
  - Poveča hipertrofijo FLR
  - Nekroza 60-80% tumorja
- SORAFENIB – neoadjuvantno??
- PIAF (cisplatin, interferon adriamycin, 5-FU)
  - Poveča resektabilnost??



Kirurška tehnika

- Anatomske resekcije
- Pringle, totalna ekskluzija, ex vivo
- CVP 0-5
- Anteriorni pristop
- Liver hanging" manever

HPB, 2006; 8: 35–37

Liver hanging maneuver for right hemiliver *in situ* donation – anatomical considerations

B. TROTOVŠEK[1], E. M. GADŽIJEV[2], D. RAVNIK[3] & M. HRIBERNIK[3]

Anatomske resekcije

- HCC se širi hematogeno
  - Najprej po portalni veni - intrahepatalne meta
  - Kasneje po venah izven jeter (pljuča, kosti, suprarenalka)
- Anatomska resekcija je NND preživetja in intervala brez bolezni.
- Varnostni rob je manj pomemben kot mikrozasevki – segmentne resekcije!!

Preprečevanje krvavitve

- Predoperativna priprava
- Kirurška tehnika
- Nizek CVP
- Velika izguba krvi je NND:
  - Zapletov
  - Smrtnosti
- Transfuzija KE
  - ↑koagulopatij
  - Imunosupresija – zgodnji recidivi – krajše preživetje

Preprečevanje krvavitve

- Pringle 15/5 varnejši pri cirozi
  - (varno do 80min) Belghiti J, Noun R, Malafosse R et al (1999) Continuous versus intermittent portal triad clamping for liver resection: a controlled study. Ann Surg 229:369–375
- TVE enako učinkovit kot Pringle – več zapletov
- Nizek CVP ↓krvavitev iz HV
- Sodobne tehnike preparacije
  - CUSA, HS, LigaSure, RF elektroda
- Dreni

Rezultati - pooperativni

- Danes sprejemljiva MR < 5%
- Zapleti v 25-50%
  - Bilomi (5%), krvavitve, abscesi, jetrna insuficienca….
  - Krvavitev = NND postoperativne umrljivosti
  - Pringle >80 min = NND manjših zapletov in obolevnosti

Rezultati - dolgoročni

- ↑preživetja na 30-50%
  - Zgodnejše odkrivanje
  - Boljši izbor bolnikov
  - Boljša kirurška oskrba
- Z resekcijo težko rešljiva težava so recidivi
- Napovedni dejavniki preživetja (register 5800 p)
  - Zajetost PV
  - Število tumorjev
  - αFP
  - Velikost tumorja
  - Stadij ciroze
  - Starost
  - R0 resekcija

Fibrolamelarni HCC

- 5-15%HCC
- Mlajši bolniki (20-30l), necirotična jetra
- Enojni tumorji, vendar veliki
- Neresektabilni srednje preživetje 14m – 2x ↑HCC
- 30% limfogeni zasevki -? Limfadenektomije
- Resektabilnost 58%, 5-l preživetje 56%

Hemming AW, Langer B, Sheiner P, Greig PD, Taylor BR (1997) Aggressive surg.ical management of fibrolamellar hepatocellular carcinoma. J Gastrointest Surg. 1:342–346

Fibrolamelarni HCC

- OPJ ni metoda izbora za te bolnike
- Resekcija/ OPJ po 5 letih 75%/36%

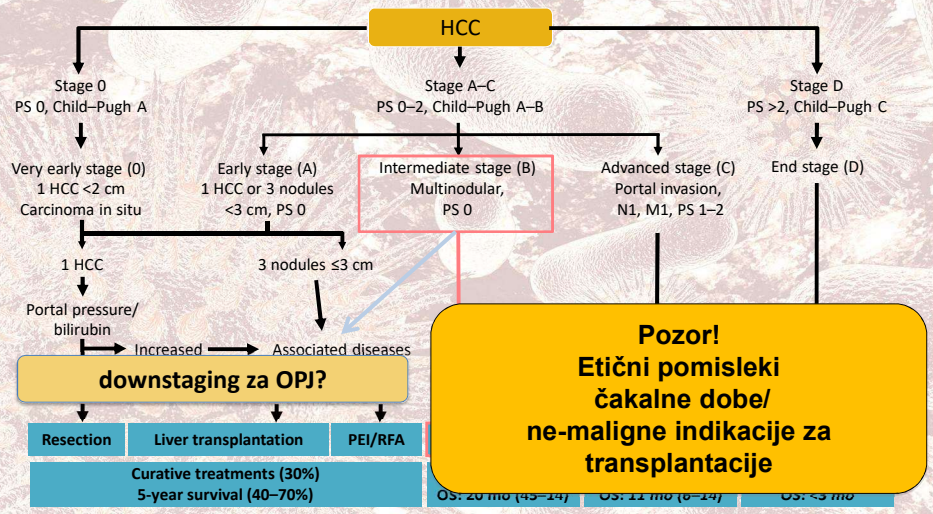
Pinna AD, Iwatsuki S, Lee RG et al (1997) Treatment of fibrolamellar hepatoma with subtotal hepatectomy or transplantation. Hepatology 26(4):877–883

Neuhaus P, Jonas S, Bechstein WO (2000) Hepatoma of the liver–resection or transplantation? Langenbecks Arch Surg. 385:171–178

Resekcija kot most do OPJ

- Resekcija pri bolnikih s HCC, ki čakajo na presaditev, lahko ob progresu bolezni bolnika ponovno vrne na listo čakajočih.
- Resekcijo za “bridging” uporabimo samo pri bolnikih z ohranjenim delovanjem jeter.
- Rezultati OPJ po predhodni resekciji so enako dobri.

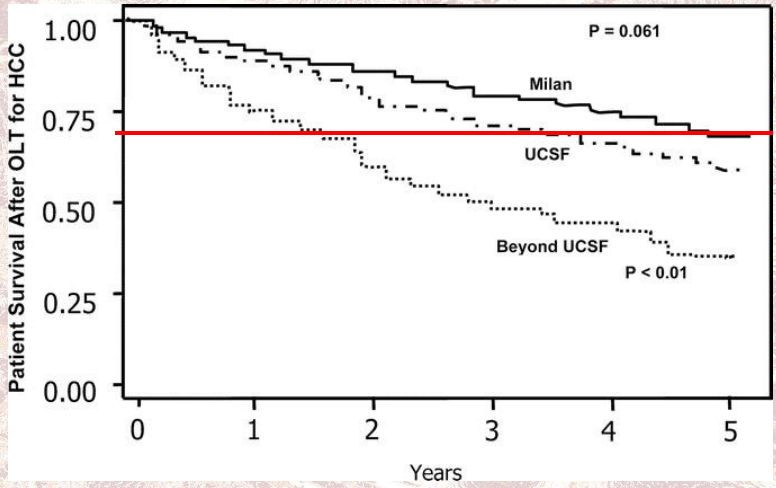
Prehajajoča (migracijska) terapija - downstaging



BSC, best supportive care; EASL, European Association for the Study of the Liver; EORTC, European Organisation for Research and Treatment of Cancer; mo, months; PEI, percutaneous ethanol injection; OLT, orthotopic liver transplantion; OS, overall survival; PS, performance status; RFA, radiofrequency ablation; TACE, transarterial chemoembolization

EASL–EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 2012;56:908–43; Available at: http://www.easl.eu/assets/application/files/d38c7689f123edf_file.pdf.

HCC in OPJ



HCC in OPJ

- Milanski kriteriji 1 <5cm, 3 <3cm (ET in SLO)
- UCSF kriteriji 1< 6.5cm, 3 < skupaj od 8cm največji < 4,5cm
- "Razširjeni Milanski kriteriji 1 <5cm, 3< skupaj od 7cm"

Mazzaferro V, Regalia E, Doci R et al (1996) Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 334:693–699

HCC in OPJ

- 5-l preživetje ≈ 70% je slabše kot pri bolnikih z nemalignimi boleznimi,
- HCV okužba in HCC – po OPJ preživetje presadka in bolnika je določal HCV in ne HCC, danes ne več.
- 10% recidivov po 5 l

3 DILEME pri HCC

- Pacienti s Child Pough A and solitarnim HCC
- Milanski kriterij
- Bridging in downstaging

Pacienti s Child Pough A in solitarnim HCC

- Resekcija (brez PH)
- Lokalne ablativne tehnike (pri PH)
- Transplantacija
  - Najnižja stopnja ponovitev HCC
  - Enako 1L in boljše 3 in 5l preživetje (dropoff)
  - PRECENJENO PREŽIVETJE
    - Rezultati le pri presajenih in ne vseh na čakalni listi.

