Združenje za
senologijo Slovenije
Slovenian Senologic
Society

Spomladansko strokovno srečanje Združenja za senologijo 2018

Teme iz razsejanega raka dojk

Radisson Blu Plaza Hotel Ljubljana

17. maj 2018

Predavatelji:

Nina Boc, dr. med., Oddelek za radiologijo, Onkološki inštitut Ljubljana

Dr. Simona Borštnar, dr. med., Oddelek za internistično onkologijo, Onkološki inštitut Ljubljana

Doc. dr. Cvetka Grašič Kuhar, dr. med., Oddelek za internistično onkologijo, Onkološki inštitut Ljubljana

Dr. Jasenka Gugić, dr. med., Oddelek za radioterapijo, Onkološki inštitut Ljubljana

Doc. dr. Andraž Perhavec, dr. med., Oddelek za onkološko kirurgijo, Onkološki inštitut Ljubljana

Ivica Ratoša, dr. med., Oddelek za radioterapijo, Onkološki inštitut Ljubljana

Urednici zbornika:

Simona Borštnar

Anja Kovač

Organizator in izdajatelj:

Združenje za senologijo pri Slovenskem zdravniškem društvu

Simpozij so finančno omogočila podjetja Amgen, AstraZeneca, Novartis, Pfizer in Roche.

Ljubljana, maj 2018

PROGRAM STROKOVNEGA SREČANJA:

16.00-16.30	*Zbiranje udeležencev*
16.30-16.40	*Ali smo dosegli napredek v obravnavi razsejanega raka dojk?* **Simona Borštnar,** Oddelek za internistično onkologijo, Onkološki inštitut Ljubljana
16.40-17.00	*Nekirurško lokalno zdravljenje jetrnih zasevkov raka dojk* **Nina Boc,** Oddelek za radiologijo, Onkološki inštitut Ljubljana
17.00-17.20	*Vloga kirurgije pri razsejanem raku dojk* **Andraž Perhavec,** Oddelek za onkološko kirurgijo, Onkološki inštitut Ljubljana
17.20-17.40	*Obravnava zasevkov v centralnem živčnem sistemu, naši rezultati* **Ivica Ratoša,** Oddelek za radioterapijo, Onkološki inštitut Ljubljana
17.40-18.00	*Zdravljenje zasevkov v centralnem živčnem sistemu s protirakavimi zdravili* **Cvetka Grašič Kuhar,** Oddelek za internistično onkologijo, Onkološki inštitut Ljubljana
18.00-18.20	*Obsevanje pri oligometastatskem raku dojk* **Jasenka Gugić,** Oddelek za radioterapijo, Onkološki inštitut Ljubljana
18.20-18.30	Razprava

Ali smo dosegli napredek v obravnavi razsejanega raka dojk?

Simona Borštnar
Oddelek za internistično onkologijo
Onkološki inštitut Ljubljana

17. maj 2018

Vsebina

- Zgodovina sistemskega zdravljenja razsejanega raka dojk
- Incidenca in prevalenca razsejanega raka dojk
- Preživetje bolnic z razsejanim rakom dojk, časovni trend
- Napoved za prihodnja leta

Posebni odtis — Separatum

Zdravstveni vestnik LETNIK 43 — ŠTEVILKA 10

GLASILO SLOVENSKEGA ZDRAVNIŠTVA LJUBLJANA 1974

MEDICAL JOURNAL OF SLOVENIA

Zdravljenje metastazirajočega raka na dojki s petimi citostatiki

Jožica ČERVEK,[1] Tatjana SUMI-KRIŽNIK[2]

UDK 616.19-006.6

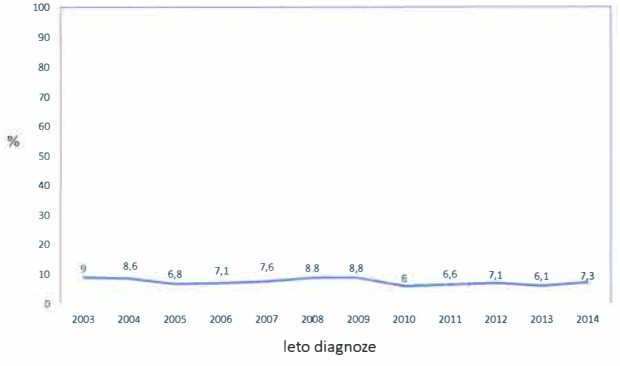
Tabela 1. *Rezultati zdravljenja s 5. citostatiki pri 40 bolnicah z generaliziranim rakom na dojki*

Table 1. *Clinical results of 5-drug therapy in 40 patients with disseminated carcinoma of the breast*

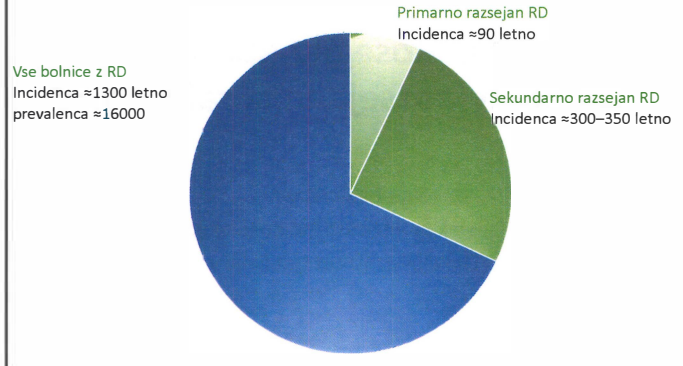
Mesto metastaz, lokalizacija / Metastatic sites	CR	PR	P	Skupaj / Total
Jetra / Liver	8	11	3	22
Pljuča, plevra, perikard / Lung, pleura, pericardium	6	5	1	12
Kosti, kostni mozeg / Bone, bone marrow	7	14	7	28
Koža, mehka tkiva / Skin, soft tissues	4		3	7
Centralni živčni sistem / Brain	2			2
Peritoneum / Peritoneum	1			1

CR — kompletna remisija — Complete remission
PR — parcialna remisija — Partial remission
P — progres — Progression

Delež bolnic z novo odkritim primarno razsejanim rakom rakom dojk v Sloveniji

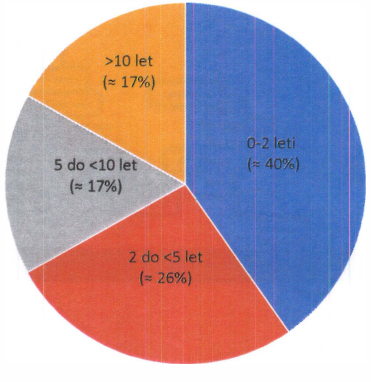


Deleži primarno in sekundarno razsejanega raka dojk



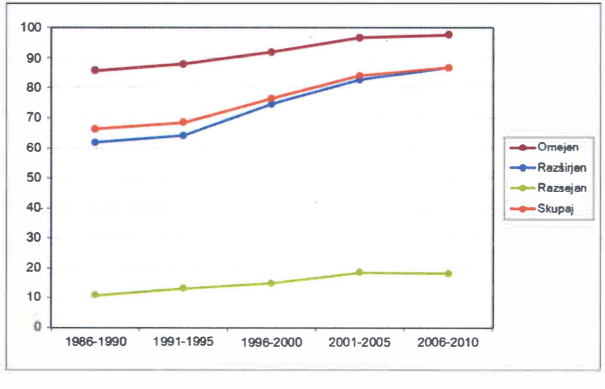
OCENA PREVALENCE RAZSEJANEGA RAKA DOJK: ≈ 1000

Deleži bolnic z razsejanim rakom dojk glede na čas od diagnoze



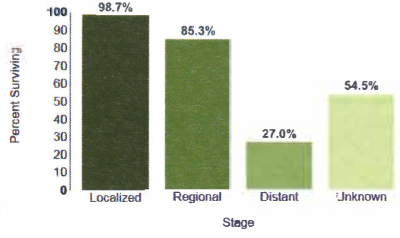
Povzeto po: Mariotto AB et al. Estimation of the Number of Women Living with metastatic breast cancer in the United states. Cancer Epidemiol Biomarkers Prev. 2017

Petletno relativno preživetje bolnic, zbolelih za rakom dojk po stadiju in obdobju diagnoze



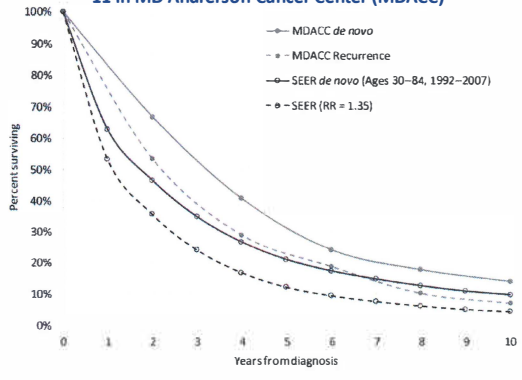
Register raka Slovenije 2014

Petletno relativno preživetje bolnic, zbolelih za rakom dojk po stadiju v obdobju 2008-2014 (ZDA, register SEER)



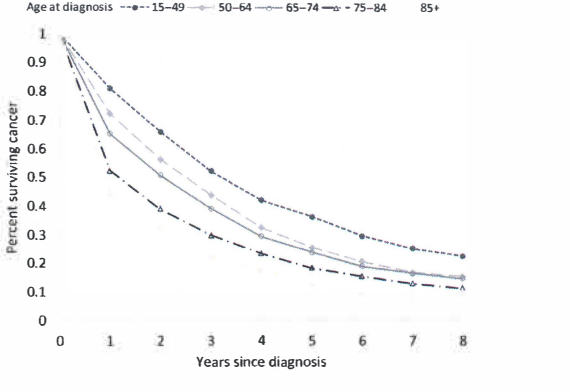
https://seer.cancer.gov/

Relativno preživetje glede na čas od diagnoze pri bolnicah s primarno in sekundarno razsejanim rakom dojk v letih 1992 do 2007 (register SEER-11 in MD Andrerson Cancer Center (MDACC)



Angela B. Mariotto et al. Cancer Epidemiol Biomarkers Prev 2017;26:809-815

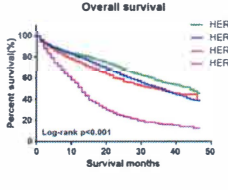
Relativno preživetje pri bolnicah s primarno razsejanim rakom dojk, zbolelih v letih 2005-2012, glede na starost (register SEER-11)



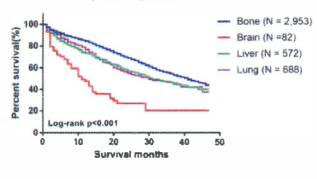
Angela B. Mariotto et al. Cancer Epidemiol Biomarkers Prev 2017;26:809-815

Preživetja bolnic z razsejanim rakom dojk glede na podtip in lokalizacijo metastaz (register SEER)

Celotno preživetje glede na podtip raka

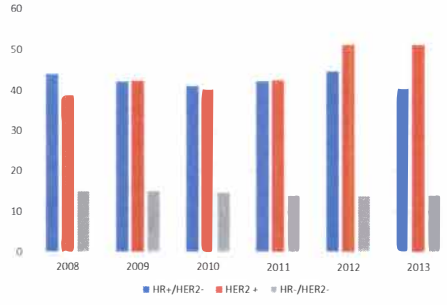


Celotno preživetje glede na lokalizacijo metastaz



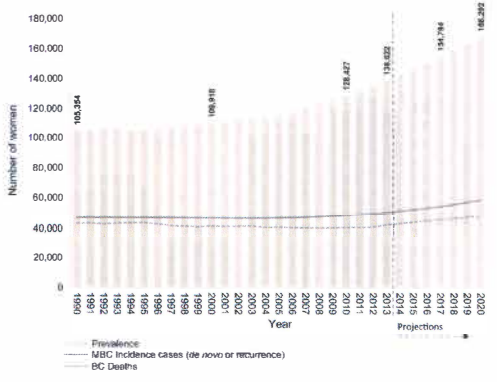
Gong Y et al. Scietific Reports 7, 2017

Srednje preživetje bolnic z razsejanim rakom dojk glede na podtip raka dojk (2008–2013)



POVZETO PO: Delaloge S, *et al.* ESMO 2017 (Abstract 1078).

Ocena prevalence razsejanega raka dojk v ZDA od 1990 do 2020



Angela B. Mariotto et al. Cancer Epidemiol Biomarkers Prev 2017;26:809-815

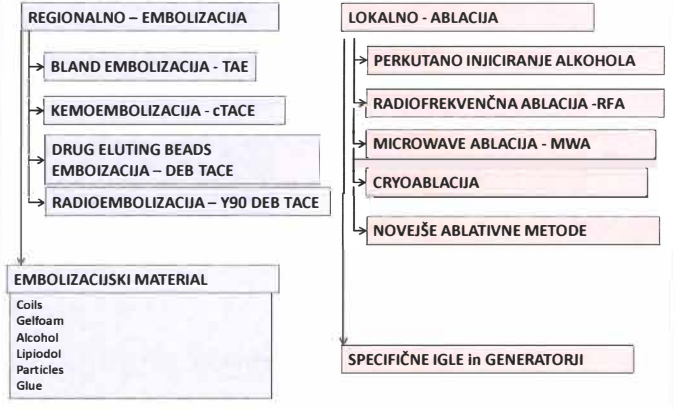
Zaključki

- V Sloveniji vsako leto odkrijemo primarno razsejan rak dojk pri 90-100 bolnicah, sekundarni razsoj pa pri okoli 300-350 bolnicah, ocenjena prevalenca razsejane bolezni je okoli 1000.
- Preživetja bolnic z razsejano boleznijo se izboljšujejo, med njimi imajo najboljša preživetja bolnice s HER2 pozitivnim rakom.

NEKIRURŠKO LOKALNO ZDRAVLJENJE JETRNIH ZASEVKOV

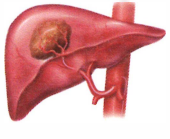
Nina Boc, dr. med.