Pacienti s Child Pough A in solitarnim HCC

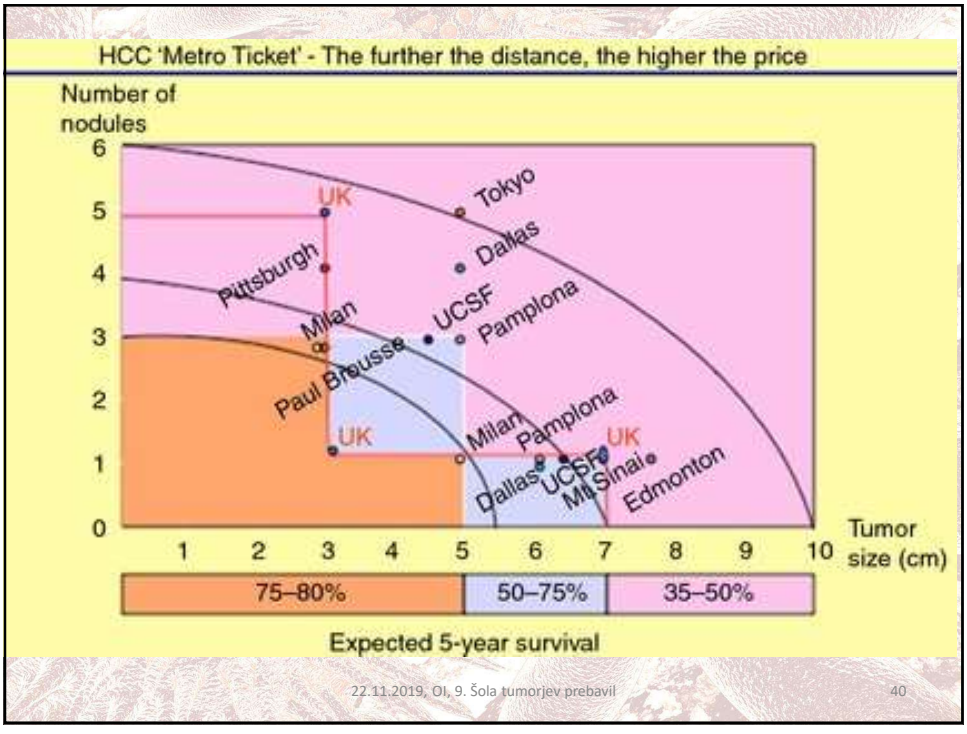
- MELD je močan napovedni dejavnik preživetja na čakalni listi za OPJ ali resekcijo.
- 5-L preživetje po resekciji (67%) in MELD < 10 in 47% pri tistih z MELD ≥10.
  - OPJ boljše preživetje MELD > 10 in tu z mikrovaskularno invazijo.
- OPJ je drago zdravljenje.
  - Cost efficient samo če je 5-L preživetje > 87.6%.

Pacienti s Child Pough A in solitarnim HCC

- Resekcija in ablacija sta prvi liniji zdravljenja in stroškovno učinkoviti.
- Ob ponovitvi HCC - “salvage LT”.
- Salvage LT dobro OS: 3 and 5-L 80 in 62%.

Milanski kriteriji

- HCC – ET +10T, ZDA priority
- Znotraj MC: ponovitev < 15%, 5-L preživetje ≈ 70%
- „Extended criteria“ izboljšajo dostopnost za OPJ do 50% pacientov.
- V metaanalizah so rezultati slabši.
- Preživetje < 60% ne opravičuje OPJ zaradi vpliva na čakalne liste.
- ???LR-OPJ



Bridging

- HCC znotraj MC pri cirozi CP B,C→ OPJ
- T1 HCC (<2cm) – 10% pacientov lahko preskoči MC na ČL- BIOLOGIJA TU
  - AFP > 500 IN RAST >1cm/3mesece
    - TACE, MWA – omogoča premostitev
    - SBRT – vloga prihodnosti

Downstaging

- Lokalne ablativne tehnike za HCC > MC, da ↓ Tu breme
- Uspešne v < 50%
- Ponovitev ↑ kot znotraj MC ≈17%
- Preživetje 5-L (70-90% - nehomogena distribucija)

Downstaging

- Zaradi nekonsistentnosti rezultatov le znotraj študij in v programih z velikim številom donorjev KO NI VPLIVA NA ČL.

Zaključek

- OPJ je trenutno edino zdravljenje dveh muh na en mah.
- OPJ pri nas v okviru Milanskih kriterijev.

9.Šola Tumorjev Prebavil 22.11.2019 Ljubljana

Medicinska fakulteta
Univerza v Ljubljani, Slovenija

Multidisciplinarni pristop k zdravljenju bolnika s HCC
Vloga interventne radiologije

Popovič Peter

Klinični Inštitut za radiologijo, UKC Ljubljana
Medicinska Fakulteta, Katedra za slikovno diagnostiko, Univerza v Ljubljani,

klinični center ljubljana
University Medical Centre Ljubljana

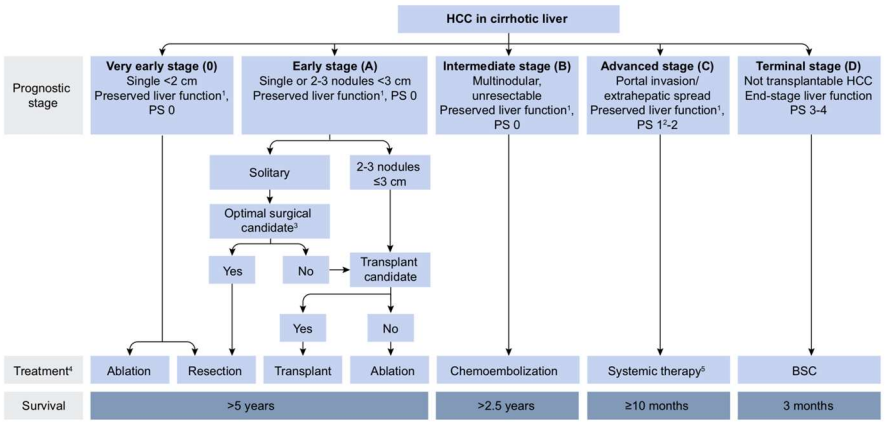
KLINIČNI INŠTITUT ZA RADIOLOGIJO

HPB konzilij

- **Interventni radiolog**
- **Gastroenterolog**
- **Radiolog**
- **Kirurg**
- **Onkolog**
- **Radioterapevt**

Sreda 9 KIR

BCLC klasifikacija



Journal of Hepatology 2018

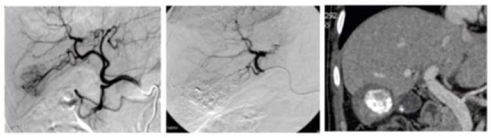
MWA - naše izkušnje

- 6.3.2018 do 8.10.2019
- 25 pacientov
- Povprečna velikost lezije: **21,6 mm** (8 do 41).

- **38 posegov** (35 lezij) :
  - 28 MWA
  - 10 TACE + MWA

Kombinirano zdravljenje TACE in ablacija

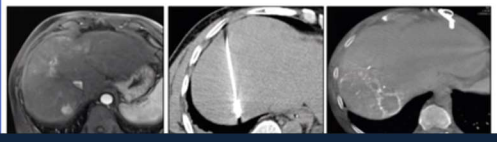
TACE first, followed by Ablation



Percutaneous Radio-frequency Thermal Ablation of Nonresectable Hepatocellular Carcinoma after Occlusion of Tumor Blood Supply[1]

Radiology 2000; 217:119-126

Ablation first, followed by TACE



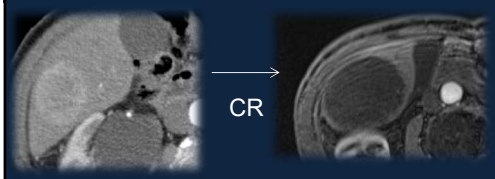
Journal of Hepatology

Doxorubicin-eluting bead-enhanced radiofrequency ablation of hepatocellular carcinoma: A pilot clinical study

J Hepatol 2008; 49:217-222

Odgovor tumorja na zdravljenje - mRECIST

Complete response (CR)	Disappearance of all intratumoral enhancement
Partial response (PR)	At least 30% decrease in the sum of the longest diameters of viable target lesions
Progressive disease (PD)	At least 20% increase in the sum of the longest diameters of viable target lesions recorded since treatment started
Stable disease (SD)	None of the above



- 1 mesec po posegu (CT&MR)
- na 3 mesece prvo leto, naprej na 6 mesecev (CT&MR)

Llovet et al. J Natl Cancer Inst 2008

Srednji štadij HCC: Prognoza - EASL, EORTC

- srednje preživetje 11- 16 mesecev (brez terapije)
- srednje preživetje 20-24 mesecev (randomizirane)
- srednje preživetje 16-48 mesecev

EASL–EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma Journal of Hepatology 2012 vol. 56 j 908–943

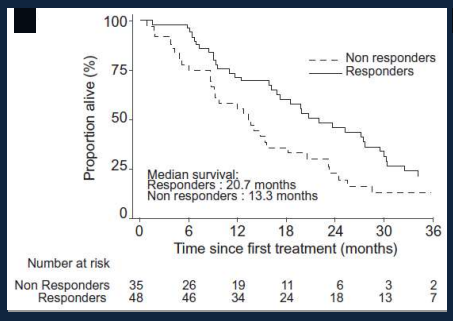
Preživetje-TACE

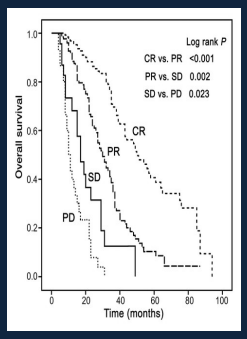
mOS 11-16 mes

	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 16-48 mes (28-37 mes)

Pomen doseganja objektivnega odgovora na zdr. – vpliv na preživetje





Primerjava krivulj preživetja po Kaplan–Meier-ju:

(A) med bolniki z doseženim obj.odg. glede na mRECIST (t.i. “responders”) in bolniki brez njega (t.i. “non-responders”);

(B) med bolniki glede na posamezno vrsto odgovora.

Gillmore R et al. Journal of Hepatology 2011

Shim JH et al. Radiology. 2012

Rezultati – večji zapleti

4/362 posegov (1,1%)

Večji zapleti	**Število**
Abscess	1
CVI	1
AMI tip 2	1
Krvavitev iz varic	1

30-dnevna smrtnost je bila 0%.

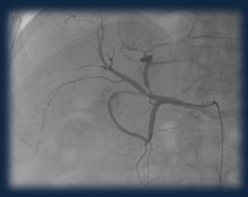
Popovic P et al. Clinical&Experimental Oncology 2018

Radioembolizacija (SIRT)

(selektivna notranja radioterapija, hepatična brahiterapija)

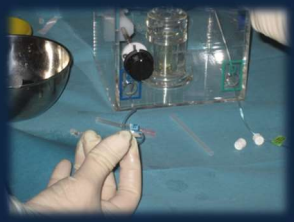
selektivna intraarterijska aplikacija zelo visoke doze sevanja v tumorje v jetrih, ob prejeti majhni dozi sevanja normalnega jetrnega tkiva

Mikrodelci (20-40 μm) Y-90

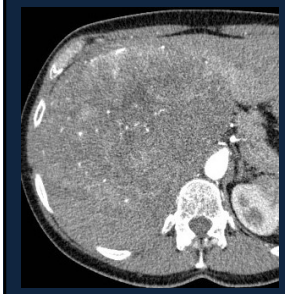


Y-90: Beta sevanje
povprečna razdalja: 2,5 mm
največja razdalja: 11 mm
doza do 3 GBg
120 Gy

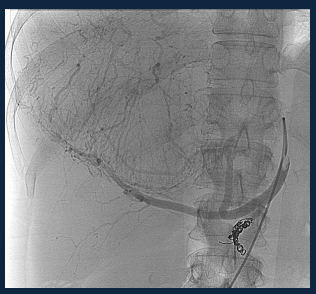
raspolovni čas: 64 h



51 let, F, HCC 18 cm, ni ciroze

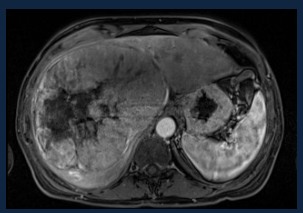


April 2015

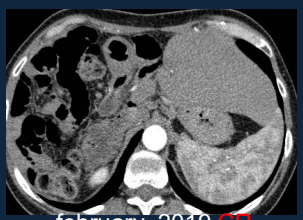


SIRT Maj 2015

Oktober 2015 PR



Surgery december 2015



february 2019 CR

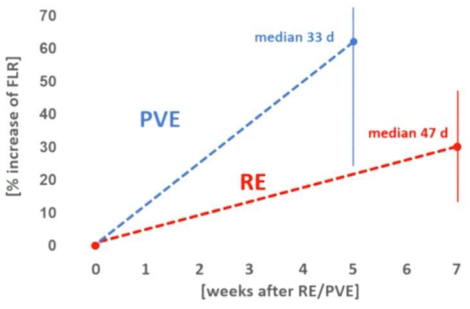
SIRT – učinkovit pri "down-sizing"

"Available data suggest that SIRT in unresectable **HCC** and **iCCA** can provide a considerable **down-sizing** of the tumors to **possibly allow resection** (....). In patients whose FLR volume represents the only surgical concern, portal vein embolization remains the treatment of choice."

Cuchetti A et al., Liver Cancer 2016

Hipertofija po PVE in SIRT

Left-Liver Hypertrophy After Therapeutic Right-Liver Radioembolization Is Substantial but Less Than After Portal Vein Embolization



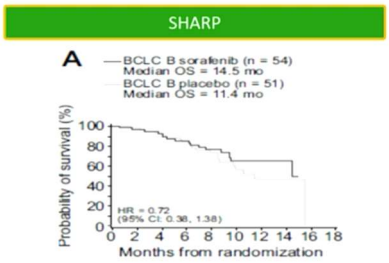
matched pair analysis

FLR increase	PVE (n=26)	RE (n=26)
> 30%	22	12
21 - 30 %	3	3
11 % - 20%	1	6
≤ 10 %	0	5
	4 %	42 %

Gorlipp B et al. Hepatology 2014

BCLC B – večji ali številni tumorji

Could be treated with Sorafenib but evidence is not robust



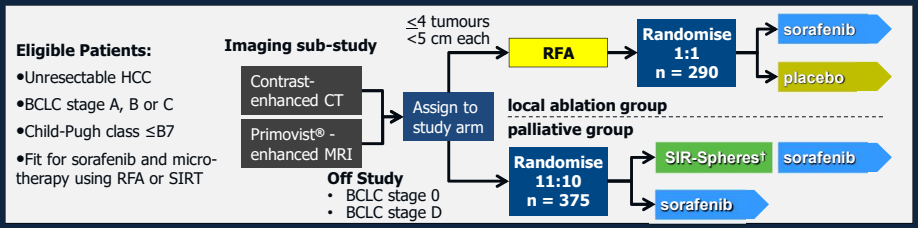
however, the wide confidence interval for OS in the BCLC B subgroup did not allow a robust conclusion in these patients.

Bruix J et al. J Hepatol 2012

SORAMIC study

Can the overall survival of patients with HCC be improved by combining sorafenib with SIR-Spheres microspheres?

Design: Prospective open-label, multi-centre, multi-national (Europe) RCT



Primary endpoints:
Imaging sub-study: Non-inferiority (1st step) or superiority (2nd step) of Primovist-enhanced MRI
Local ablation: Time-to-recurrence
Palliative: Overall survival
Sponsor: University of Magdeburg
PIs: Prof. Peter Malfertheiner; Prof. Jens Ricke
Status: dec.2015

Secondary endpoints:
- Quality of life
- Biomarker analysis

Imaging sub-study:
- Detected lesions and diagnostic confidence

Local ablation group:
- Detection of recurrence
- Safety and toxicity

Palliative group:
- Safety and toxicity
- Overall survival for patients with or without PVT

Research Article
Cancer

JOURNAL OF HEPATOLOGY

Impact of combined selective internal radiation therapy and sorafenib on survival in advanced hepatocellular carcinoma

Jens Ricke[1,*], Heinz Josef Klümpen[2], Holger Amthauer[3], Irene Bargellini[4], Peter Bartenstein[5], Enrico N. de Toni[6], Antonio Gasbarrini[7], Maciej Pech[8], Markus Peck-Radosavljevic[9], Peter Popovič[10], Olivier Rosmorduc[11], Eckart Schott[12], Max Seidensticker[13], Chris Verslype[14], Bruno Sangro[15,#], Peter Malfertheiner[16,#]

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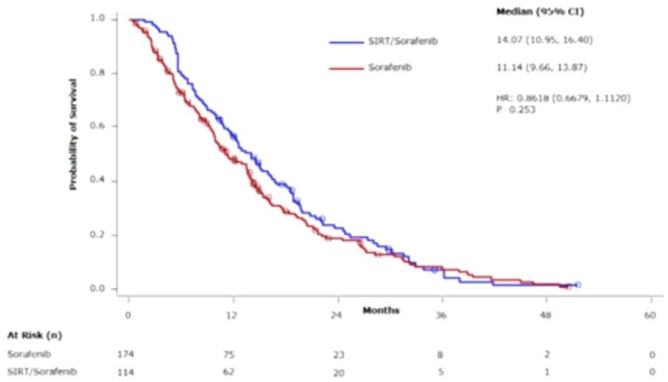
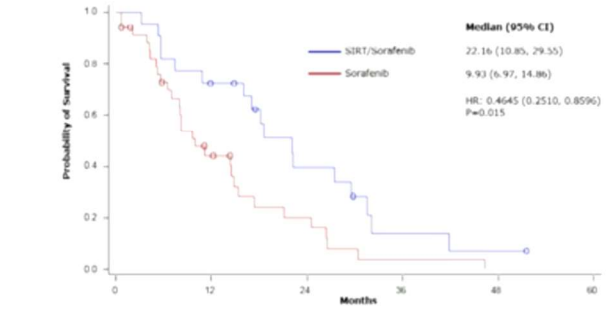
2019