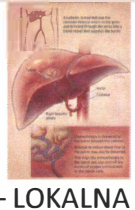
MINIMALNO INVAZIVNO ZDRAVLJENJE ZASEVKOV



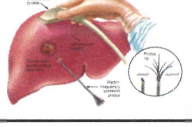
MINIMALNO INVAZIVNO ZDRAVLJENJE ZASEVKOV - pristopi

- Perkutani žilni pristopi – REGIONALNA TERAPIJA = EMBOLIZACIJA





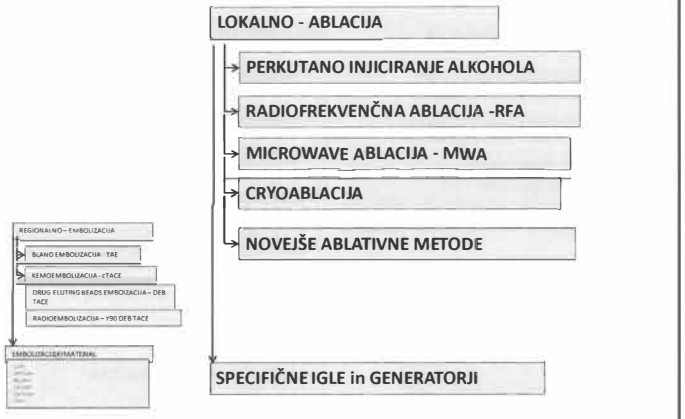
- Perkutani nežilni pristopi – LOKALNA TERAPIJA = ABLACIJA



MINIMALNO INVAZIVNO ZDRAVLJENJE

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

MINIMALNO INVAZIVNO ZDRAVLJENJE SPREMEMB

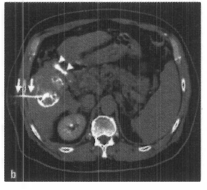


ABLACIJA

- Direktno injiciranje (alkohol, vroča FR..)
- Vročina (RFA, MWA, HIFU..)
- Zmrzovanje (krioablacija)

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

PEI



- Perkutano injniciranje alkohola
- Dobra lokalna kontrola pri pseudoinkapsuliranih 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

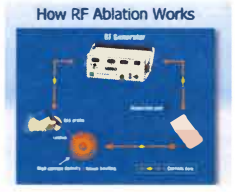
*Arii S, Yamaoka Y, Futagawa S et al.: Resultsof surgical and nonsurgicaltreatment for smallsized hepatocellular carcinoma: a retrospective and nation wide survey in Japan. The Liver Cancer Study Groupof Japan. Hepatology 2000; 32: 1224–9

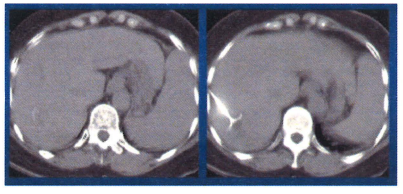
RADIOFREKVENČNA ABLACIJA - RFA

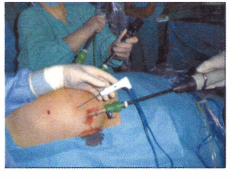
- INDIKACIJE:
  - Neresektabilni tumorji (primarni/sekundarni)
  - Multiple lezije ≤3
  - Velikost ≤ 5 cm
- KONTRAINDIKACIJE:
  - Koagulopatije
  - Ascites (perkutani pristop)
  - Neugoden položaj lezije (perkutani pristop)
  - Bližina pomembnih struktur (žolčni vodi, velike žile)
  - Ekstrahepatična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

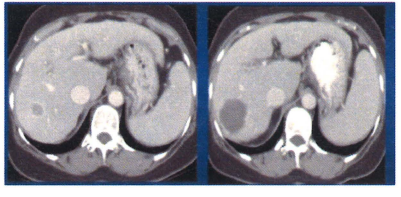
Lau et. Al. Annals of Surgery 2003
Koda M et al. Complications of radiofrequencyablationfor hepatocellular carcinoma in a multicenter study: Ananalysisof 16346 treatednodules in 13283 patients. Hepatol Res 2012; 42

RADIOFREKVENČNA ABLACIJA - RFA

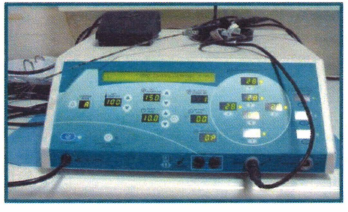


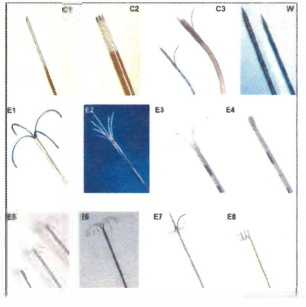






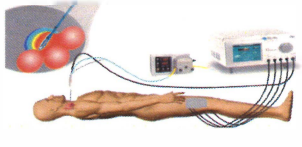
RFA GENERATOR in IGLE





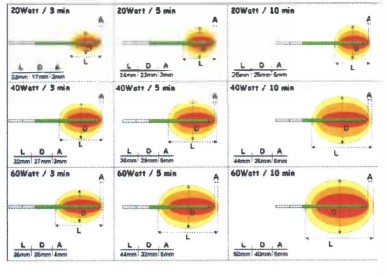
MICROWAVE ABLACIJA - MWA

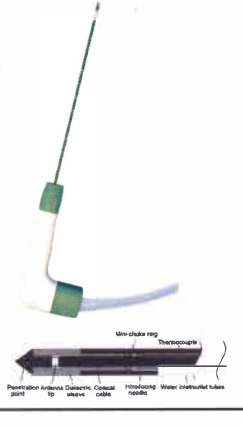
- INDIKACIJE (podobne kot za RFA)
  - Velikost je lahko večja do 5 cm
- KONTRAINDIKACIJE – enake kot RFA
- ZAPLETI
  - Pomembne komplikacije 4,6% (RFA 4,1%), smrtnost 0,23% (RFA 0,15%), krvavitev, tromboza portalne vene, bilomi, abscesi, plevralniizlivi, tumor seeding



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

MWA GENERATOR IN IGLE

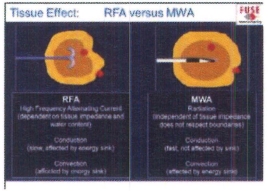


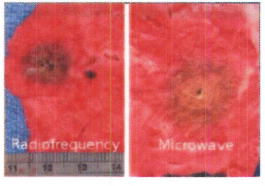


RFA vs. MWA

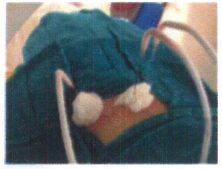
Lower intratumoral temperatures	Higher intratumoral temperatures
More peri-procedural pain	Less peri-procedural pain
Unpredictable ablation zone	More predictable ablation zone
Heat-sink effect	Less susceptible to heat-sink effect
Single lesion can be treated	Simultaneous treatment of multiple lesions
More procedural time	Shorter procedural time
Less ablation volume	Larger ablation volume
Similar complications and complication rate	
Surgical clips or pacemaker are contraindications	Surgical clips or a pacemaker not a contraindication

RFA: Radiofrequency; MWA: Microwave ablation.



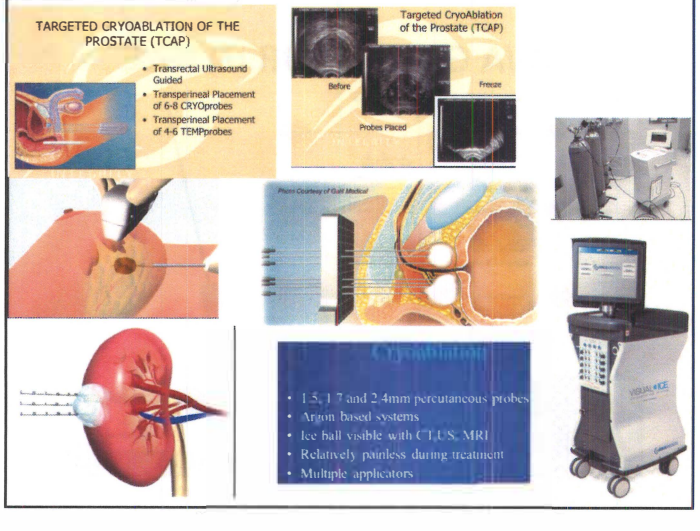


KRIOABLACIJA



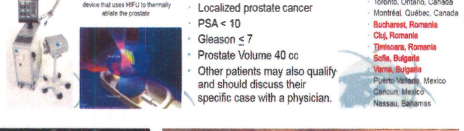
- INDIKACIJE (enake kot za RFA)
- KONTRAINDIKACIJE
  - enake kot za RFA
- SLABOSTI
  - Variabilna velikosti – multiple krioprobe
  - Manjši zmrzovalni efekt ob hepatačnih žilah
- PREDNOSTI
  - Boljša vizualizacija ledene krogle med posegom
- ZAPLETI – več pomembnih zapletov v primerjavi z RFA (29% vs. 8% ali 41% vs. 3%)
  - Krvavitve, poškodbe žolčnih vodov (lahko tudi pozni zapleti), prileznih organov – kriošok (izplavljanje citokinov – sistemski odziv z vročino, tahikardijo, tahipnejo),
  - Adam et al[17
  - Manjše komplikacije 48.6% - vročina, bolečina, plevralni izliv, AV fistula

Adam R, Hagopian EJ, Linhares M, Krissat J, Savier E, Azoulay D, Kunstlinger F, Castaing D, Bismuth H. A comparison of percutaneous cryosurgery and percutaneous radiofrequency for unresectable hepatic malignancies. Arch Surg 2002



(ŠE)NOVEJŠE METODE

(MR-) HIFU



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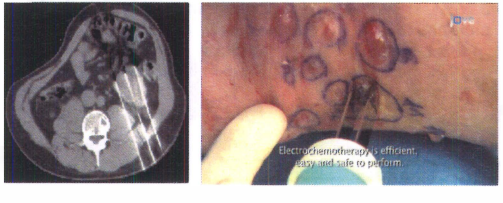


PRIMERJAVA ABLATIVNIH TEHNIK ZDRAVLJENJA

Table 1 Comparison of various ablation techniques (31)

Type of ablation	Mechanism	Advantages	Disadvantages
Cryoablation	Killing tumor tissue by cooling and reheating (Freeze-thaw cycle)	Less pain; can create large lesion and is effective in multiple lobes of tumors	Significantly affected by blood flow; high complication rate
Ultrasound	Heating generated by focusing low energy ultrasound beams from multiple sources	Compatible with MRI. Ability to focus the area of treatment without direct contact. Good depth of penetration. Fast development of image-guided high intensity focused ultrasound (HIFU) applications	Requires general anesthetic. Not small enough for use in catheters. Ablation time is long. Cannot be directed through air-filled viscera such as the lung
Radiofrequency	Resistive heating by alternating radiofrequency electrical current	Widely available. Simple design and proven effectiveness. Ability to treat different tumor types	Direct contact with object required. Incomplete ablation near blood vessels due to heat removal by blood flow
Microwaves	Heating by propagating electromagnetic waves	High temperature available. Capable of forming large lesions in the presence of blood perfusion	Complications include pleural effusion, hemorrhage, and abscess
Laser	Laser light induced heating using different wavelengths	Fully compatible with MRI. Can deliver controlled low energy through various fiber configurations to achieve thin, continuous lesions	Expensive equipment. Small ablation zone. Tissue charring around the tip of the fiber

Quant Imaging Med Surg 2017;7(3):356-368; Image-guided thermal ablation with MR-based thermometry Mingming Zhu, Ziqi Sun, Chin K. Ng

PRIMERJAVA HCC

TABLE 1. Role of Ablation in the Treatment of HCC

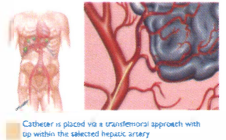
Population, Type of Study	Setting/Premise	Results	Reference
N = 161, resectable HCC; RCT	RFA vs surgery	Similar 4-year OS (67.9 vs 64) and DFS (46.4% vs 51.6%)	Chen et al, 2006[64]
N = 105, resectable HCC; RCT	RFA vs surgery	Similar 3-year OS (87.1 vs 86.4) and DFS (51.3% vs 82.34%)	Lu et al, 2006[65]
N = 232. HCC; RCT	RFA vs PEI	Improved 4-year OS (74% vs 57%); smaller risk of death, recurrence, and local progression (46%, 43%, and 88%, respectively)	Shiina et al, 2005[66]
N= 117, HCC; retrospective	RFA + TACE vs surgery	Similar OS at 1, 3, and 5 years	Kagawa et al, 2010[67]
N = 360, HCC; RCT	Cryoablation vs RFA	Improved local tumor progression rates at 1, 2, and 3 years (3%, 7%, and 7%, respectively vs 9%, 11%, and 11%, respectively); no difference in tumor progression and OS rates	Wang et al, 2015[68]
N = 107, HCC; retrospective	MWA vs surgery	Similar 1-, 3-, and 5-year OS; lower DFS with MWA if Milan criteria met or similar DFS for solitary <3 cm HCC	Shi et al, 2014[69]
N = 53, HCC; retrospective	RFA vs MWA	Similar response, recurrence, and PFS rates	Vogl et al, 2015[11]

DFS, disease-free survival; HCC, hepatocellular carcinoma; MWA, microwave ablation; OS, overall survival; PEI, percutaneous ethanol injection; RCT, randomized controlled trial; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.

AJHO, jan 2016; Liver-Directed Therapy for Hepatic Malignancies Murthy R. Chamarthy, MD, and Sanjeeva P. Kalva, MD

MINIMALNO INVAZIVNO ZDRAVLJENJE SPREMEMB V JETRIH

- REGIONALNO – EMBOLIZACIJA
  - BLAND EMBOLIZACIJA - TAE
  - KEMOEMBOLIZACIJA - cTACE
  - DRUG ELUTING BEADS EMBOIZACIJA – 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

- LOKALNO - ABLACIJA
  - PERKUTANO INJICIRANJE ALKOHOLA
  - RADIOFREKVENČNA ABLACIJA -RFA
  - MICROWAVE ABLACIJA - MWA
  - CRYOABLACIJA
  - NOVEJŠE ABLATIVNE METODE
- SPECIFIČNE IGLE in GENERATORJI

TRANS-ARTERIJSKA EMBOLIZACIJA

- Bland embolizacija -> lipiodol
- Konvencionalna kemoembolizacija -> lipiodol+citostatik
- Drug-eluting kemoembolizacija -> delci +citostatik
- Radioembolizacija -> delci + Y sevalec

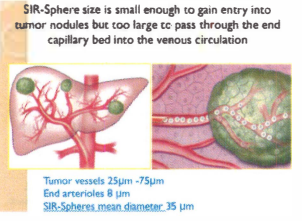
- Princip = embolizacija feeding arterije in citostatik/sevalec lokalno

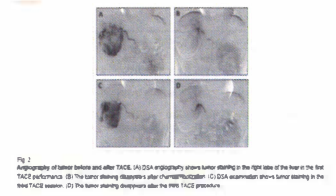
- Kemoembolizacija in radioembolizacija = paliativno zdravljenje
- Lahko kombiniramo z ostalimi ablativnimi tehnikami

TAE/cTACE/DEB-TACE

- INDIKACIJE
  - Tumorji, ki niso primerni za druge ablativne metode
- KONTRAINDIKACIJE
  - Obsežne metastaze v jetrih
  - Encephalopathy
  - 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





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

PRIMERJAVA HCC

TABLE 2. Role of Chemoembolization in the Treatment of HCC

Population, Type of Study	Setting, Premise	Results	Reference
N = 80, HCC; RCT	TACE vs conservative	Improved 1-, 2-, and 3-year survival rates (57%, 31%, 26%, respectively vs 32%, 11%, 3%, respectively)	Lo et al, 2002[25]
N = 112, HCC; RCT	TACE vs bland embolization vs conservative	Improved 1- and 2-year survival probabilities (82% and 63%, respectively, 75% & 50%; 63% & 27%)	Llovet et al, 2002[26]
N = 100, HCC; RCT	TACE vs systemic chemotherapy	Higher PR (32% vs 10%); median PFS (32 vs 26 weeks)	Mabed et al, 2009[11]
N = 177, HCC; RCT (PRECISION ITALIA)	cTACE vs DEB-TACE	No difference in local and overall tumor response or survival rates	Golfieri et al, 2014[28]
N = 307, HCC; RCT (SPACE trial)	DEB-TACE + sorafenib vs DEB-TACE	Prolonged TTP (HR, 0.797) and time to VI/EHS (HR, 0.621)	Lencioni et al, 2012[22]
N = 192, HCC; prospective single-arm study (START trial)	TACE + sorafenib	CR: 52.6%; PR: 16.8%; disease progression: 5.8%; 3-year OS: 86.1%	Chao et al, 2015[49]
N = 212, HCC; RCT (PRECISION V)	cTACE vs DEB-TACE	Higher rates of CR, ORR, and disease control without superiority (27% vs 22%, 52% vs 44%, and 63% vs 52%, respectively), but selective benefit in advanced cases, and decreased toxicity	Lammer et al, 2010[35]

CR, complete response; cTACE, conventional transarterial chemoembolization; DEB-TACE, drug-eluting beads-transarterial chemoembolization; HCC, hepatocellular carcinoma; HR, hazard ratio; m, months; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; RCT, randomized controlled trial; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; TTP, time to progression; VI/EHS, vascular invasion or extrahepatic spread.