OVERALL SURVIVAL: SIRT/SORAFENIB VS SORAFENIB (PER PROTOCOL POPULATION)

soramic

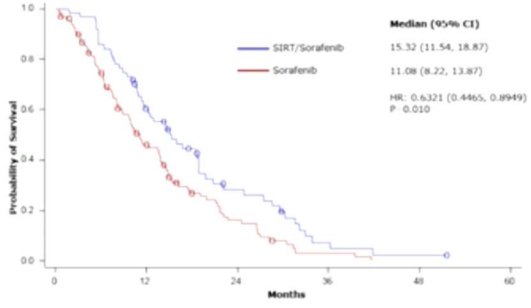


OVERALL SURVIVAL: NON-CIRRHOTIC PATIENTS
(PER PROTOCOL POPULATION)



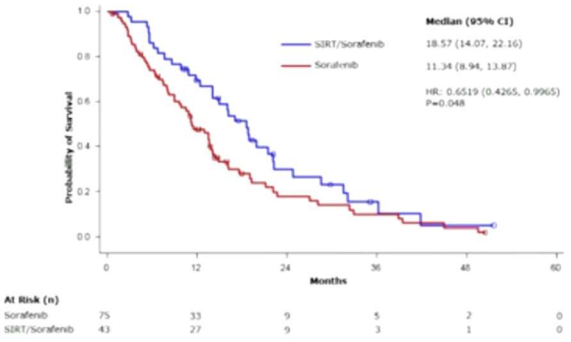
At Risk (n)						
Sorafenib	35	13	5	1	0	
SIRT/Sorafenib	22	15	7	2	1	0

OVERALL SURVIVAL: PATIENTS WITH NON-ALCOHOLIC AETIOLOGY (PER PROTOCOL POPULATION)



At Risk (n)						
Sorafenib	101	41	12	2	0	
SIRT/Sorafenib	64	36	13	3	1	0

OVERALL SURVIVAL: PATIENTS <65 YEARS OF AGE (PER PROTOCOL POPULATION)



KLINIKUM DER UNIVERSITÄT MÜNCHEN
KLINIK UND POLIKLINIK FÜR RADIOLOGIE

SARAH

To determine whether radioembolisation with SIR-Spheres microspheres is more effective on overall survival in advanced HCC than sorafenib

Design: Prospective open-label, multi-centre, national (France) RCT

Eligible Patients:

- Unresectable HCC
- BCLC stage C or
- BCLC stage A/B:
  - New lesions post-radical therapy and unsuitable for further radical therapy or
  - No objective response after ≤2 TACE sessions
- Child-Pugh class A or B ≤7 points
- ECOG performance status 0–1
- Fit for sorafenib and SIRT

Stratify
- ECOG performance status
- Vascular invasion
- Prior TACE
- Institution

→ **Randomise 1:1 n = 400** → sorafenib / SIR-Spheres †

Primary endpoint: Overall survival

Sponsor: Assistance Publique – Hôpitaux de Paris (AP-HP)

PI: Prof. Valérie Vilgrain

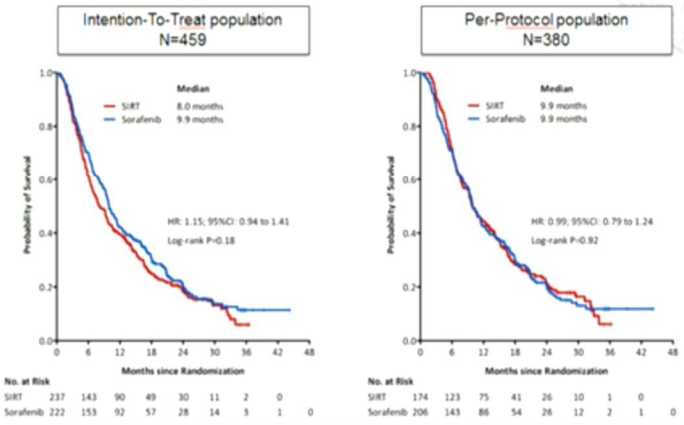
Status: Currently enrolling

Secondary endpoints:
- Safety and toxicity
- Quality of life
- Healthcare costs
- Progression-free survival (PFS) at 6 months

http://clinicaltrials.gov/ct2/show/NCT01482442;

SARAH

Overall survival



No significant difference in overall survival between groups

26.6% of patients didn't get SIRT & 7.2% sorafenib per protocol

Phase III multi-centre open-label randomized controlled trial of selective internal radiation therapy (SIRT) versus sorafenib in locally advanced hepatocellular carcinoma: The SIRveNIB study.

Pierce K.H. Chow
National Cancer Center Singapore, Singapore
DukeNUS Medical School, Singapore

Mihir Gandhi
Singapore Clinical Research Institute, Singapore
DukeNUS Medical School, Singapore

THE Asia-Pacific Hepatocellular Carcinoma Trials Group

National Cancer Centre Singapore
SingHealth

DukeNUS Medical School

On behalf of

The Asia-Pacific Hepatocellular Carcinoma Trials Group

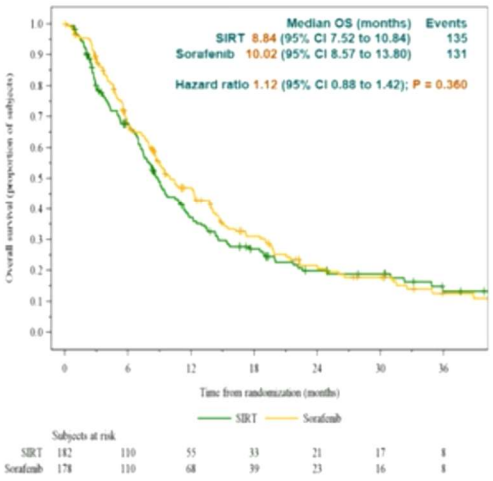
(http://www.scri.edu.sg/crn/asia-pacific-hepatocellular-carcinoma-ahcc-trials-group/about-ahcc/)

ClinicalTrials.gov: NCT01135056

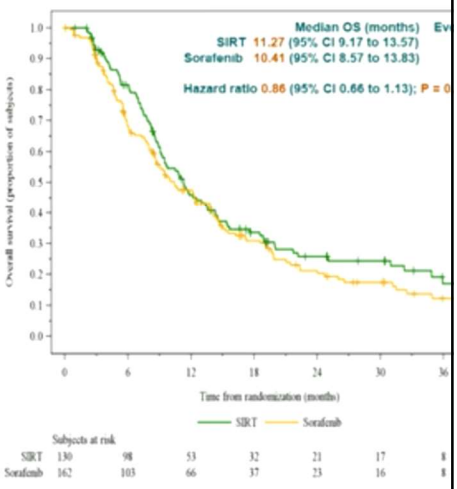
SCRI Singapore Clinical Research Institute

Efficacy: Overall Survival

Intent-to-treat population



Treated population



SARAH&SIRveNIB
827 pts

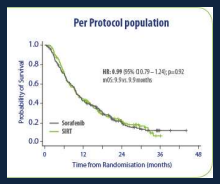
SIRT proti Sorafenib BCLC C

Signifikantno manj stranskih učinkov

Bolniki boljše prenašajo SIRT

Signifikantno boljša kvaliteta življenja

Preživetje enako



Vilgrain et al.Lancet Oncol 2017

SIRT- naše izkušnje

- junij 2012-februar 2019
- 20 posegov (HCC-slabi kandidati za TACE, velik tumor >10 cm, bilobarna bolezen, progres po TACE)
- povprečna doza Y^{90} - 1,4 GBq (razpon 0,42 – 2,57)

Popovic P in sod. 4th International Alps - Adria - Danube meeting 2019

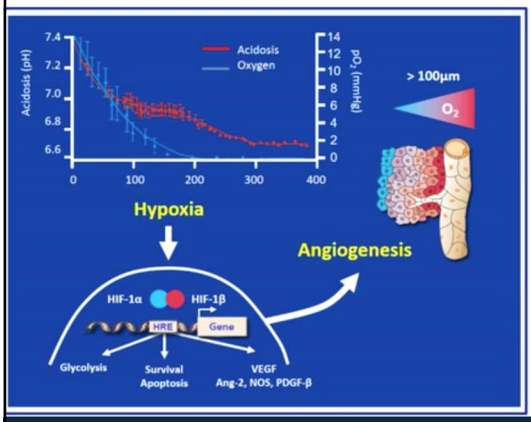
Rezultati -zapleti

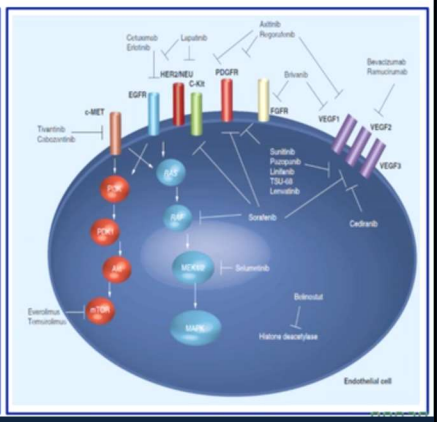
3/20 posegov (15%)

Manjši zapleti		
zaplet	**število**	**zdravljenje**
bolečina	3	Ne opijatni analgetiki

Popovic P in sod. 4th International Alps - Adria - Danube meeting 2019

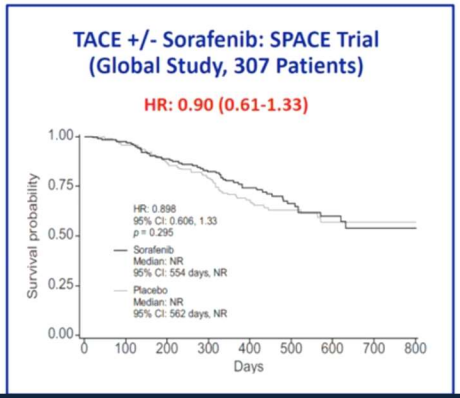
Kombinirano zdravljenje TACE in biološka zdravila

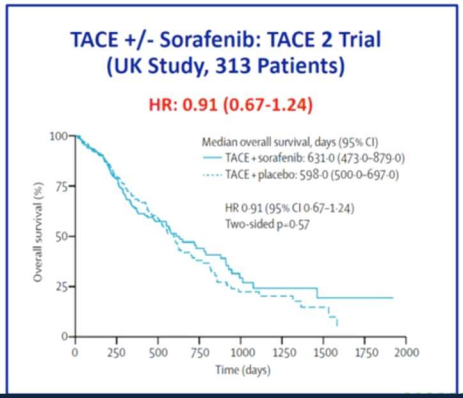




McNamara MG.Hepatic Oncol 2014

TACE in biološka zdravila *randomizirane raziskave*



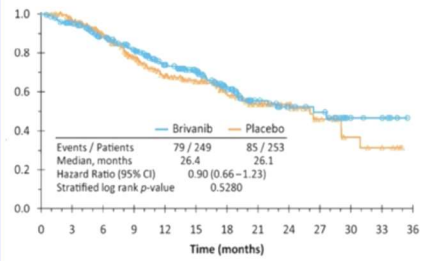


Lencioni R in sod. J Hepatol 2016 *Mayer T in sod. Lancet Gastroenterolo Hepatol 2017*

TACE in biološka zdravila
randomizirane raziskave

TACE +/- Brivanib: BRISK-TA Trial (Global Study, 502 Patients)

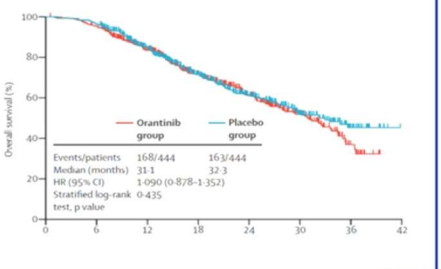
HR: 0.90 (0.66-1.23)



Kudo M et al. Hepatology 2014

TACE +/- Orantinib: ORIENTAL Trial (Japanese Study, 888 Patients)

HR: 1.09 (0.88-1.35)



Kudo M in sod. Lancet Gastroenterol Hepatol 2018

TACE in biološka zdravila
EMERALD -1

A Phase III, Randomised, Double-Blind, Placebo-Controlled Study
International Coordinating Investigators: R. Lencioni, B. Sangro

Study population

- Confirmed HCC
- Unsuitable for curative therapy, e.g. surgical resection, ablation, transplantation
- Disease amenable to TACE
- No extrahepatic disease
- Child-Pugh A to B7
- ECOG 0 or 1
- Exclude Vp3 and Vp4

R

N=600

Arm A
TACE + durvalumab

Arm B
TACE + durvalumab + bevacizumab

Arm C
TACE + placebo

Primary endpoint:
PFS for Arm A versus Arm C (BICR)

Secondary endpoints:
PFS for Arm B versus Arm C (BICR), OS, PROs

Other endpoints:
Safety, PK

BICR, blinded independent central review; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PROs, patient-reported outcomes.

www.clinicaltrials.gov

Zaključek

- Bolnike v zgodnjem stadiju bolezni zdravimo z ablativnimi metodami
- Kemoembolizacija je metoda izbora v srednjem stadiju bolezni
- SIRT lahko izvajamo v sklopu raziskav ali pa pri izbrani skupini bolnikov BCLC B in BCLC C, ki so slabi kandidati za TACE in v primeru progresa po TACE
- kombinirano zdravljenje različnih metod intervencijske radiologije in biološkega zdravljenja
- Multidisciplinarni pristop

Prikaz primera
multidisciplinarni pristop

Zdenko Kikec
SB Slovenj Gradec

Ljubljana, 22. november 2019

Prikaz primera

- 58 letni delovno aktiven moški
- prosi za gastroskopijo zaradi spahovanja in postprandialnega tiščanja v epigastriju
- status in pridružene bolezni olezni:
  - *status performans po WHO 0*
  - *sladkorna bolezen na insulinski terapiji*

Prikaz primera

- **Gastroskopija** (2.4.2019)
  - *normalen požiralnik, EG prehod, fundus, korpus želodca in duodenum*
  - *blago pordela sluznica antruma*
  - *ureazni test je po 24 urah negativen*
  - *Histološki izvid: blag kemični gastritis*

- **Laboratorijski izvidi** (2.4.2019)
  - KKS
  - CRP 100
  - elektroliti
  - urea
  - kreatinin
  - amilaza
  - lipaza
  - LDH
  - PSA

Prikaz primera

- **Gastroskopija** (2.4.2019)
  - *normalen požiralnik, EG prehod, fundus, korpus želodca in duodenum*
  - *blago pordela sluznica antruma*
  - *ureazni test je po 24 urah negativen*
  - *Histološki izvid: blag kemični gastritis*

- **Laboratorijski izvidi** (2.4.2019)
  - KKS
  - CRP 100
  - elektroliti
  - urea
  - kreatinin
  - amilaza
  - lipaza
  - LDH
  - PSA
  - ***CEA 31,5***
  - ***Ca 19-9 > 10 000***

Prikaz primera

- **UZ abdomna** (3.4.2019)
  - *35 mm velika hipoehogena sprememba glave trebušne slinavke*
  - *številne fokalne hipoehogene sprememb v različnih jetrnih segmentih*
- **CT abdomna** (4.4.2019)
  - *38 x 35 x 45 mm velika tumorska formacija v glavi trebušne slinavke*
  - *suspektno preraščanje duodenuma*
  - *zasevki v več jetrnih segmentih (vsaj 10)*
  - *posamezne povečane bezgavke med želodcem in trebušno slinavko*
  - *tumorski tromb v. porte*

Prikaz primera

- **Biopsija jeter** (5.4.2019)
  - *normalni hepatociti*
- **Endoskopski UZ z igelno biopsijo** (15.4.2019 KOGE Lj)
  - *adenokarcinom trebušne slinavke*

Je vedno potrebna histološka potrditev?

Sladkorna bolezen!!

Prikaz primera

- **Laboratorij** (23.4.2019)
  - *bilirubin 230/213*
  - *AST 3,7*
  - *ALT 8,9*
  - *gamaGT 28,7*
  - *AF 4,4*

Prikaz primera

- **Laboratorij** (23.4.2019)
  - *bilirubin 230/213*
  - *AST 3,7*
  - *ALT 8,9*
  - *gamaGT 28,7*
  - *AF 4,4*

Obstrukcijski ikterus zaradi tumorja glave trebušne slinavke

Prikaz primera

- **ERCP** (24.4.2019)
  - *endoskopist v naši ustanovi ne uspe vstaviti stenta*
- **Zunanja biliarna drenaža**
  - *v drugi ustanovi ne uspe*
- **ERCP** (26.4.2019 KOGE)
  - *uspešno vstavljen samoraztezni kovinski stent*

Prikaz primera

- **Kemoterapija 1. reda**
  - *FOLFIRINOX*
  - *prva aplikacija na OI Ljubljana*
  - *prejme 4 cikluse*
  - *brez pomembnejših stranskih učinkov*
- **Kontrolni CT**
  - *velikost tumorja je manjša*
  - *jetrne metastaze so večje in številčnejše*
  - *brez tromba v. porte*
  - *Ca 19-9 je ves čas nad 10 000*

Prikaz primera

- **Kemoterapija 2. reda**
  - *nab Paklitaksel in Abraksan*
  - *terapijo odlično prenaša*
  - *Ca 19-9 750*
  - *prejme 3 cikluse*
- **Kontrolni CT** (25.10.2019)
  - *tumor trebušne slinavke stagnira*
  - *metastaze v jetrih - regres*

Prikaz primera

- **27.10.2019**
  - *febrilen*
  - *abdominalna bolečina*
  - *subikteričen*
- **Laboratorij** (28.4.2019)
  - *Lkc 35 000*
  - *CRP 350*
  - *bilirubim 45/38*
  - *gama GT 23*
  - *AF 6,3*

Prikaz primera

- **UZ abdomna in CT jeter**
  - *absces jeter*
  - *dva abscesa subdiafragmalno*
  - *drenaža abscesov*
  - *antibiotična terapija (Tazocyn, Garamicin)*
- **ERCP**
  - *delna obstrukcija stenta*
  - *ponovna vstavitev stenta*

Prikaz primera

- **18.11.2019**
  - *odpuščen*
  - *brez znakov vnetja*
  - *brez ikterusa*
  - ***sam si je zaželel malo odmora do***
- **Nadaljevanja kemoterapije**
  - *predvidene za 26.11.*
  - *shema enaka*

Zaključki

- *Incidenca raka trebušne slinavke je v porastu*
- *Bolezen le redko odkrijemo v zgodnjem stadiju*
- *Anatomska lega trebušne slinavke je strateško zelo pomembna*
- *Obravnava bolnikov je zahtevna*
- *Obravnava zahteva multidisciplinaren pristop:*
  - *internist gastroenterolog*
  - *interventni endoskopist*
  - *rentgenolog*
  - *interventni rentgenolog*
  - *onkolog*
  - *patolog*
  - *citolog*
  - *mikrobiolog*
  - *abdominalni kirurg*

Zdravljenje HCC s SBRT

Pripravila: Nika Dobnikar, dr. med.
Mentorica: izr. prof. dr. Irena Oblak, dr. med.