AJHO, jan 2016; Liver-Directed Therapy for Hepatic Malignancies
Murthy R. Chamarthy, MD, and Sanjeeva P. Kalva, MD

PRIMERJAVA LOKALNE TERAPIJE HCC

Table 1 Main characteristics, indications and disadvantages of the different bridging techniques

Technique	Advantages	Limits
Resection	Potentially curative treatment; best results in left lobe and single subcapsular nodules	Unfeasible in patients with decompensated liver disease, severe portal hypertension or thrombocytopenia
TACE	More effective using the superselective technique, in well-vascularized nodules with large feeding arteries; possibility to treat multiple nodules	Unfeasible in patients with portal thrombosis (consider superselective approach), hepatic arteriovenous fistulas, renal failure or CTP C class
TARE	Possible better effectiveness than TACE in cases with multiple and large nodules; allowed in case of portal thrombosis	Less experience than TACE; high cost
RFA	More effective in nodules ≤3 cm	Risk of bleeding in patients with impaired clotting parameters or lesions located superficially; heat-sink effect; dangerous for nodules near the gallbladder, major vessels, bile ducts, or bowel loops
PEI	More effective in nodules <3 cm; more suitable in patients with impaired clotting parameters or lesions near the gallbladder or bowel	Less effective than RFA for nodules >2 cm
MWA	Possible better effectiveness than RFA in nodules ≥3 cm; safe procedure for nodules located near large vessels	Less experience with MWA than RFA; potentially dangerous in patients with impaired clotting parameters or with lesions located superficially or near the gallbladder, major bile ducts, or bowel loops
HIFU	Indication in case of portal thrombosis	Dangerous for lesions adjacent to the central biliary system
SBRT	Indication for nodules near the major bile ducts	Risk of bowel perforation

TACE, transarterial chemoembolization; TARE, transarterial radioembolization; RFA, radiofrequency ablation; PEI, percutaneous ethanol injection; MWA, microwave ablation; HIFU, high intensity focused ultrasound; SBRT, stereotactic body radiotherapy.

Transl Gastroenterol Hepatol 2017;2:78; Bridging patients with hepatocellular cancer waiting for liver transplant: all the patients are the same? Martina Coletta, Daniele Nicolini, Andrea Benedetti Cacciaguerra, Susanna Mazzocato, Roberta Rossi, Marco Vivarelli

PRIMERJAVA mCRC

TABLE 4. Role of Locoregional Therapy for Colorectal Metastatic Disease

Population, Type of Study	Setting/Product	Results	Reference
N = 74, mCRC; RCT	DEBIRI vs systemic chemotherapy	Higher median OS (22 mo vs 15 mo); longer PFS (7 mo vs 4 mo)	Fiorentini et al, 2012[35]
N = 97*, mCRC; meta-analysis	Y-90 treatment response	Average CR: 0%; PR: 31%; median TTP: 9 mo; median OS: 12 mo	Saxena et al, 2014[36]
N = 1373, mCRC; meta analysis	Y-90 vs Y-90 + chemotherapy	Nonprogression (29%-90% vs 59%-100%); 1-year survival (37%-59% vs 43%-74%)	Rosenbaum et al, 2013[37]

CR, complete response; DEBIRI, drug-eluting beads preloaded with irinotecan; mCRC, metastatic colorectal cancer; mo, months; OS, overall survival; PFS, progression-free survival; PR, partial response; RCT, randomized controlled trial; TTP, time to progression.

AJHO, jan 2016; Liver-Directed Therapy for Hepatic Malignancies
Murthy R. Chamarthy, MD, and Sanjeeva P. Kalva, MD

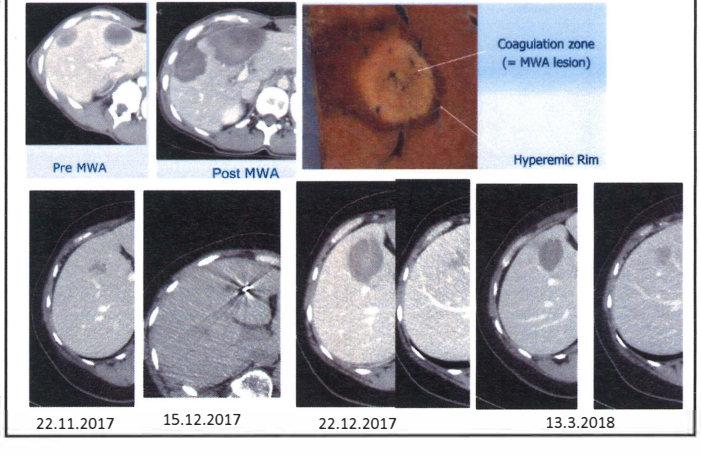
PRIPRAVA BOLNIKA

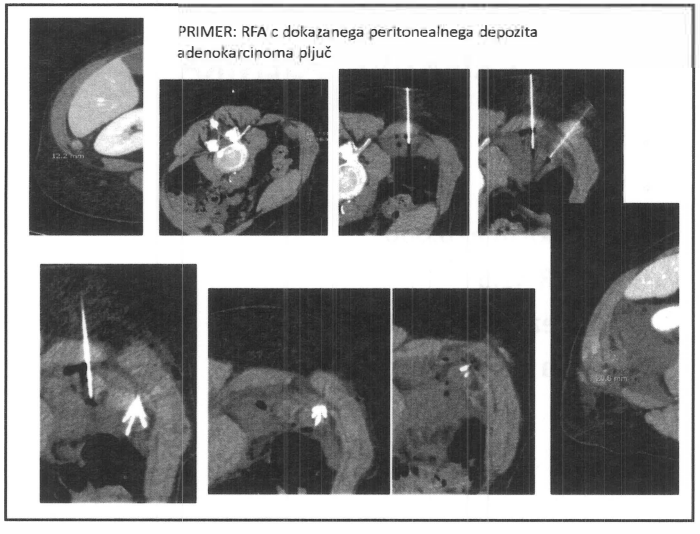
- TEŠČ 6 ur
- WBC/ANC
- Trombociti >70.000
- PČ/INR <1,5
- Analgezija pri DEBIRI
- Zaščita z antibiotikom

OCENA UČINKA LOKALNE TERAPIJE - mRECIST

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
PR/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 at at least 1 cm interval growth	

mRECIST




PRIMER: RFA c dokazanega peritonealnega depozita
adenokarcinoma pljuč

Vloga kirurgije pri razsejanem raku dojk

Spomladansko strokovno srečanje združenja za senologijo 2018

Andraž Perhavec

Uvod

- 20 – 30 % bolnic z rakom dojk razvije sinhrone ali metahrone oddaljene zasevke
- Prognoza bolnic v stadiju IV se izboljšuje
  - 1987-1993: 11%
  - 1994-2000: 28% 5-letno preživetje
  - Od leta 1990: 5%/5 let
- Boljše preživetje zvišuje možnost lokalnih problemov

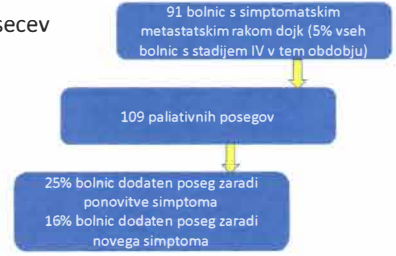
Caudle AS. Advanced therapy of breast nacer, 3rd Edition, 2012
Park JH et al. JCO, 2015
Di Meglio A. Breast Cancer Res Treat, 2016

Vloga kirurgije

- Paliacija
  - Lokoregionalni problem (eksulceracija, krvavitev, bolečina)
  - Urgentna stanja pri sistemskem razsoju (možganski zasevki, kompresija hrbtenjače, patološka fraktura, ileus …)
- Boljša prognoza?
  - Resekcija primarnega tumorja in regionalnih bezgavk
  - Resekcija oddaljenih zasevkov

Paliativno kirurško/intervencijsko zdravljenje

- MSKCC: Jul 2002 – Jun 2003
- Mediano preživetje 37.4 mesecev



Morrogh M et al. Cancer, 2010

Paliativno kirurško/intervencijsko zdravljenje

All Primary Palliative Procedures, N=109	No. of Patients (%)
Surgical procedures	67 (61)
Craniotomy with/without resection	19 (17)
Orthopedic ORIF	19 (17)
Creation of VP shunt	5 (5)
Spinal decompression plus fixation	5 (5)
VATS with/without pleurodhesis	4 (4)
Mastectomy with/without reconstruction	3 (3)
Laparotomy with/without diversion	3 (3)
Laryngoplasty	3 (3)
Cystoscopy and insertion of ureteric stents	2 (2)
VATS plus cardiac window	2 (2)
Creation of Ekeesor flap	1 (1)
Excision of abdominal wall lesion plus reconstruction	1 (1)
Interventional radiology	39 (36)
Placement of thoracostomy tube with/without pleurodhesis	29 (27)
Paracentesis with/without placement of Denver shunt/Tenkoff catheter	5 (5)
Biliary drainage	5 (5)
Endoscopic procedures	3 (3)
PEG tube insertion	3 (3)

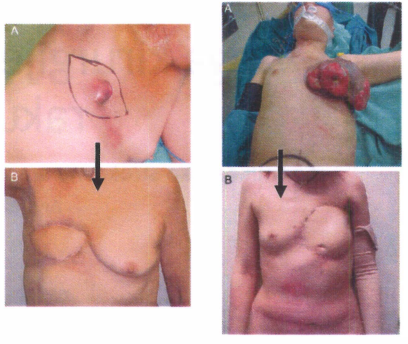
Odprava simptoma:
- 30 dni: 91%
- 100 dni: 81%
- do konca: 70%

Zapleti 20% (15% gradus 1-2), smrtnost 0%

5% vseh bolnic s stadijem IV - premalo?

Paliativno lokoreg. kirurško zdravljenje

- 15 bolnic z resekcijo celotne torakalne stene, 1998-2003
- 14 recidivov, 1 primarni tu z ali brez zasevkov
- Simptomi: bolečine (5), smrad (3) velika masa (4), deformacija prsne stene (2), asimptomatska (1)
- 11 (73%) R0 resekcija
- brez večjih zapletov, 20% manjših zapletov
- 13/15 dobra kontrola simptomov



Veronesi G et al. Results of chest wall resection for reccurent or locally advanced breast malignancies. The Breast, 2007

„Preventivno" paliativno lokoreg. zdravljenje

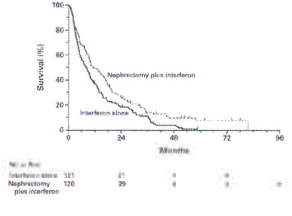
- SEER database, 2005 – 2012
- 3660 bolnic z de novo T4M1 rakom dojk
- 1558 (43%) lokalna terapija: 19% krg, 15% RT, 9% oboje

Symptom	New morbidity after LT in asymptomatic patients prior to LT (n = 1435)	Baseline morbidity in patients not undergoing LT (n = 2102)	P value
Bleeding	≤ 10 (0.0%)	≤ 10 (0.0%)	0.563
Cellulitis	48 (3.3%)	18 (0.9%)	< 0.001
Abscess	37 (2.6%)	40 (1.9%)	0.177
Brachial plexopathy	22 (1.5%)	14 (0.7%)	0.012
Axillary neuropathic pain	≤ 10 (0.0%)	≤ 10 (0.0%)	1
Wound dehiscence	≤ 10 (0.0%)	NA	NA
Cancer-related pain	98 (6.8%)	50 (2.4%)	< 0.001
Lymphedema	58 (4.0%)	≤ 10 (0.0%)	< 0.001
Seroma	14 (1.0%)	NA	NA
Any symptom	285 (19.9%)	141 (6.3%)	< 0.001

Fairweather M et al. Breast cancer Res and Treat., 2018

VPLIV NA PROGNOZO – resekcija primarnega tumorja

- **Dokazi pri drugih rakih:**
  - Rak ledvic: 2 RCT dckazali korist krg+sistemske th vs. sistemske th



Flanigan et al. NEJM, 2001
Mickisch GHJ et al. Lancet, 2001

Mehanizem

- odstranimo „rezervoar“ tumorskih matičnih celic
- zmanjšamo izločanje citokinov (TGF-β) iz primarnega tumorja, ki stimulirajo implantacijo in rast zasevkov
- zmanjšamo tumorsko povzročeno imunosupresijo (miši)

Karnoub AE et al. Nature, 2007
Danna EA et al. Cancer Research, 2004

VPLIV NA PROGNOZO, retrospektivne raziskave

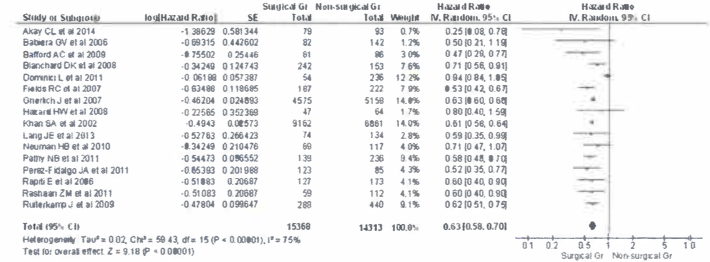


Figure 1. Forest plot of hazard ratios and pooled analysis for overall mortality for surgery, vs. no surgery in patients with stage IV breast cancer.

Headon H et al. Molecular and Clinical Oncology, 2016

VPLIV NA PROGNOZO, SEER database

- 29.916 bolnic v stadiju IV, 1988 – 2011
- 15.129 (51%) krg, 14.787 (49%) brez krg

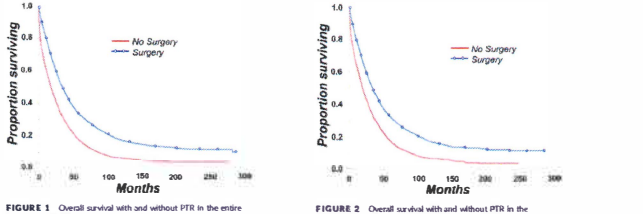


FIGURE 1 Overall survival with and without PTR in the entire cohort (n = 29 916) [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 2 Overall survival with and without PTR in the propensity score-matched pairs(n = 18 954) [Color figure can be viewed at wileyonlinelibrary.com]

Vohra NA et al. Breast J, 2017

VPLIV NA PROGNOZO – RCT

DRŽAVA	OBDOBJE VKLJUČEVANJA	N	PRIMARNA TERAPIJA	STATUS
Indija	2005 – 2012	350	Sistemska	Podatki na voljo
Turčija	2008 – 2012	274	Kirurgija	Podatki na voljo
Avstrija	2010 – 2021	254	Kirurgija	Še poteka
ZDA, Kanada	2011 – 2022	391	Sistemska	Še poteka
Japonska	2011 - ?	600	Sistemska	Še poteka
Nizozemska	2011 – 2016	10	Kirurgija	Zaključena zaradi slabega vključevanja

Locoregional treatment versus no treatment of the primary tumour in metastatic breast cancer: an open-label randomised controlled trial

Rajendra Badwe, Rohini Hawaldar, Nita Nair, Rucha Kaushik, Vani Parmar, Shabina Siddique, Ashwini Budrukkar, Indraneel Mittra, Sudeep Gupta

- 350 bolnic z *de novo* stadijem IV rakom dojk (Feb 2005 – Jan 2013) z odgovorom na KT (6 ciklov antraciklinov)
- Randomizacija
  - LRT: kirurgija + RT (kot pri stadiju I-III), N=173
  - Brez LRT, N=177
- F/U, mediana: 23 mesecev

Badwe R et al. Lancet Oncology, 2015

Locoregional treatment versus no treatment of the primary tumour in metastatic breast cancer: an open-label randomised controlled trial

Rajendra Badwe, Rohini Hawaldar, Nita Nair, Rucha Kaushik, Vani Parmar, Shabina Siddique, Ashwini Budrukkar, Indraneel Mittra, Sudeep Gupta

	LRT (N=173)	Brez LRT (N=177)	HR (95% CI)	P
celokupno preživetje, mediana	18.8	20.5	1.07 (0.82 – 1.4)	0.6
2-letno celokupno preživetje	40.8%	43.3%	1.00 (0.76 – 1.33)	0.98

Le 9/107 bolnic z Her-2 pozitivnim tumorjev je prejemalo antiHer-2 terapijo

Badwe R et al. Lancet Oncology, 2015

A randomized controlled trial evaluating resection of the primary breast tumor in women presenting with de novo stage IV breast cancer

- 274 bolnic z *de novo* stadij IV rakom dojk (Nov 2007 – Nov 2012) brez predhodne sistemske terapije
- Randomizacija:
  - LRT: kirurgija + RT pri ohranitveni kirurgiji, sistemska terapija N=138
  - Brez LRT, sistemska terapija N=136
- F/U, mediana: 40 mesecev
- V skupini z LRT več bolnic z ER+, Her2- tumorji, mlajše, s solitarnimi kostnimi zasevki (boljša prognoza)

Soran A et al. JCO 2016, (Suppl):Abstract 1005

A randomized controlled trial evaluating resection of the primary breast tumor in women presenting with de novo stage IV breast cancer

	LRT (N=138)	Brez LRT (N=136)	P
Preživetje, mediana (m)	46	37	0.005
Lokoreg. progres	1%	11%	0.001

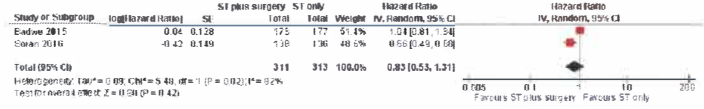
- Ostali pomembni progn. dejavniki:
  - ER+, Her2-
  - starost < 55 let
  - solitarni kostni zasevki

Soran A et al. JCO, 2016

Cochrane Library

Cochrane Database of Systematic Reviews

Breast surgery for metastatic breast cancer (Review)

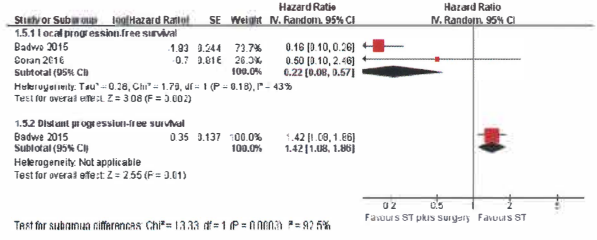


Tosello G et al. Cochrane Database of Systematic Reviews, 2018

Cochrane Library

Cochrane Database of Systematic Reviews

Breast surgery for metastatic breast cancer (Review)



Tosello G et al. Cochrane Database of Systematic Reviews, 2018

Cochrane Library

Cochrane Database of Systematic Reviews

Breast surgery for metastatic breast cancer (Review)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with systemic treatment	Risk with breast surgery plus systemic treatment			
Overall survival at 2 years Follow-up: range 23 months to 40 months	Study population		HR 0.83 (0.53 to 1.31)	624 (2 RCTs)	⊕◯◯◯ VERY LOW [1,2,3]
	511 per 1000	448 per 1000 (318 to 608)			
Local PFS at 2 years Follow-up: range 23 months to 40 months	Study population		HR 0.22 (0.08 to 0.57)	607 (2 RCTs)	⊕⊕◯◯ LOW [3]
	500 per 1000	141 per 1000 (54 to 326)			
Distant PFS at 2 years Follow-up: 23 months	Study population		HR 1.42 (1.08 to 1.86)	350 (1 RCT)	⊕⊕⊕◯ MODERATE [4]
	548 per 1000	676 per 1000 (576 to 772)			

KIRURGIJA ZASEVKOV

- Pogostnost (prvo mesto razsoja):
  - Kosti (41,1%)
  - Pljuča (22,4%)
  - Jetra (7,3%)
  - CŽS (7,3%)
  - Ostalo (22,9%)
- Vedno najprej sistemska terapija
  - 5-letno preživetje po resekciji jetrnih zasevkov:
    - PR – 42%
    - SD – 12%
    - PD – 0%

Berman AT et al. Clin Breast Cancer, 2013
Golse N et al. Clin Breast Cancer, 2017

JETRNI ZASEVKI

Preživetje?

The principal question relative to LMBC resection remains proof of its usefulness. Because of the lack of evidence in the literature, it is difficult to draw any definitive conclusions, and the answer may differ depending on whether you are a surgeon or an oncologist.

Gulec N et al. Clin Breast Cancer, 2017

JETRNI ZASEVKI

Table 3 Morbidity, Mortality, and Long-Term Survival After the Resection of LMBC (Principal Series Published Since 2000)

First Author, Year, (Reference)	n	Follow-up, mo	(21 – 61 %) 5-y Survival, %	(0 – 10 %) Postoperative Mortality, %	(15 – 44 %) Postoperative Morbidity Clavien <III/≥III, %
Abbott, 2012 (7)	66	62	43.6	0	15/6
Adam, 2006 (8)	85	38	37	0	19/5
Adam, 2008 (9)	460	NA	41	NA	NA
Bacalbasa, 2014 (4)	43	NA	58	0	16 (all grades)
Dittmer, 2013 (10)	34	NA	28	0	24 (all grades)
Elias, 2003 (2)	54	32	34	0	13 (all grades)
Kim, 2014 (6)	13	NA	NA	NA	NA
Kostov, 2013 (11)	42	60	38	5	12/24
Lubrano, 2008 (12)	16	28	33	0	37 (all grades)
Mariani,* 2013 (1)	100	NA	50	0	18 (all grades)
Martinez, 2006 (13)	20	39	33	NA	NA
Pocard, 2001 (14)	65	41	(4-y) 46	0	18 (all grades)
Ruiz,* 2015 (3)	139	55	47	3	21 (all grades)
Sakamoto, 2005 (15)	34	72	21	0	NA
Thelen, 2008 (5)	39	24	42	0	13 (all grades)
Vlastos, 2004 (16)	31	25	61	0	NA
van Weltum, 2012 (17)	32	26	37	0	44 (all grades)
Zhou, 2014 (18)	46	52	NA	NA	NA

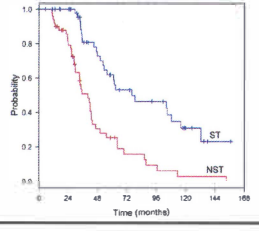
Gulec N et al. Clin Breast Cancer, 2017

JETRNI ZASEVKI

- 2 raziskavi primeri-kontrole

Institut Curie; 1988-2007 (izolirani jetrni zasevki ali pridruženi kostni zasevki)

- 51 bolnic krg + sist. th. vs. 51 bolnic samo sist. th.
- 3-letno preživetje: 81% vs 51% (p<0.0001); RR 3.04 (95% CI 1.87-4.92)

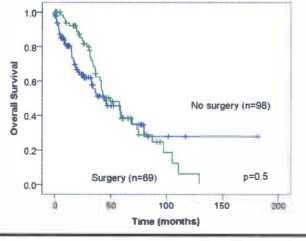


Mariani P et al. Eur J Surg Oncol, 2013

JETRNI ZASEVKI

MSKCC; 1991-2014 (bolnice z izoliranimi jetrnimi zasevki)

- 69 bolnic krg/ablacija + sist. th. vs. 98 bolnic samo sist. th.
- razlike v HR (↑krg), prejemanju trastuzumaba (↑sist. th.), deležu kirurgije primarnega tumorja (↑krg), deležu metahronih zasevkov (↑krg), številu jetrnih zasevkov (↑sist. th.)
- ni razlik v preživetju



Sador E et al. Ann Surg, 2016

JETRNI ZASEVKI

- Prednosti kirurgije
  - možnost dolgotrajnega preživetja
  - material za patologijo
  - zmanjšanje števila kemoterapij („treatment free holiday"): ↑QoL, ↓stroški
    - za bolnice pomembnejše preživetje brez ponovitve bolezni kot celokupno preživetje

Golse N et al. Clin Breast Cancer, 2017
Spolverato G et al. Ann Surg, 2016
Hurvitz SA et al. Breast Cancer Res Treat, 2013

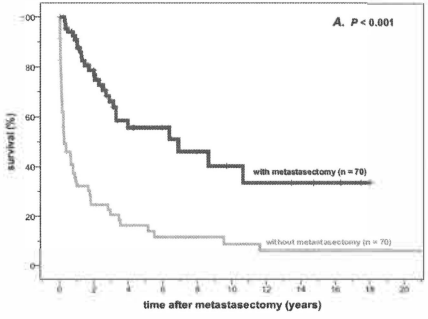
JETRNI ZASEVKI

- **Najboljše rezultate lahko pričakujemo pri:**
  - Majhnih zasevkih (<4-5 cm), ki ne zahtevajo večje resekcije
  - Radikalni resekciji (R0 ali vsaj R1)
  - Vsaj stabilni bolezni med sistemsko terapijo
  - Dolgem prostem intervalu (več kot 1-2 leti)
  - Tumorjih z več tarčami (HR+, Her-2+)

Golse N et al. Clin Breast Cancer, 2017

ZASEVKI V PLJUČIH

- 1982-2007



Meimarakis G et al. Ann Thorac Surg, 2013

ORIGINAL ARTICLE – THORACIC ONCOLOGY

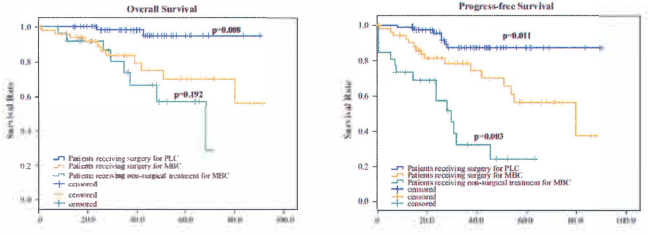
Surgical Outcomes of Isolated Malignant Pulmonary Nodules in Patients with a History of Breast Cancer

- 147 bolnic z rakom dojk in solitarnim pljučnim nodusom < 3 cm
- Jan 2007 – Dec 2014
- 3 skupine:
  - 1. skupina: primarni pljučni rak, zdravljen kirurško, n=70
  - 2. skupina: metastaza raka dojk, zdravljena kirurško, n=52
  - 3. skupina: metastaza raka dojk, zdravljena s sist. th., n=25
- Povprečen premer nodusa: 1.1 ± 0.36 cm
- F/U, mediana: 36 mesecev

Song Z et al. Ann Surg Oncol, 2017

ORIGINAL ARTICLE – THORACIC ONCOLOGY

Surgical Outcomes of Isolated Malignant Pulmonary Nodules in Patients with a History of Breast Cancer



Song Z et al. Ann Surg Oncol, 2017

ZAKLJUČEK

- PALIATIVNO ZDRAVLJENJE
  - zahtevnejše resekcije primarnega tumorja/LR → **DA**
  - preventivno paliativno lokoregionalno zdravljenje → **NE**
  - paliativni posegi zaradi simptomatskih zasevkov → **DA**
- IZBOLJŠANJE PROGNOZE
  - resekcija primarnega tumorja → **???**
  - resekcija jetrnih zasevkov → najbrž **DA** pri skrbno izbranih bolnicah
  - resekcija pljučnih zasevkov → najbrž **DA** pri skrbno izbranih bolnicah

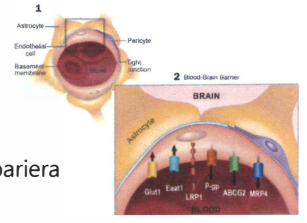
Obravnava zasevkov v centralnem živčnem sistemu, naši rezultati

Ivica Ratoša, dr. med.
Sektor radioterapije, OILJ

Ljubljana, 17.5.2018

Onkološki inštitut Ljubljana
Institute of Oncology Ljubljana
80 let years

CENTRALNI ŽIVČNI SISTEM



- "svetišče" – možgansko krvna bariera
- zasevki v možganih: 10 – 30 % bolnic z rakom dojk

Tveganje za razvoj zasevkov:
Luminal A: 9%
Luminal B: 11%
TNBC: 15%
HER2: 17%

- mlade bolnice, ER-, pT>5 cm, G3, HER-2+

O'Sullivan Sem Oncol 2017

- natančnejša slikovna diagnostika
- izboljšanje sistemskega zdravljenja → daljša preživetja

povečanje kumulativne incidence možganskih zasevkov pri bolnicah z rakom dojk

O'Sullivan Sem Oncol 2017

MOŽGANSKI ZASEVKI IN OBSEVANJE

Kontrola bolezni v CŽS

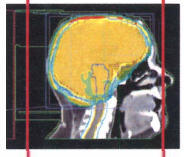
Obsevanje celotne glave (**WBRT**)

Obsevanje celotne glave s ščitenjem hipokampusa (**HA-WBRT**)

Stereotaktično obsevanje zasevkov (**SRS**)

Delno obsevanje glave (visoka natančnost)

Opazovanje



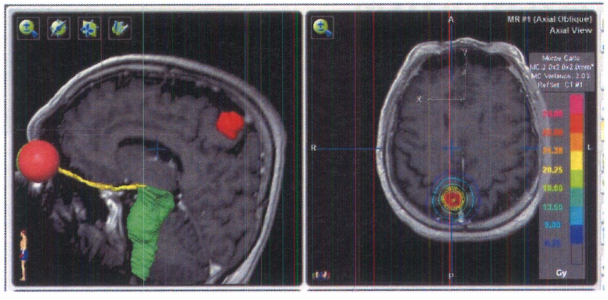
Toksičnost zdravljenja

Neželeni učinki:

Takojšnji: slabost, bruhanje, utrujenost, izpadanje las...