Ljubljana, 22.11.2019

HCC je radiosenzitiven tumor v radiosenzitivnem organu.

SBRT visoko natančna tehnika obsevanja, ki omogoča uporabo ablativnih doz.

SBRT pri zdravljenju HCC velja za:

- učinkovito metodo zdravljenja za izbrane bolnike;
- omogoča odlično lokalno kontrolo ob ugodnem toksičnem profilu.

1. *UpToDate: Overview of treatment approaches for hepatocellular carcinoma, november 2019;*
2. *Gerum S, et al. SBRT in HCC: A mini-review. World Journal of Gastrointestinal Oncology 2019; 11(5): 367-76;*
3. *C.H. Rim et al.: A meta-analysis of feasibility and efficacy of SBRT for HCC, Radiotherapy and Oncology 131 (2019) 135–144*

C.H. Rim, et al.: A meta-analysis of feasibility and efficacy of SBRT for HCC, Radiotherapy and Oncology 131 (2019) 135–144

Avtor	Leto	Vrsta raziskave	Število bolnikov	1y/2y/3y LC (%)	1y/2y/3y OS (%)
Feng M	2018	prospektivna	69	99/95/95	63/36/22
Kubo K	2018	retrospektivna	65	100/100/100	90/72/56,3
Que J	2016	retrospektivna	115	86,3/81,6/NA	63,5/41,3/NA
Uemoto K	2018	retrospektivna	121	95/91,5/91,5	78/66,8/50
Sapir E	2018	retrospektivna	125	96,5/91,3/91,3	74,1/34,9/NA
Baumann BC	2018	retrospektivna	37	95/95/95	87/50/43
…	…	…	…	…	…

Metaanaliza 32 raziskav, 1950 pacientov s HCC, zdravljeni s SBRT:

- 1y LC 85,7%; 2y LC 83,6%, 3y LC 83,9%
- G ≥3 jetrna toksičnost: 4,7%; GI 3,9%
- OS in LC – korelacija z velikostjo TU
- ↓toksičnost ob boljši jetrni funkciji (Child-Pugh A, izjemoma B)

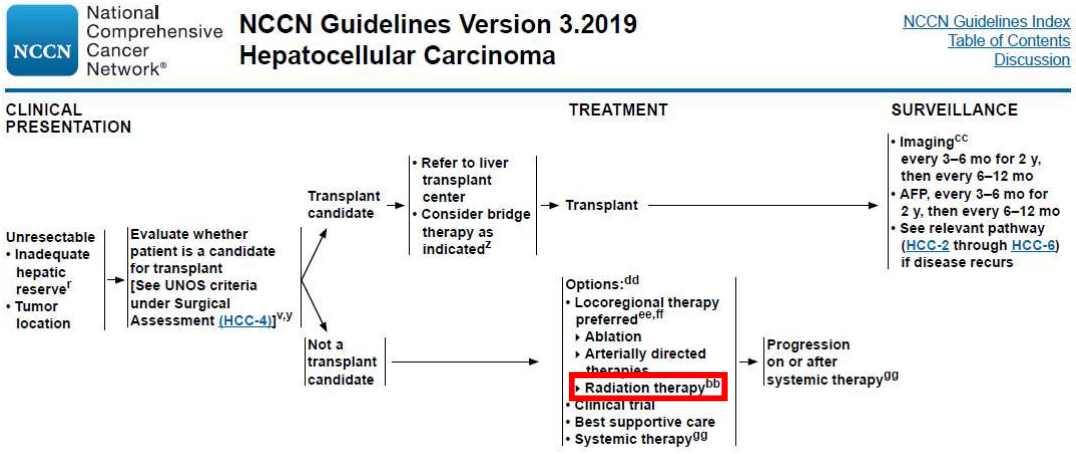
Gerum S, et al. SBRT in HCC: A mini-review. World Journal of Gastrointestinal Oncology 2019; 11(5): 367-76

Avtor	Leto	Vrsta raziskave	Število bolnikov	1y LC (%)	1y OS (%)
Cardenes et al	2010	faza I	17	100	75
Sanuki et al	2014	retrospektivna	185	99	95
Scorsetti et al	2014	faza II	43	86	78
Su et al	2016	retrospektivna	132	91	94
Moon et al	2018	faza II	23	82	36
Jeong et al	2018	retrospektivna	119	99	99
…	…	…	…	…	…

16 vključenih raziskav:

- 1y LC 65%-100%, 1y OS 32%-94%, nizka toksičnost
- Praviloma SBRT izbrana v primeru, ko bolniki niso bili primerni za druge metode zdravljenja.

Vloga SBRT?


NCCN
National Comprehensive Cancer Network®
NCCN Guidelines Version 3.2019
Hepatocellular Carcinoma
NCCN Guidelines Index
Table of Contents
Discussion
CLINICAL PRESENTATION
TREATMENT
SURVEILLANCE
Unresectable
• Inadequate hepatic reserve[r]
• Tumor location
Evaluate whether patient is a candidate for transplant [See UNOS criteria under Surgical Assessment (HCC-4)][v,y]
Transplant candidate
• Refer to liver transplant center
• Consider bridge therapy as indicated[z]
Transplant
Not a transplant candidate
Options:[dd]
• Locoregional therapy preferred[ee,ff]
‣ Ablation
‣ Arterially directed therapies
‣ Radiation therapy[bb]
• Clinical trial
• Best supportive care
• Systemic therapy[gg]
Progression on or after systemic therapy[gg]
• Imaging[cc] 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-6) if disease recurs