Pozni: morebiten kognitivni upad predvsem pri bolnikih, ki imajo pričakovano preživetje več kot 6 mesecev

STEREOTAKTIČNO OBSEVANJE GLAVE



OBSEVANJE CELOTNE GLAVE (WBRT) vs. samo OPAZOVANJE PO SRS

- 1 do 3 zasevki
- Predvsem korist za mlajše od 50 let
- NI randomiziranih raziskav za 4 zasevke ali več

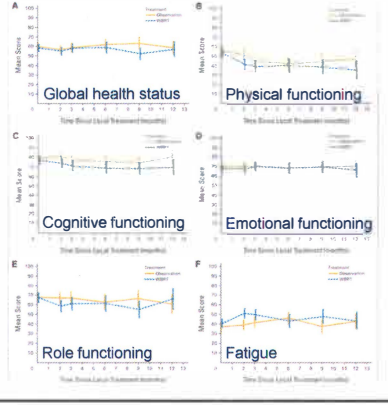
Table 2 Hazard ratio estimates for SRS alone versus SRS plus WBRT at different ages for overall survival and distant brain failure

Age*	HR (95% CI) for† Overall survival	Distant brain failure
35	**0.46 (0.24-0.9)**	0.90 (0.42-1.94)
40	**0.52 (0.29-0.92)**	1.05 (0.56-1.98)
45	**0.58 (0.35-0.95)**	1.23 (0.73-2.05)
50	**0.64 (0.42-0.99)**	1.43 (0.95-2.15)
55	0.72 (0.49-1.05)	**1.67 (1.19-2.35)**
60	0.80 (0.56-1.14)	**1.95 (1.40-2.71)**
65	0.90 (0.62-1.29)	**2.27 (1.55-3.33)**
70	1.0 (0.67-1.49)	**2.65 (1.64-4.27)**
75	1.12 (0.71-1.76)	**3.09 (1.70-5.61)**
80	1.24 (0.73-2.11)	**3.60 (1.75-7.44)**

Abbreviations: CI = confidence interval; HR = hazard ratio.
* Because treatment effect depends on the patient's age (as it was a significant effect modifier), estimates of effects (HRs) and corresponding 95% CIs are presented at patients' ages from 35 to 80 years at intervals of 5 years.
† Estimates were obtained from adjusted analysis for important confounders and prognostic factors. Significant estimates (boldface) with HR < 1 and HR > 1 suggest protective and harmful effects, respectively, of SRS alone at the corresponding age on the respective outcome.

Shahgal, IJROBP, 2015

OBSEVANJE CELOTNE GLAVE (WBRT) vs. OPAZOVANJE PO OPERACIJI ALI SRS

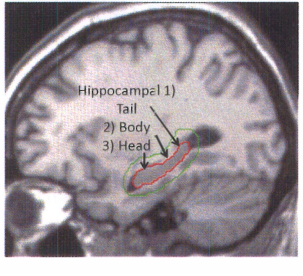


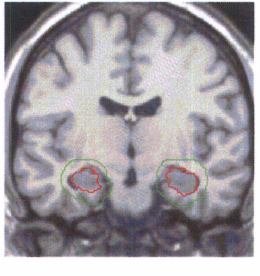
Kognitivne funkcije

Aoyama, JAMA 2006
Chang , Lancet Oncol 2009
Kocher, EORTC 22952-26001, JCO 2011
Soffietti, JCO 2013

HIPOKAMPUS

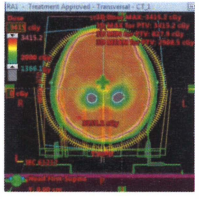
MRI _T1
Red: Hippocampus
Green: Hippocampal Avoidance Zone
Subgranularna cona

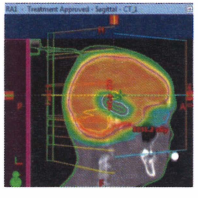




RTOG Contouring Atlas-Hippocampus (https://www.rtog.org/CoreLab/ContouringAtlases/HippocampalSparing.aspx)
MR Images courtesy of: Holmes CJ, Hoge R, Collins L, et al. "Enhancement of MR Images Using Registration for Signal Averaging" Journal of Computer Assisted Tomography 22, 324-333 (1998)RTOG

RT glave z zaščito HIPOKAMPUSA (HA-WBRT)





RTOG 0933, faza II
HA-WBRT 10 x 3 Gy

Ocena kognitivne funkcije in QoL:
izhodiščno stanje (0), 2, 4, 6 m

Kontrola s skupino, ki je bila zdravljena pred leti

Izhodišče → čez 4 mesece:
Povprečna relativna ocena po testu HVLT-R DR* 30% vs. 7.0% (p<0.001)

*Hopkins Verbal Learning Test-Revised Delayed Recall (HVLT-R DR)

Gondi, JCO, 2014

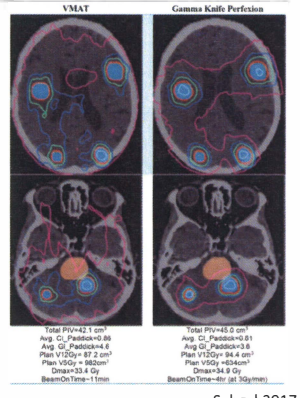
OBSEVANJE CELOTNE GLAVE (WBRT) ALI SRS ZA ≥4 ZASEVKE?

- SRS za ≥4 metastaze?

Primer→ 9 zasevkov, (volumen 1.7 cm^3 to 10.2 cm^3, skupni volumen zasevkov = 40 cm^3)

Predpisana doza 1 x 18 Gy

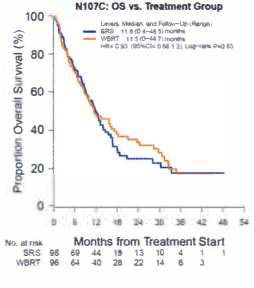
Vijolična barva =5 Gy; V5Gy = 40 do 60 % normalnega tkiva možgan



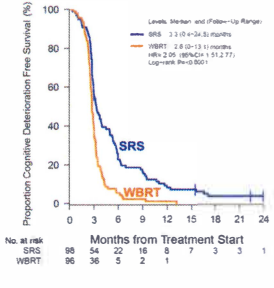
Sahgal 2017

RT po operaciji: WBRT ali SRS?

brez razlik v preživetju

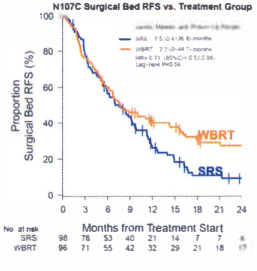


slabša kognitivna funkcija z WBRT



Brown, Lancet Oncology 2017

RT po operaciji: WBRT ali SRS?



WBRT vs. SRS:
Približno enaka lokalna kontrola, po nekaj mesecih boljša z WBRT
Brez razlik v preživetju

WBRT:
Nekoliko slabša kvaliteta življenja
Več neželenih učinkov
Obsevanje časovno daljše

Brown, Lancet Oncology 2017

ZASEVKI raka dojk V CŽS

→Različni molekularni podtipi raka dojk
→Terapevtske in prognostične razlike
→Obseg bolezni v in izven CŽS
→Stanje zmogljivosti in starost bolnika

PROGNOSTIČNE LESTVICE

B-RPA (Breast cancer recursive partitioning analysis prognostic index)

1–2 zasevka, brez - ali kontrolirana ekstrakranialna bolezen, KPS = 100	**Razred I**
Vsi ostali bolniki	**Razred II**
Številni zasevki, KPS ≤ 60	**Razred III**

SS-BM (Simple survival score for patients with brain metastases from breast cancer)

	Točke		Točke
KPS <70	1	Ekstrakranialna bolezen	3
KPS ≥70	6	Brez ekstrakranialne bolezni	6

B-GPA (Breast Graded Prognostic Assessment)

	Točke		Točke	Starost	Točke
KPS ≤ 50	0	TN	0	≥ 60	0
KPS 60	0.5	HR+/HER2-	1	< 60	0.5
KPS 70–80	1	HR-/HER2+	1.5		
KPS 90–100	1.5	HR+/HER2+	2		

MB-GPA (Modified Breast Graded Prognostic Assessment)

	Točke		Točke	Starost	Točke	Število zasevkov	Točke
KPS ≤ 50	0	TN	0	≥ 50	0	>3	0
KPS 60	0.5	HR+/HER2-	0.5	< 50	0.5	1–3	0.5
KPS 70–80	1	HR-/HER2+	1				
KPS 90–100	1.5	HR+/HER2+	1.5				

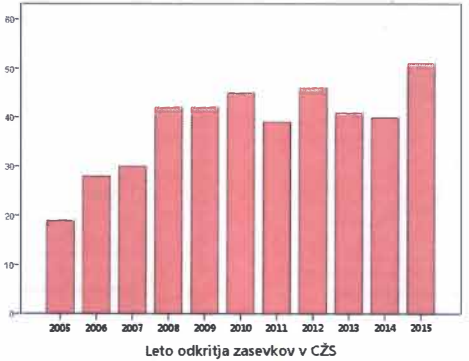
B-RPA (Niwińska, 2012); SS-BM (Rades, 2013); B-GPA (Sperduto, 2010); MB-GPA (Grigiuolo, 2018)

Rezultati zdravljenja na OILJ 2005 - 2015

[zasevki raka dojk v možganih ali na možganskih ovojnicah, zdravljeni z obsevanjem]

nabor podatkov:
TANJA ŽNIDARIČ
IVICA RATOŠA
Tim RT dojke

ŠTEVILO ZDRAVLJENIH GLEDE NA LETO



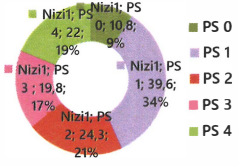
ZNAČILNOSTI BOLNIC

N= 423, možganski zasevki in/ali prizadetost mening

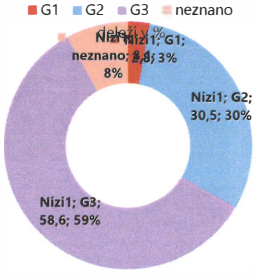
Starost (mediana), leta:
Ob diagnozi raka dojk: **52** (22–80)
Ob diagnozi zasevkov CŽS: **58** (28 – 83)
Ob smrti: **59** (30 – 84)

Ekstrakranialna bolezen
Kosti (60,1 %)
Jetra (37,5 %)
Pljuča (37,0 %)
Drugo (48,8 %)

Stanje zmogljivosti bolnic pred pričetkom obsevanja (delež bolnic)



ZNAČILNOSTI PRIMARNIH TUMORJEV

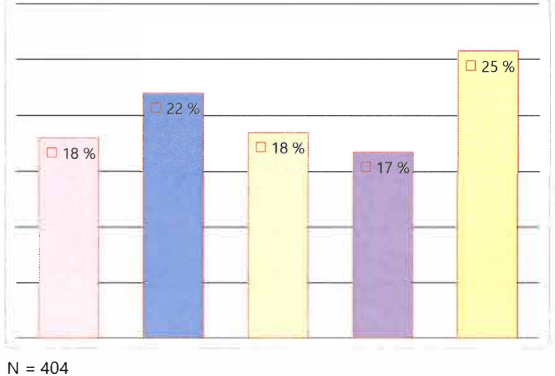


HER2 status:
neg→226 (53,4%)
poz→170 (40,2%)

Histološki podtip:
IDC→344 (81,3%)
ILC→40 (9,5%)

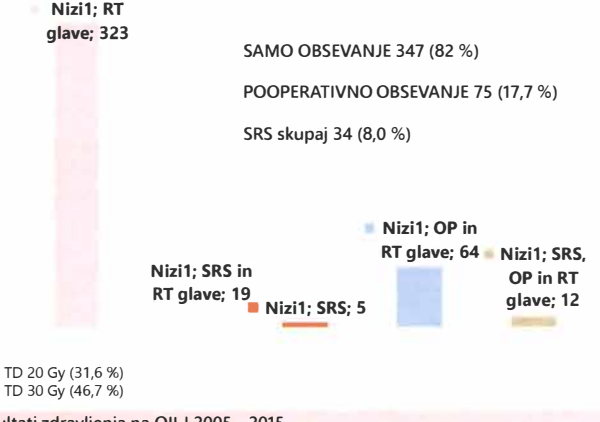
HR status:
ER+ →267 (63,1%)
ER- →153 (36,2%)

molekularni podtipi primarnega tumorja

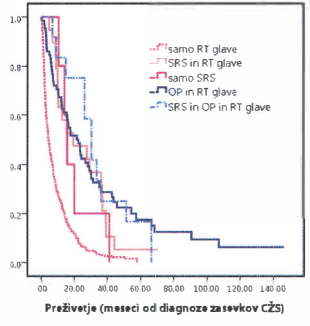


N = 404

ZDRAVLJENJE (N = 423)



PREŽIVETJE po diagnozi zasevkov v CŽS



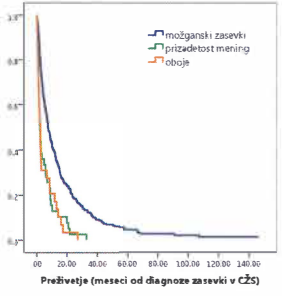
	OS (meseci)	95 % CI
RT glave	4.4	3.5–5.3
SRS in RT glave	19.3	0–40.6
SRS	15.8	12.2–19.4
OP in RT glave	21.5	14.2–28.7
SRS, OP in RT glave	30.4	23.4–37.5

Srednje celokupno preživetje za celotno skupino:

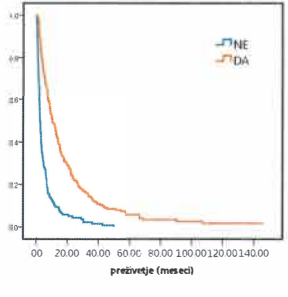
6,9 mesecev (CI 5,7-8,1)

ZASEVKI V CŽS IN PRIZADETOST MENING

	N	OS (m)	95 % CI
Možganski zasevki	**353** (83,3 %)	**7,5**	6,3–8,8
Prizadetost mening	**41** (9,7 %)	**2,3**	1,5–3,2
Oboje	**29** (6,8 %)	**2,7**	2,1–3,3



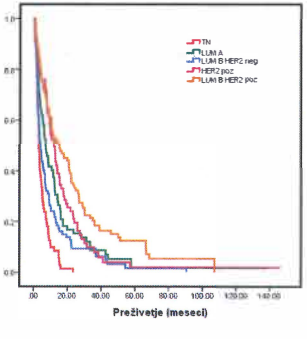
VPLIV OBSEVANJA NA IZBOLJŠANJE SIMPTOMOV



	število	preživetje
NE	142 (33,6 %)	2,4 [1,9–2,9]
DA	281 (66,4 %)	10,5 [8,5–12,5]

P<0,0001

PREŽIVETJE OD DIAGNOZE ZASEVKOV V CŽS



	OS (meseci)	95 % CI
TN	3,1	2,3–3,9
LUM B HER2-	3,9	2,3–5,6
LUM A	7,0	4,3–9,8
HER2+	12,1	8,3–15,9
LUM B HER2+	15,4	8,7–22,1

P<0.0001

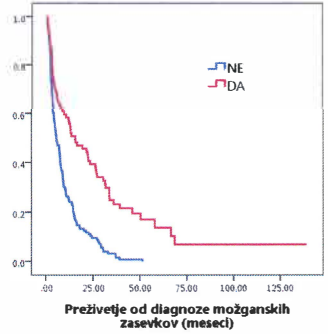
N = 404

SISTEMSKA TERAPIJA

Sistemska terapija:
394 (93 %)

Bolezen pod nadzorom s sistemsko terapijo:
(N = 215)
NE (32,1%)→ **5,5 m** (CI 3,5–7,4)
DA (18,6 %) → **15,6 m** (6,7 – 24,4)

P=0,0001



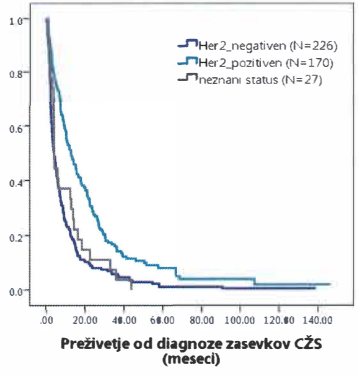
HER2+ status primarnega tumorja

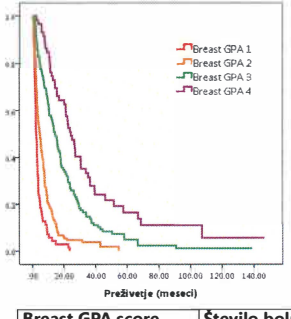
HER2 pozitiven
(**12,9 m**; CI 9,4-16,4)

HER2 negativen
(**4,2 m**; CI 3,1-5,3)

Neznan status
(**4,2 m**; CI 4,0-4,5)

P=0,0001



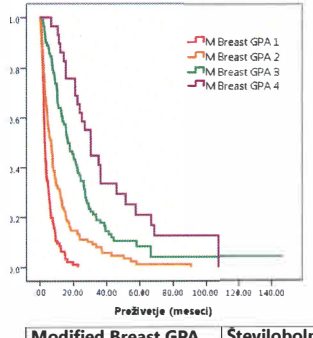


Breast-GPA

KPS , starost in molekularni podtip

Breast GPA score	Število bolnic (%)	Mediano preživetje (95% CI)
0-1.0	73 (17.3%)	2.2 (1.7-2.8)
1.5-2.0	151 (35.7%)	4.7 (3.4-5.9)
2.5-3.0	112 (26.5%)	14.2 (11.4-17.0)
3.5-4.0	59 (13.9%)	24.3 (19.6-29.0)

P<0,0001



Modified Breast-GPA

KPS , starost, molekularni podtip in število zasevkov

Modified Breast GPA score	Številobolnic (%)	Mediano preživetje (95% CI)
0-1.0	96 (22.7%)	2.7 (2.2-3.2)
1.5-2.0	137 (32.4%)	6.7 (4.9-8.5)
2.5-3.0	92 (21.7%)	16.8 (12.8-20.7)
3.5-4.0	29 (6.9%)	30.4 (24.0-36.8)

P<0,0001

ZAKLJUČKI

- **BOLNIKI Z DOBRO PROGNOZO** (npr. en zasevek v CŽS in brez ekstrakranialne bolezni, dober PS→ agresivno lokalno fokalno zdravljenje (OP ali/in SRS) in opustitev zgodnje WBRT ali ev. HA-WBRT, sledenje s slikovnimi preiskavami
- **BOLNIKI S SLABO PROGNOZO** (npr. progresivna sistemska bolezen, slab PS→pričakujemo korist od obsevanja celotne glave, kljub možnim neželenim učinkom.
- Pomisliti na prognostične lestvice (dobra lokalna kontrola vs. paliativen pristop)
- Naši rezultati primerljivi z ostalimi objavljenimi podatki
- **V BODOČE**: tehnologija za visoko natančna obsevanja je na voljo, vendar manjkajo še rezultati raziskav; čas, osebje, dražja tehnika; nova sistemska zdravljenja in sočasno obsevanje? (WBRT/SRS)

Zdravljenje zasevkov v centralnem živčnem sistemu s protirakavimi zdravili

Cvetka Grašič Kuhar,
Oddelek za internistično onkologijo
Onkološki inštitut Ljubljana

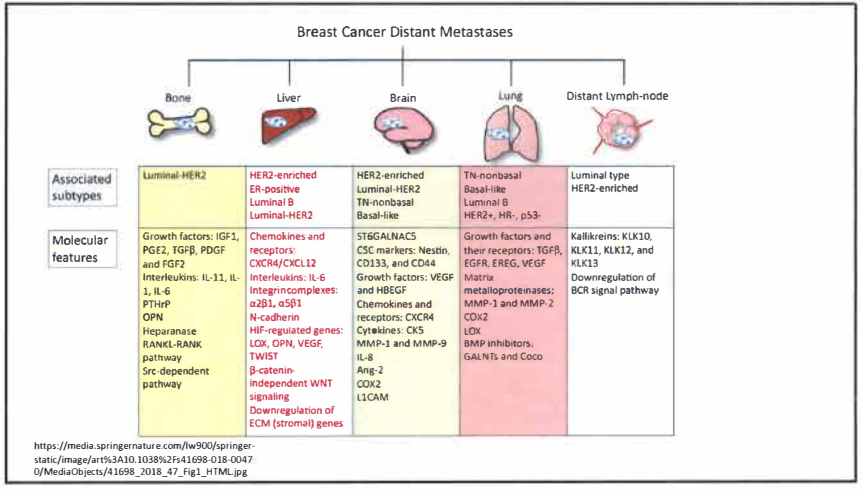
Incidenca možganskih metastaz in metastaz na meningah pri bolnicah z rakom dojk

- Možganske metastaze: 10-30 % vseh bolnic
- Metastaze na meningah: 5 %

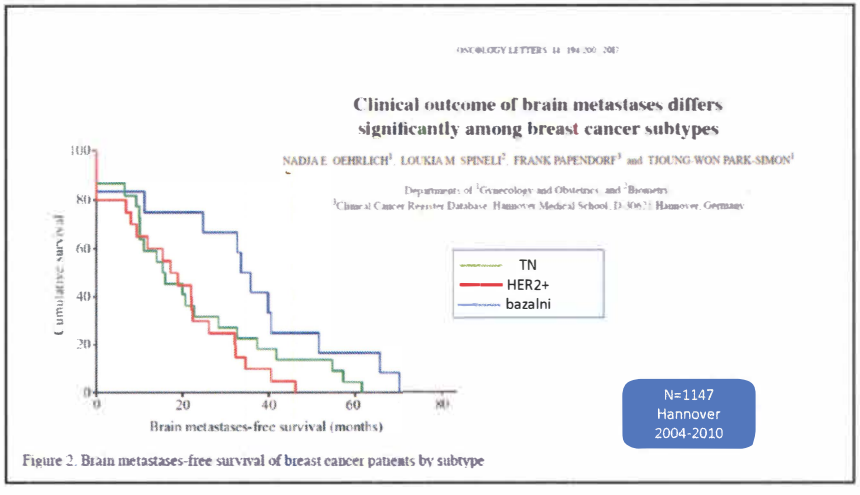
- Skrivno mesto za razvoj metastaz
- Prognoza slabša glede na ostala mesta metastaz

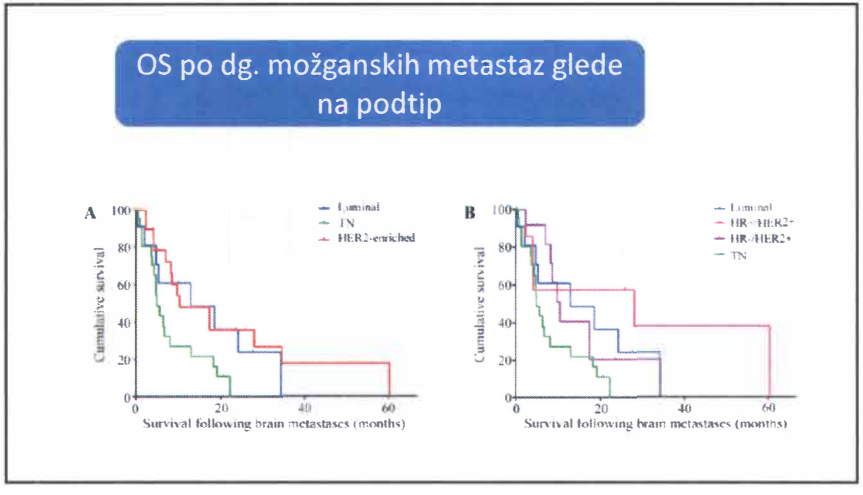
Faktorji, povezani z razvojem CŽS zasevkov

- Starost (mlajše več CŽS zasevkov)
- ER-
- HER2+
- Gradus III
- Tumor>5cm



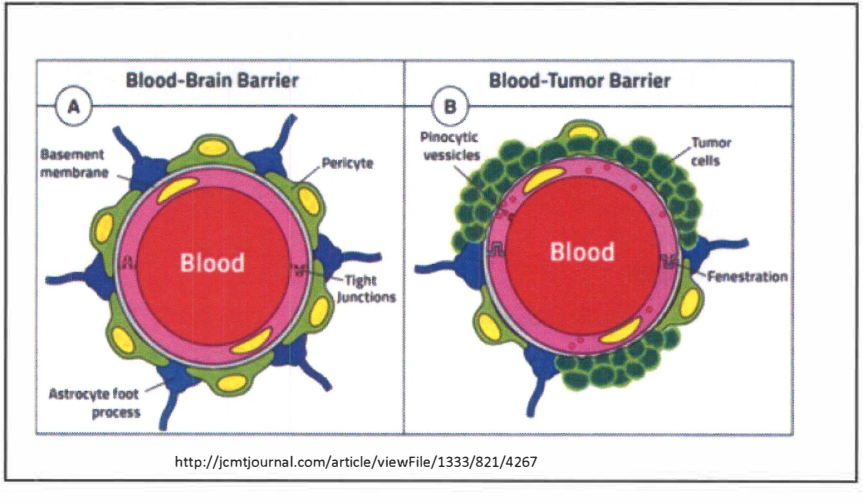
https://media.springernature.com/lw900/springer-static/image/art%3A10.1038%2Fs41698-018-0047-0/MediaObjects/41698_2018_47_Fig1_HTML.jpg

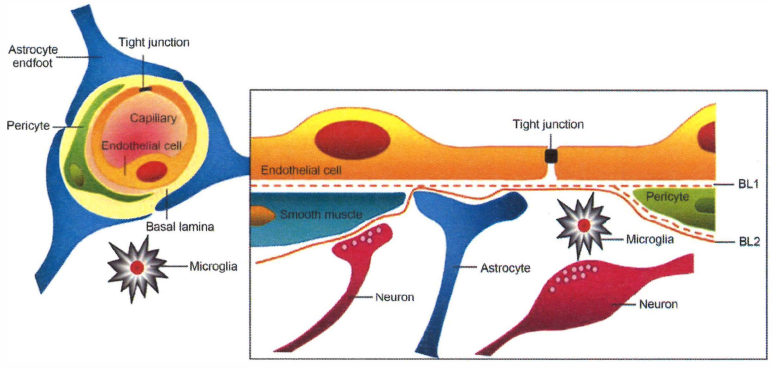




Preživetje možganskih metastaz po podtipih raka dojk

Podtip	n	Čas do pojava možg. metastaz mes (mediana, rang)	Število metastaz (med,rang)	mOS od dg. Raka (95 % IZ)	mOS od th možg. Meta (95 % IZ)
Bazalni	90	27,5 (15,7-44,8)	3 (1-4)	39,6 (32,2-44,9)	7,3 (4,9-9,5)
HER2+	119	35,8 (13,4-69,2)	2 (1-4)	66,4 (44-96,3)	17,9 (13,4-22,9)
Luminalni B	98	47,4 (26,3-70,5)	2 (1-5)	90,3 (73,3-98,4)	22,9 (16,1-29,5)
Luminalni A	76	54,4 (23-92,6)	3 (2-5)	72,7 (60,6-100)	10 (7,4-19,5)
p		p>0,01	p=0,29	p<0,01	p<0,01





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Neuro-Oncology
XX(XX), 1–11, 2018 | doi:10.1093/neuonc/noy044 | Advance Access date 16 March 2018

Breast cancer brain metastasis: molecular mechanisms and directions for treatment

Genetski prediktorji za CŽS metastaze (m.m.)

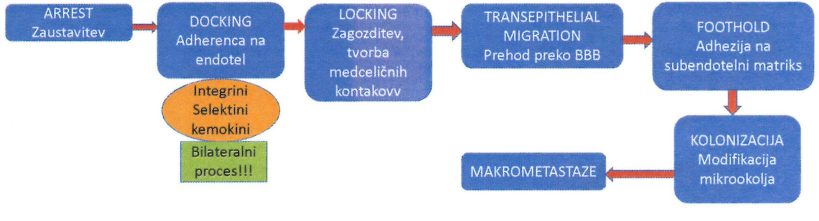
- V možganskih metastazah:
  - 16-22% HER2-postane HER2+
  - Še več spremeni ER status
  - Pomnožitev EGRF: ‚brain-seeking'
  - PTEN mutacija (21%), pomanjkanje izražanja PTEN proteina (31%)
- Pri isti osebi so možg. metastaze uniformne

Vloga imunskega sistema

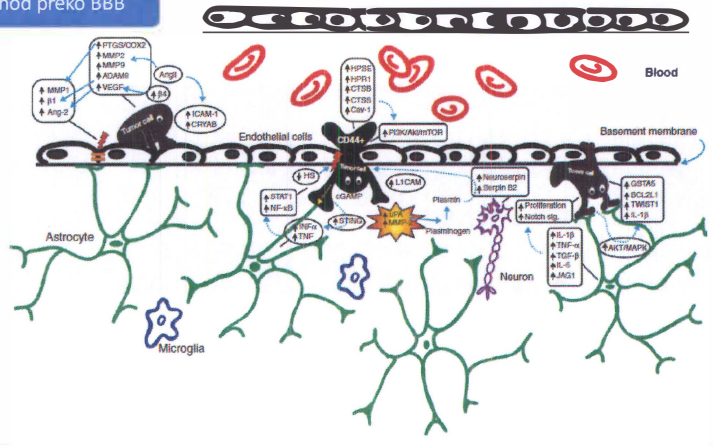
Ključen je odgovor T celic na primarni tumor;
T celice spremenijo proteom tumorske celice
Kultura BBB + T celice

Stopnje metastaziranja raka dojke v možgane

(C)TC pri prehodu preko BBB posnemajo imunske celice; tesni stiki (TJ)



Prehod preko BBB



Prehod TC preko BBB

Zelo invazivni fenotip TC
CD44high/CD24low

Kateri receptor bo postal biomarker za pojav možganskih metastaz?