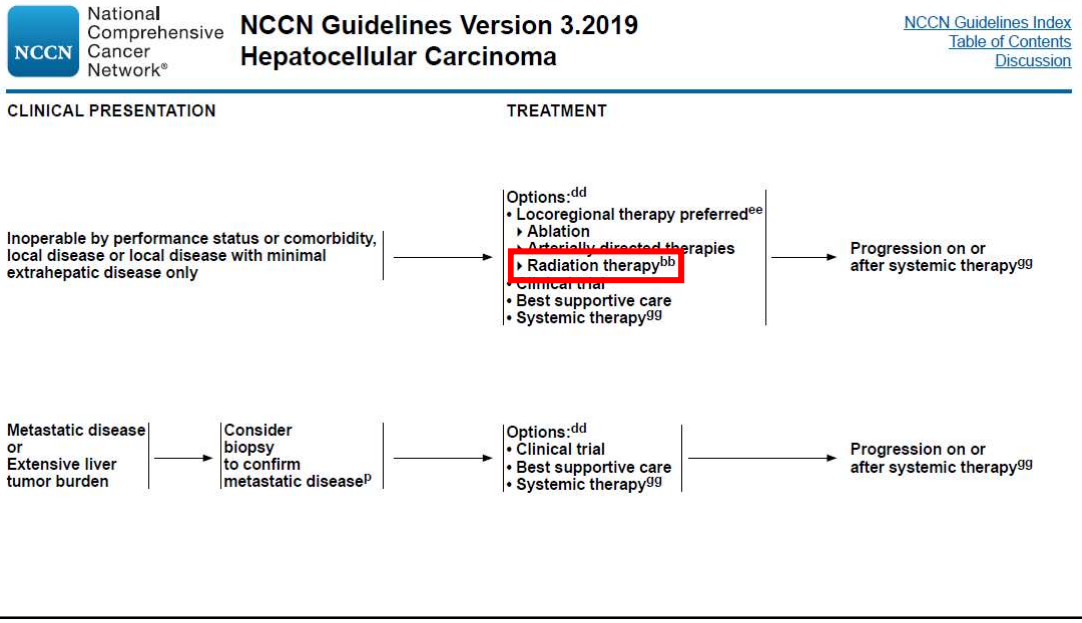

NCCN
National Comprehensive Cancer Network®
NCCN Guidelines Version 3.2019
Hepatocellular Carcinoma
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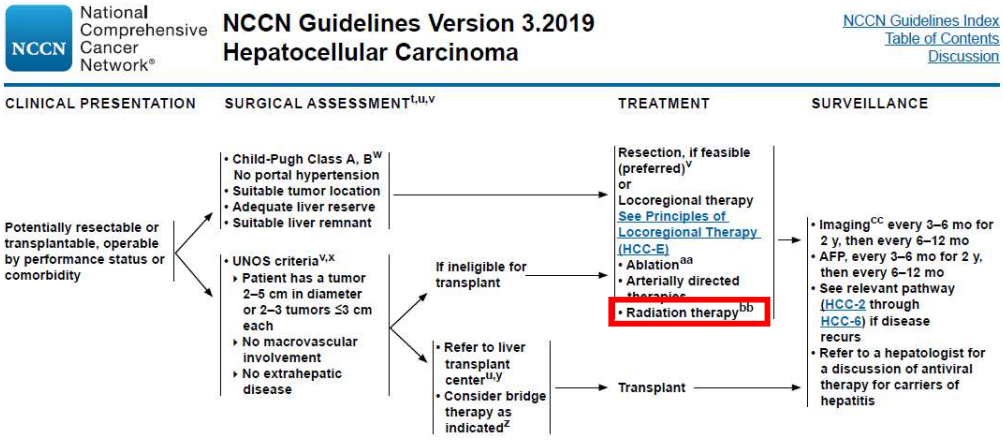
Table of Contents
Discussion
CLINICAL PRESENTATION
TREATMENT
Inoperable by performance status or comorbidity, local disease or local disease with minimal extrahepatic disease only
Options:[dd]
• Locoregional therapy preferred[ee]
‣ Ablation
‣ Arterially directed therapies
‣ Radiation therapy[bb]
• Clinical trial
• Best supportive care
• Systemic therapy[gg]
Progression on or after systemic therapy[gg]
Metastatic disease or Extensive liver tumor burden
Consider biopsy to confirm metastatic disease[p]
Options:[dd]
• Clinical trial
• Best supportive care
• Systemic therapy[gg]
Progression on or after systemic therapy[gg]



BCLC staging and treatment options according to level of evidence and approval status

BCLC stage		Treatment (standard of care)	Indication constraints based on tumour burden and liver function	Alternative treatment Not yet EMA-approved	Alternative treatment
0 – A	Single tumour any size or up to 3 nodules ≤ 3 cm Preserved liver function ECOG PS 0	Resection [III, A]	Adequate size and function of remnant liver		SBRT [III, C] HDR brachytherapy [III, C] SIRT [III, C]
		Transplantation [III, A]	Size ≤ 5 cm, number ≤ 3		
		Thermal ablation [III, A]	Size ≤ 3 cm, not adjacent to vessels or bile duct		
		TACE [I, A]	Contraindications against resection and thermal ablation. Bridging to transplantation		

Hepatocellular Carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, Ann Oncol (2018) 29 (Suppl 4): iv238–iv255

Primerjava SBRT z ostalimi metodami zdravljenja

Avtor	Leto	Vrsta	Primerjava	1y LC	1y OS	Toksičnost	Komentar
Su et al	2017	pm	SBRT vs.	84%	100%	slabost	LK/OS primerljiva, razlika v NU
			OP	72%	97%	krvavitev, bolečina	
Wahl et al	2016	retro	SBRT vs.	97%	74%	(G3+) 3%	Tu>2cm = SBRT ↑LC
			RFA	84%	70%	(G3+) 11%	
Sapir et al	2018	retro	SBRT vs.	97%	75%	(G3+) 8%	Brez razlik pri OS
			TACE	47%	74%	(G3+) 13%	

Gerum S, et al. SBRT in HCC: A mini-review. World Journal of Gastrointestinal Oncology 2019; 11(5): 367-76

Premostitveno zdravljenje s SBRT do transplantacije

Avtor	Leto	Število bolnikov	Čas do transplantacije	LC do transplantacije	Patološki popolni odg.	Toksičnost G3+
Katz et al	2012	12	6,3 mesece	100%	20%	0

(Katz AW, Chawla S, Qu Z, Kashyap R, Milano MT, Hezel AF. Stereotactic hypofractionated radiation therapy as a bridge to transplantation for hepatocellular carcinoma: clinical outcome and pathologiccorrelation. Int J Radiat Oncol Biol Phys 2012; 83: 895-900)

Avtor	Leto	Število bolnikov	Čas do transplantacije	LC do transplantacije	Patološki popolni odg.	Toksičnost G3+
O'Connor et al	2012	11	3,8 mesece	83%	27%	0

(O'Connor JK, Trotter J, Davis GL, Dempster J, Klintmalm GB, Goldstein RM. Long-term outcomes of stereotactic body radiation therapy in the treatment of hepatocellular cancer as a bridge to transplantation. Liver Transpl 2012; 18: 949-954)

→ Dobra lokalna kontrola in patološki odgovor ob nizki toksičnosti

Primerjava SBRT z ostalimi premostitvenimi tehnikami:

- dobra in primerljiva lokalna kontrola ter patološki odgovor
- ugodnejši toksični profil pri SBRT in SIRT

Metoda	Število bolnikov	Povprečen premer lezije (cm)	LC (%)	Mean patological necrosis (%)	Toksičnost G3+ (%)
TACE	37	2,6	80,6	68	11
SBRT	24	3	91,4	56	0
RFA	9	2,5	77,8	70	22
SIRT	9	3,4	77,8	94	0

→ SBRT konkurenčna premostitvena metoda

Mohamed M, Katz AW, Tejani MA, Sharma AK, Kashyap R, Noel MS, Qiu H, Hezel AF, Ramaraju GA, Dokus MK, Orloff MS. Comparison of outcomes between SBRT, yttrium-90 radioembolization, transarterial chemoembolization, and radiofrequency ablation as bridge to transplant for hepatocellular carcinoma. Adv Radiat Oncol 2015; 1: 35-42

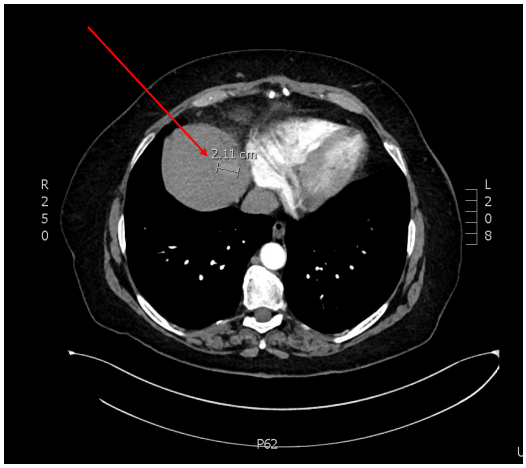
Predstavitev primera

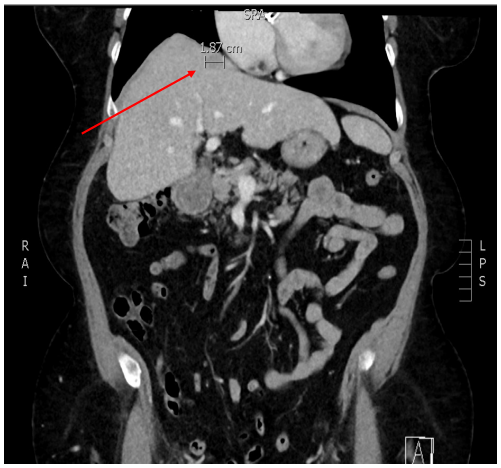
R.M., 71 let

- St. po AVR (biološka zaklopka) 2017, mitralna insuficienca, pljučna hipertenzija, AH, hiperlipoproteinemija, st. po holecistektomiji
- Kronični hepatitis B, na antivirusni th (ob tem bolezen v mirovanju), jetrna ciroza (Child-Pugh A), brez portalne hipertenzije
- Junij 2018: ↑ AFP (182)
- CT trebuha: med 6.,7. in 1. segmentom lezija suspektna za HCC
- December 2018: elektrokemoterapija, pooperativne težave z dolgo hospitalizacijo
- Frebruar 2019: kontrolni CT pokaže kompletni odgovor na EKT

Junij 2019: kontrolni CT

- Nova hipervaskularna lezija premera 27 mm visoko v 8. segmentu subdiafragmalno v višini srca (5 mm stran) – nov HCC



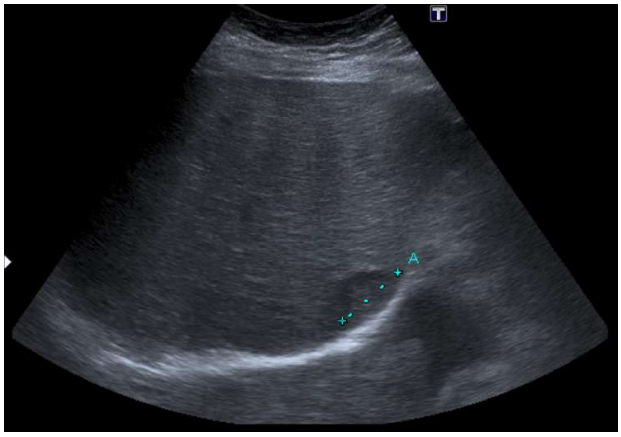


- Jetrni konzilij: glede na lokacijo, velikost in bolničine želje - poskus SBRT solitarnega HCC-ja.