Cancer initiating cells

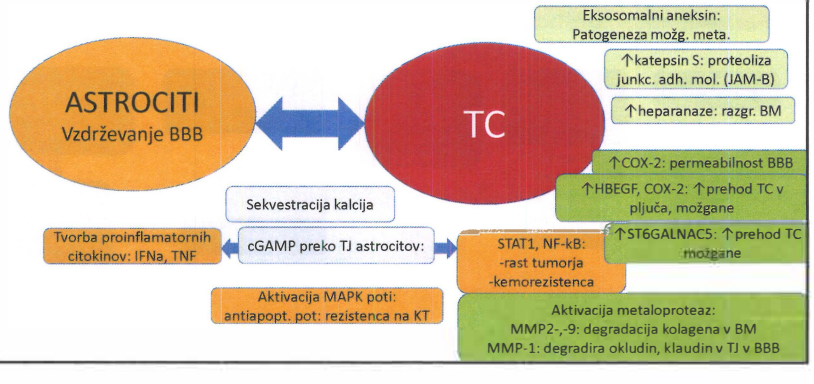
Pro-invazivni geni:
IL-1a, IL-6, IL-8, uPA, MMP-2

Integrini v TC:
-tvorba tromba okrog TC: zaustavitev TC
-↑ VEGF: ↑permeab. žilja

P-selektini: zamaskirajo TC pred imunskim odgovorom

Kemokini: CXCL-12/CXCR4: migracija preko BBB

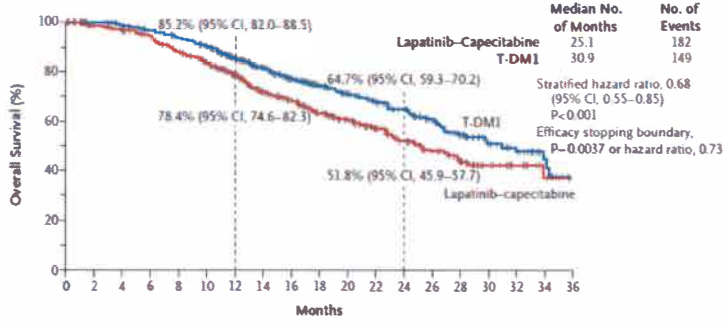
Intracerebralna progresija



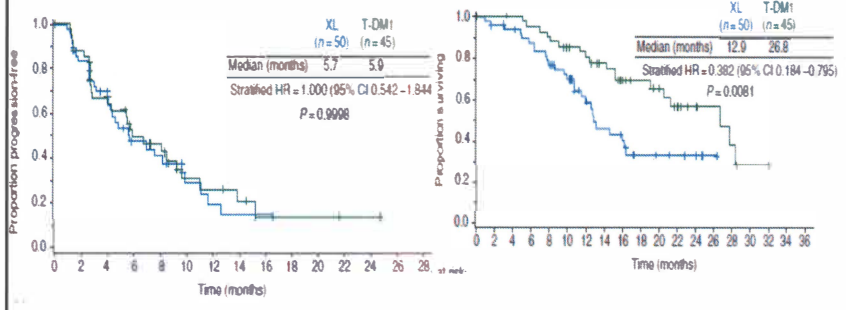
HER2+ raki

- Raziskave: antiHER2 terapija (trastuzumab): velika učinkovitost kontrole sistemske bolezni, podaljšan PFS, OS,
  - vendar trastuzumab kot velika molekula slabo prehaja BBB
  - Lapatinib-mala molekula, prehaja BBB, vendar zmanjšana razpoložljivost zaradi črpanja (efflux system) in rezistenčnih proteinov TC
- Raziskava *lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on trastuzumab:* roka z lapatinibom je imela manj možganskih zasevkov
- Po progresu v CŽS, če dober PS, preživetje še 23,5 mes

Raziskava EMILIA
(lapatinib+kapecitabin vs. TD-M1)



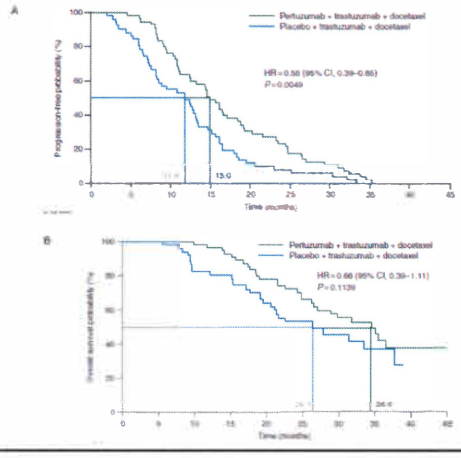
EMILIA
CŽS meta (PFS, OS)



Raziskava CLEOPATRA

Čas do progresa v možgane kot 1. mesto

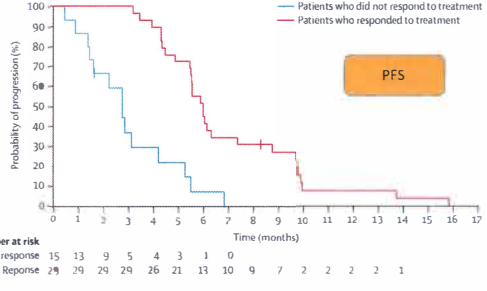
OS po progresu v možgane kot 1. mesto



Raziskava LANDSCAPE

Faza II, odprta,
CŽS progres, **RT naivni**
N=45
ORR: 66% (vse PR)
mOS= 17 mes
mPFS (CŽS)=5,5 mes

Poteka raziskava RT+lapatinib



Overview of actionable targets and clinical studies on targeted therapies in established brain metastasis

Target	Targeted Agent	Pretreatment with Radiotherapy	Response Rate	Progression-free Survival (mo)	Overall Survival	Type of Trial
HER2, EGFR	Lapatinib	Yes	6%	2.4	6.4	Phase II
	Lapatinib + Capecitabine	No	66%	5.5	70% (1 y)	Phase II
Her2	Neratinib	Yes	8%	1.9	8.7	Phase II
	Neratinib + Capecitabine	Yes	49%	NA	63% (1 y)	Phase II
	Tucatinib (ONT-380) + (TDM1)	Yes	33%	6.5	NA	Phase I
PARP	Iniparib [c]	Yes	27%	2.14	NA	Phase II

Overview of actionable targets and clinical studies on targeted therapies in established brain metastasis

HER2	Pertuzumab + High-dose Trastuzumab (intravenous)	Yes	NA	NA	NA	Phase II	NCT02536339
	Pertuzumab + Trastuzumab (intrathecal)	No	NA	NA	NA	Phase I	NCT02598427
	Tucatinib (ONT-380) + Trastuzumab	Yes	NA	NA	NA	Phase I	NCT019221335
CDK4/6	Abemaciclib	Yes	NA	NA	NA	Phase II	NCT02774681
	Palbociclib	No	NA	NA	NA	Phase II	NCT02308020
P13K/Akt	Everolimus	Yes	NA	NA	NA	Phase II	NCT01305941 [a] NCT01783756 [b]
PARP	Veliparib	Yes (in association)	NA	NA	NA	Phase II	NCT00649207

Učinkovitost tarčne terapije možganskih metastaz pri HER2+ raku dojk

Table 1. Clinical efficacy of targeted therapies in BCBMs

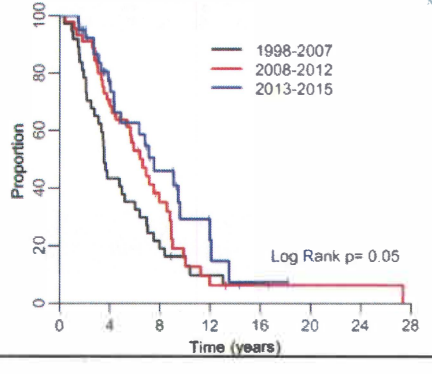
Regimen	Target	Breast cancer subtypes	CNS response rate	Reference
Afatinib	HER2/EGFR	HER2+	0%	Cortes et al. (76)
Neratinib	HER2/EGFR	HER2+	8%	Freedman et al. (21)
Neratinib + capecitabine	HER2/EGFR, antimetabolite	HER2+	49%	Freedman et al. (24)
Tucatinib	HER2	HER2+	7%	Metzger et al. (77)
Tucatinib ± capecitabine or trastuzumab	HER2, antimetabolite	HER2+	42%	Hamilton et al. (78)
Lapatinib	HER2	HER2+	6%	Lin et al. (79)
Lapatinib + capecitabine	HER2, antimetabolite	HER2+	18%–38% (pretreated); 66% (untreated)	Lin et al. (80); Bachelot et al. (81)
Buparlisib + trastuzumab	PI3K + HER2	HER2+	11%	Pistilli et al. (82)
Everolimus + trastuzumab + vinorelbine	mTOR + HER2 + anti-mitotic	HER2+	4%	Anders et al. (83)

NOTE: A summary of CNS ORRs to targeted therapies in patients with HER2-positive BCBMs.

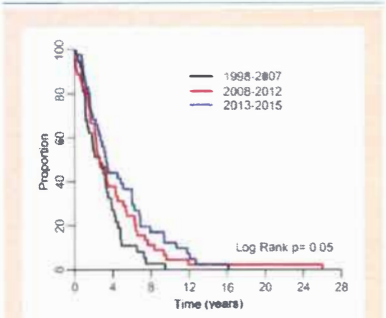
OS glede na leto dg. raka

Changing Natural History of HER2–Positive Breast Cancer Metastatic to the Brain in the Era of New Targeted Therapies

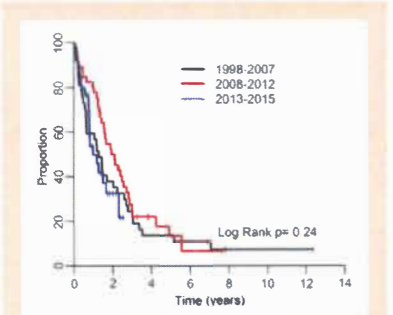
Lousa A. Mourssey[1], Allison M. Deal[2], Kevin C. Keith[1], Julia M. Benbow[2], Shlomit S. Shachar[2,6], Timothy Zagar[2,3,5], E. Claire Dees[2,4], Lisa A. Carey[2,4], Matthew G. Ewend[2,5], Carey K. Anders[2,4]



Čas do diagnoze možganskih metastaz

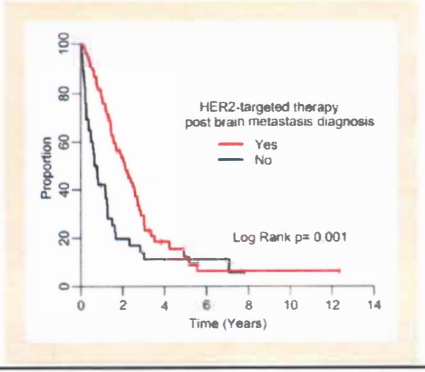


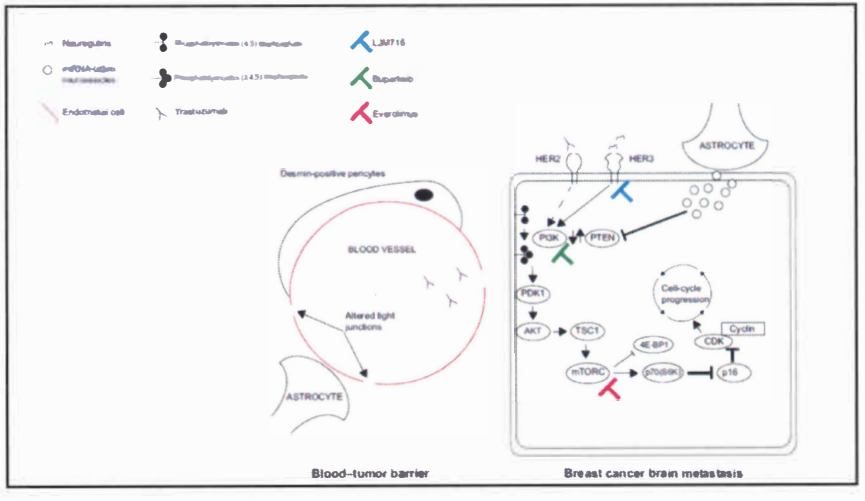
OS z možganskimi metastazami



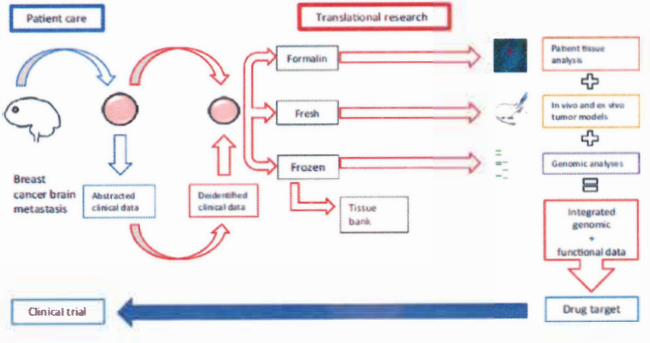
OS po dg. možganskih metastaz glede na prejemanje anti HER terapije

N=123





Potreba po translacijskih raziskavah!



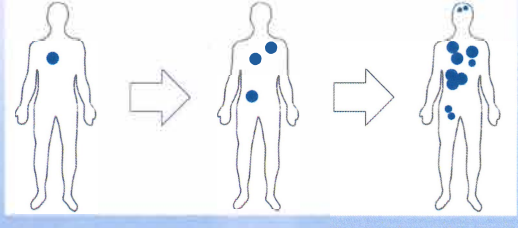
Obsevanje pri oligometastatskem raku dojk

Jasenka Gugić

Spomladansko strokovno srečanje Združenja za senologijo 2018
Ljubljana, 17.5.2018

Oligometastatska rakava bolezen

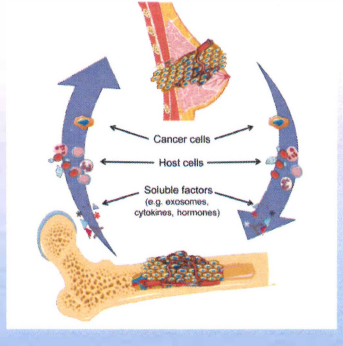
- Prehodna oblika med lokalno in razširjeno boleznijo
- Definicija oligometastatske bolezni?
- 3 do 5 zasevkov v 1 ali 2 organa



Hellman & Weichselbaum, Am J Clin Oncol, 1999; OligoCare project 2018

Metastaziranje

- Izguba celičnih vezi
- Povečana gibljivost celic
- Invazija tumorskih celic in preživetje v obtoku
- Invazija v tarčni organ
- Kolonizacija tarčnega organa



Pienta, Clin Cancer Res, 2013

Metastaziranje

- Pomankljivost pri katerikoli potrebni biološki zahtevi → omejeno metastatsko širjenje
- Specifični tumorski geni za:
  - Iniciacijo – invazija tumorskih celic v obtok
  - Progresijo – nadaljnji procesi, potrebni za kolonizacijo tarčnega organa
  - Virulenco – selektivna možnost kolonizacije tarčnega organa

Fidler, Nat Rev Cancer, 2003; Gupta, Cell, 2006

Zdravljenje oligometastatske bolezni

- Zlati standard → sistemsko zdravljenje in omejene možnosti lokalnega zdravljenja s paliativnim namenom
- Sprememba paradigme zdravljenja → dobra lokalna kontrola primarnega raka in zasevka(ov) z ablacijo
- Ablacija → klasično kirurška, zaradi tehnološkega napredka tudi obsevanje, in sicer:
  - SBRT/SABR (Stereotactic Body Radiotherapy/Stereotactic Ablative Radiotherapy) in
  - SRS (Stereotacic Radiosurgery)

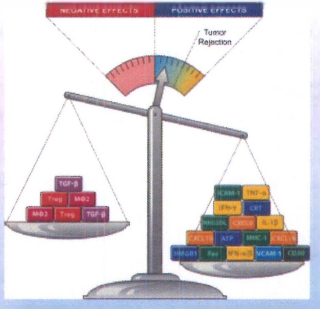
Reyes, Oncotarget, 2015

Zdravljenje s stereotaksijo

- SBRT, SRS – obsevanje tarče z visokimi odmerki (več ali ena sama frakcija), medtem ko okolna zdrava tkiva prejmejo nizke odmerke → manj dolgoročnih posledic
- Primerno za: neoperabilne bolnike (spremljajoče bolezni in/ali slab PS, tehnično neoperabilni zasevki), možnost povzročitve dodatne morbiditete z operacijo, npr. globoki zasevki, zasevki v kosteh…
- Prednosti: neinvazivna metoda, povzroča manjšo morbiditeto
- Slabosti: ni možnosti histopatološke preiskave (robovi!), neprimerno pri velikih lezij, neustrezni legi, obliki…