- Prvi pregled na OI:
  - Jezikovna bariera, svojci ne želijo odkritega pogovora o diagnozi
  - Odklanja operativni poseg, želi si obsevanja
  - PS po WHO 1, v statusu sistolni šum, sicer brez pomembnejših odstopanj
  - Laboratorij: ↑AFP (227), mejno povišana gamaGT in AF, povišani dušični retenti
  - Jetrna ciroza ocenjena s Child-Pugh A

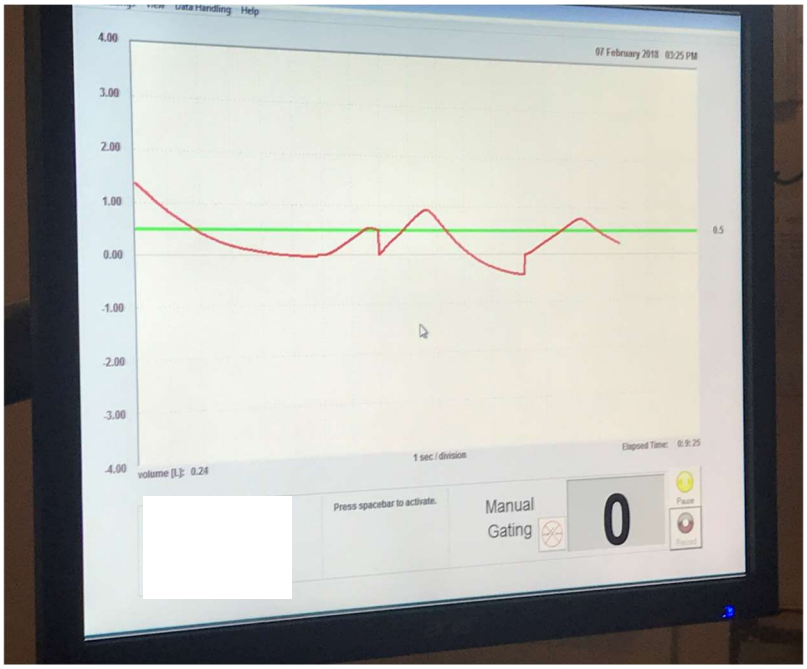
- Dodatna konzultacija z radiologom: tehnična izvedljivost SBRT problematična zaradi bližine srca.

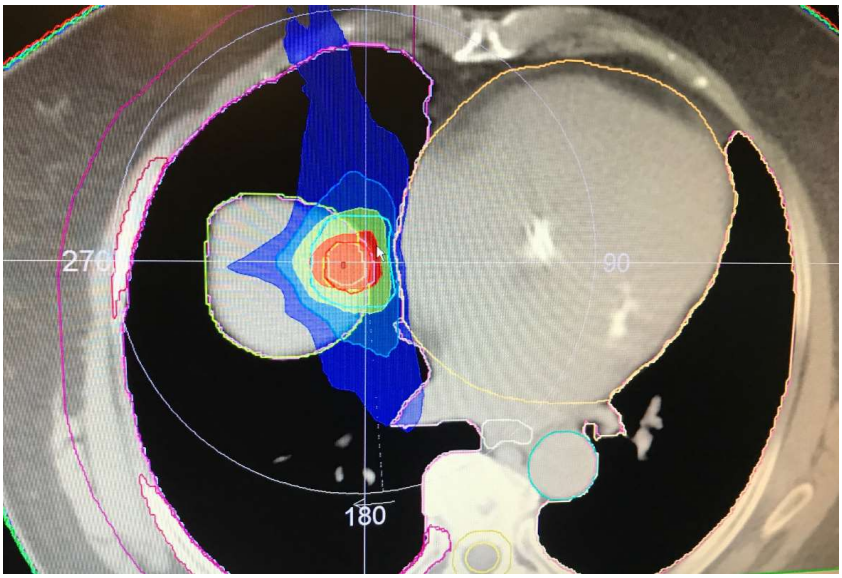
- Vstavitev zlatih zrn pod UZ kontrolo (pozicioniranje bolnika med obsevanjem s pomočjo CBCT, kjer so jetrne lezije slabo vidne)

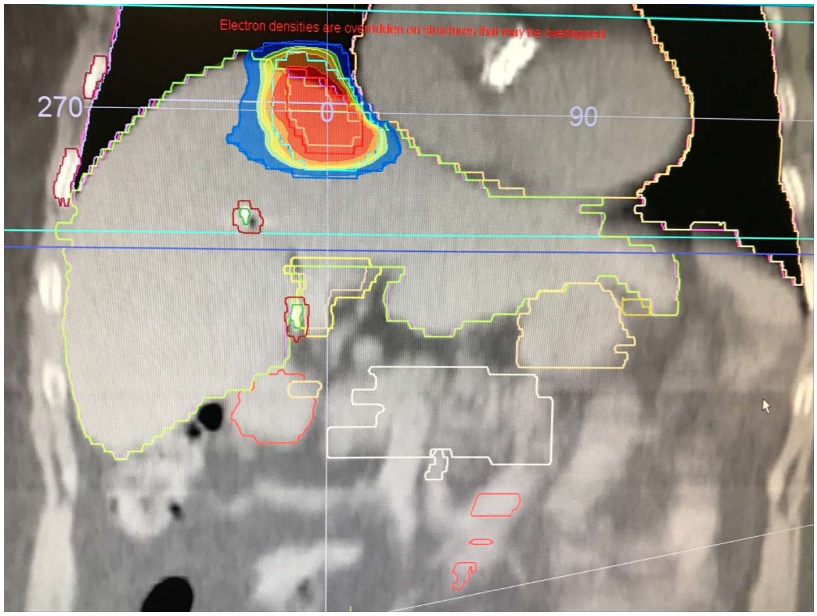


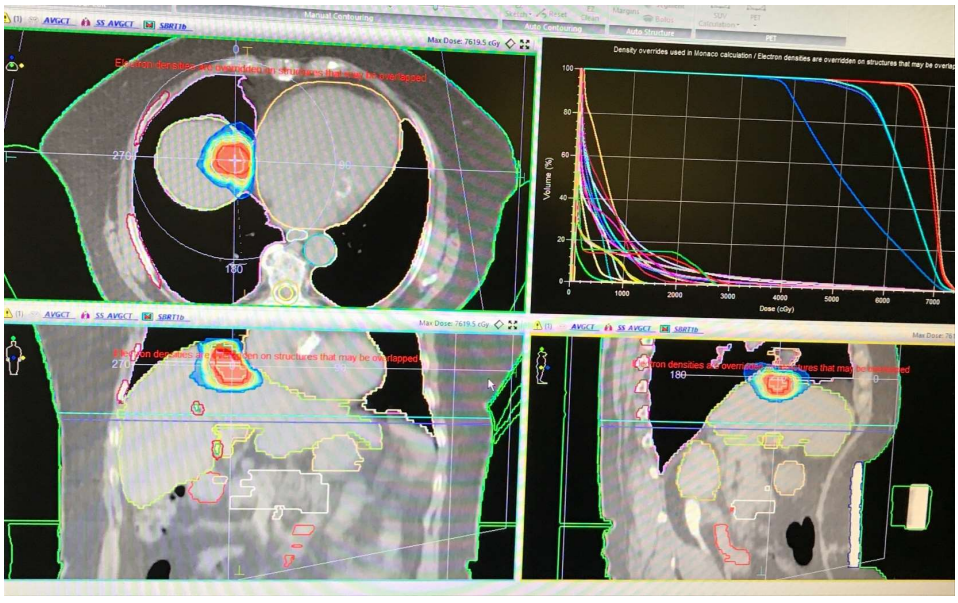
- Pregled dokumentacije z med. fizikom: svetovano RT z ABC tehniko (odmik srca od tarče).

- Priprava na 4D CT simulatorju
  - poskus z ABC tehniko - slabo sodelovanje → abdominalna kompresija


Data Handling
Help
07 February 2018 03:25 PM
4.00
3.00
2.00
1.00
0.00
-1.00
-2.00
-3.00
-4.00
0.5
1 sec / division
Elapsed Time: 0:9:25
volume [L]: 0.24
Press spacebar to activate.
Manual
Gating
0
Pause


270
90
180


Electron densities are overridden on structures that may be overlapped
270
0
90


Density overrides used in Monaco calculation / Electron densities are overridden on structures that may be overlapped
Volume (%)
Dose (cGy)

Avgust 2019: pričetek obsevanja

- 5 frakcij, vsak drugi dan (protokol ima 3 fr.-bližina srca)
- Ob tem dobrega počutja in brez težav
- Lab: ↑AFP (474), v preostalem brez dinamike

Gastroonkološki konzilij: indicirano sledenje

September 2019: 1. kontrolni pregled po zaključenem obsevanju

- Dobrega počutja
- Lab: **↓ AFP (113)**

December 2019: kontrolni CT trebuha, laboratorijske preiskave

9. ŠOLO TUMORJEV PREBAVIL SO PODPRLE NASLEDNJE DRUŽBE:

ROCHE

SERVIER

BRISTOL MYERS-SQUIBB

BAYER

MSD

MERCK

TEVA

ELI LILLY

MYLAN

CELGENE

MEDIAS

AMGEN

PHARMASWISS

SANOFI GENZYME

LEK