Obsevanje in antitumorska imunost

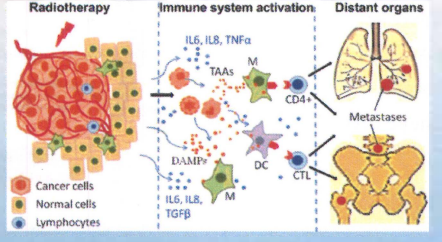
- Obsevanje → imunosupresivni učinek
- Hipofrakcionirano obsevanje → stimulacija antitumorske imunosti preko CD 8+ T-limfocitov in celičnih stresnih signalov:
  - Sproščanje antitumorskih citokinov
  - Stimulacija imunskega sistema s poškodovanim tkivom



Formenti, J Natl Cancer Inst, 2013; Matzinger, Science, 2002

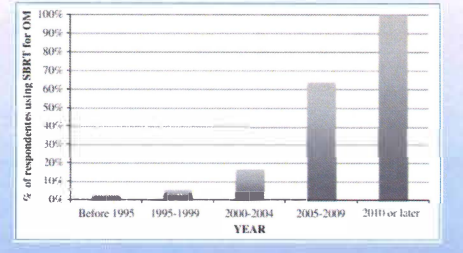
„Abscopal“ efekt

- Pojav pri zdravljenju metastatske bolezni, ko obsevanje tumorja/zasevka ne povzroči le zmanjšanje tega, ampak tudi zasevka(ov) izven polja obsevanja



Uporaba SBRT

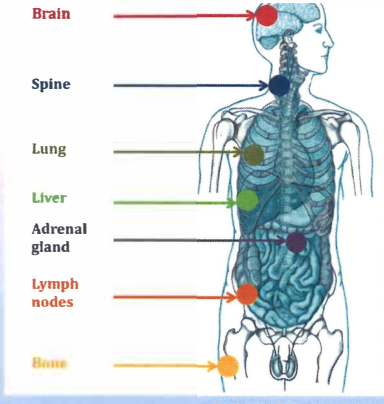
- Anketa o uporabi SBRT v klinični praksi pri 1007 radioterapevtov iz 43 držav po vsem svetu



Lewis, A, J Clin Oncol, 2015

Izsledki dosedanjih raziskav

- Kaj vemo?
- Številne nerandomizirane študije - varno in učinkovito zdravljenje
- Cca 80% lokalna kontrola
- 2-5-letno preživetje brez napredovanja bolezni cca 20%



Tree, Lancet Oncol, 2013

Izsledki dosedanjih raziskav

- Male in heterogene skupine bolnikov (heterogene glede primarne bolezni, lokacije zasevkov, zdravljenja, vključitvenih kriterijev…)
- Vprašanje zaporedja zdravljenja (lokalno/sistemsko)
- Dobri rezultati – realno ali le poledica izbire bolnikov

1. avtor, leto	Prosp./retro, obdobje	Št. bol.	Izbira bolnikov	Zdravljenje	Rezultat	Zaključek
Kobayashi, 2012	R, 1980-2010	75	1-2 organa, ≤5 zas./organ, ≤5cm v premeru	+/- KT, +/- lokalno zdravljenje, KT	10-let. OS 59.2%, 20-let. OS 34.1%	oligomet. prognostično ugodneja, kot metast.
Bojko, 2004	P, 1995-2001	48	1 organ z 1-nekaj zas.	operacija/RT, KT, PKMC	med. OS 42.4 mes., med. čas do progresa 17.5 mes.	kombinirano zdrav. je varno pri oligomet., obetavno preživetje
Milano, 2009	P, 2001-2006	40	≤5 zas.	SBRT	4-let. OS 59%	dolgoročno preživetje po SBRT, verjetno tudi pozdravitev pri izbrani populaciji
Bourgier, 2010	R, 1990-2003	239	1 področje zasevanja	RT vs. RT in operacija	3-let. OS 39%vs. 57%	obetavno preživetje brez bolezni
Scorsetti, 2016	P, 2010-2016	33	1-3 zas. v jetrih, 1-3 zas. v pljučih, <5 zas., premera <5 cm	SBRT	1-let. in 2-let. OS je 93 % in 66 %, 1-let. in 2-let. preživetje brez bolezni je 48 % in 27 %	dobra lokalna kontrola in preživetje po SBRT

Prognostični dejavniki/splošno

- Prognostični dejavniki pri oligometastatski bolezni:
  - Histologija tumorja
  - Čas do ponovitve bolezni
  - Število zasevkov
  - Velikost zasevka(ov)/velikost PTV
  - Čas pojava zasevka(ov) – sinhroni vs. metahroni
  - Odmerek obsevanja
  - Uporaba bolj enostavnih tehnik za kontrolo premikov med obsevanjem

Tree. Lancet Oncol, 2013; de Vin, Ann Oncol, 2014; Klement, Radiother Oncol, 2017

Prognostični dejavniki/rak dojke

- Prognostični dejavniki pri raku dojke:
  - Status hormonskih receptorjev
  - Sistemsko zdravljenje po ali pred SBRT
  - Bolezen izven jeter/pljuč
  - Status her-2 receptorjev
  - Število pozitivnih bezgavk

Scorsetti, Breast, 2016; Nieto, Int J Radiat Oncol Biol Phys, 2008; Klement, Radiother Oncol, 2018

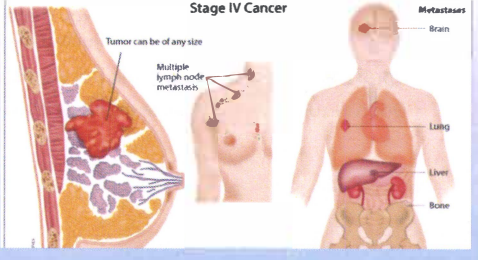
Potekajoče raziskave

- NRG BR002, *Standard of care with or without stereotactic radiosurgery and/or surgery in treating patients with limited metastatic breast cancer* – 1 ali 2 zasevka
- SABR COMET, *Stereotactic ablative radiotherapy for comprehensive treatment of oligometastatic tumors* – ≤3 zasevka v 1 organu
- CORE, *Conventional care versus radioablation (stereotactic body radiotherapy) for extracranial oligometastases (CORE)* - ≤3 zasevka, ≤2 organa
- OligoCare (ESTRO/EORTC), *A pragmatic observational basket study to evaluate radical radiotherapy for oligo-metastatic cancer patients* – 3-5 zasevkov v 1-2 organa

https://ClinicalTrials.gov; OligoCare project, 2018

Metastaski/oligometastatski rak dojke

- Metastaski rak dojke - 3.5-7% vseh novoodkritih rakov dojke oz. 30-40% vseh rakov dojke,
- Delež oligometastatskih - 1-3% vseh metastatskih
- Mediano preživetje: 8-24 mesecev, 18-24 mesecev, 2-4 leta



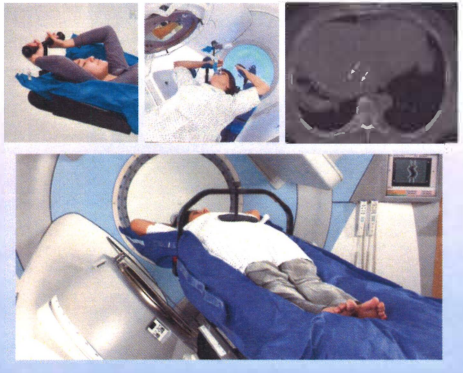
Reyes, Oncotarget, 2015; Scorsetti, Breast, 2016

SBRT jeter

- Primerno za zasevke blizu velikih žil, v primeru portalne karcinomske venske tromboze
- Tehnično zahtevnejša zaradi večje gibljivosti (premiki zaradi dihanja, predvsem levi jetrni reženj) in različne polnjenosti (želodec, črevo) sosednjih organov → večji intrafrakcijski premiki, posebej v kranio-kavdalni smeri, do 39.5 mm (povprečno 17.6 mm)

SBRT jeter - fiksacijski pripomočki, podlage

- Wing-Board, vakuumska blazina, Body Fix System, različne podlage, 4D CT, ev. abdominalna kompresija, sistem za kontrolo dihanja (ABC), vstavitev fiducialnih markerjev (sledljivost z natančnostjo 1 mm)



SBRT jeter

- Planiranje:
  - 3D CRT (Three Dimensional Conformal Radiotherapy)
  - VMAT (Volumetric Modulated Arc Therapy)
  - IMRT (Intensity Modulated Radiotherapy)
  - DAT/DCAT (Dynamic Conformal Arc Therapy)
- IGRT (Image Guided Radiotherapy) - CBCT (Cone Beam CT), pred in po vsakem obsevanju, ev. intrafrakcijsko, poravnava na markerje ali konturo jeter

SBRT jeter

- Zasevki v jetrih - kolorektalni, rak trebušne slinavke, želodca, požiralnika, dojk, pljuč, melanoma
- 30-70 % bolnikov s kolorektalnim rakom
- 70–90% bolnikov je neoperabilnih

Velikost lezije	Predpisana doza
<3 cm	48-60 Gy
3-6 cm	60-75 Gy

	Primerni bolniki	Vprašljivi	Neprimerni
Št. zasevkov	≥3	4	>4
Premer	1-3 cm	3-6 cm	>6 cm
Oddaljenost od OARs	>8 mm	5-8 mm	<8 mm
Funkcija jeter	Child A	Child B	Child C
Zdravi jetrni volumen (cc)	>1000	700-1000	<700

1. avtor, leto	Št. bol./št. lezij	Histologija (št. primerov)	Odmerek RT/ št. fr.	Lokalna kontrola	Celokupno preživetje
Scorsetti, 2013	61/76	kolorektalni (29), dojka (11), gineko. (7), drugo (14)	75 Gy/3 fr.	1-let. LC 94%	1–let. OS83.5%
Goodman, 2010	29 (19met.)/40	kolorektalni (6), pankreas (3), želodec (2), jajčnik (2), drugo (6)	18–30 Gy/1 fr.	1-let. lokalni neuspeh 23%	2-let. OS 49% (samo met.)
Ambrosino, 2009	27/NP	kolorektalni (11), drugo (16)	25–60 Gy/3 fr.	Stopnja LC 74%	NP
Rusthoven, 2009	47/63	kolorektalni (15), pljuča (10), dojka (4), jajčnik (3), požiralnik (3), hepatocel. (2), drogo (10)	36–60 Gy/3 fr.	1-let. LC 95%, 2-let. LC 92%	med. OS 20.5 mes.
Lee, 2009	68/143	kolorektalni (40), dojka (12), sečni mehur (4), pljuča (2), analni (2), melanom (2), drugo (6)	27.7–60 Gy/6 fr.	1-let. LC 71%	med. OS 17.6 mes.
Mendez Romero, 2006	25 (17 met.)/34	kolorektalni (14), pljuča (1), dojka (1), karcinoid (1	30–37.5 Gy/3 fr.	2-let. LC 86%	2-let. OS 62%
Hoyer, 2006	64 (44 met.)/141	kolorektalni (44)	45 Gy/3 fr.	2-let. LC 79% (za tumor), 64% (zabolnika)	2-let. OS 38%
Herfarth, 2004	35/?	NP	14–26 Gy/1 fr.	1–let. LC 71%, 18–mes. LC 67%	1–let. OS 72%

SBRT jeter

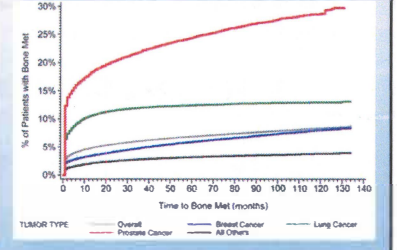
- 2-letna lokalna kontrola 70-100% (100% pri zasevkih < 3 cm)
- 2-letno celokupno preživetje 60–90%
- RILD (Radiation Induced Liver Disease) – med 2. in 7. mesecem po obsevanju

Aitken, Clin Oncol, 2015; Scorsetti, Breast

Metastaze v kosteh

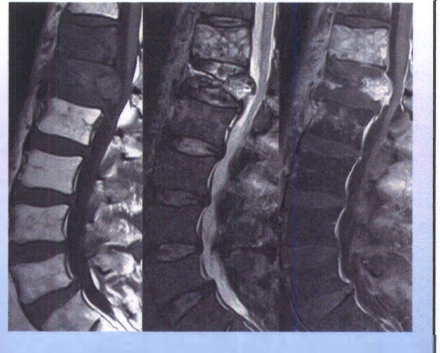
Tumor type	5-Year worldwide prevalence (1000s)	Incidence of bone metastases in patients with advanced metastatic disease (%)	Median survival from diagnosis of bone metastases (months)
Breast	3089	65–75	19–25
Prostate	1555	65–75	12–53
Lung	1334	30–40	6–7
Bladder	1009	40	6–8
Renal cell	668	20–25	12
Thyroid	475	60	48
Melanoma	832	14–40	6

Tumor type	Incidence of bone metastases (%)			
	1-year (95% CI)	2-year (95% CI)	5-year (95% CI)	10-year (95% CI)
All tumor types combined (N = 382,735)	4.8 (4.7–4.8)	5.6 (5.5–5.6)	6.9 (6.8–7.0)	8.4 (8.3–8.5)
Breast (N = 137,720)	3.4 (3.3–3.5)	4.2 (4.1–4.3)	6.0 (5.8–6.1)	8.1 (7.9–8.3)
Prostate (N = 22,801)	18.0 (17.5–18.5)	20.4 (19.9–20.9)	24.5 (23.9–25.1)	29.2 (28.3–30.1)
Lung (N = 59,344)	10.4 (10.2–10.7)	11.5 (11.3–11.8)	12.4 (12.1–12.7)	12.9 (12.6–13.2)
Colorectal (N = 46,832)	1.0 (0.9–1.1)	1.4 (1.3–1.5)	2.1 (2.0–2.3)	2.7 (2.5–2.9)
Gastrointestinal (N = 32,874)	2.3 (2.1–2.5)	2.7 (2.6–2.9)	3.2 (3.0–3.4)	3.6 (3.3–3.8)
Gynecological (N = 21,075)	1.1 (0.9–1.2)	1.3 (1.2–1.5)	1.9 (1.7–2.1)	2.4 (2.1–2.7)
Malignant melanoma (N = 12,152)	1.6 (1.4–1.8)	2.0 (1.7–2.2)	2.5 (2.2–2.8)	3.0 (2.6–3.4)
Renal (N = 17,717)	5.8 (5.5–6.2)	6.9 (6.6–7.3)	8.4 (8.0–8.9)	9.9 (9.3–10.5)
All other tumors (N = 32,218)	2.0 (1.8–2.1)	2.5 (2.3–2.7)	3.2 (3.0–3.4)	3.9 (3.5–4.2)



Spinalni kostni zasevki

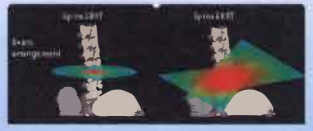
- 60% vseh so spinalni
- 20-40% vseh bolnikov z rakom ima spinalne kostne zasevke
- Pri cca 10% bolnikov s spinalnimi zasevki → kompresija hrbtenjače

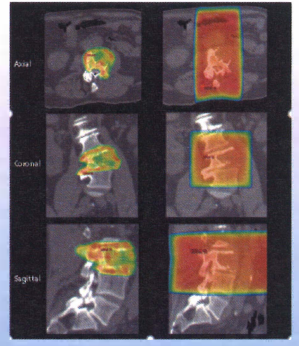


2017, Laufer, Oncologist, 201

Možnosti zdravljenja z obsevanjem

- Klasično kirurško zdravljenje in EBRT (External Beam Radiotherapy) ali samo EBRT → sedaj vse več SBRT/SABR ali SBRS (kot edini način zdravljenja ali pooperativno)

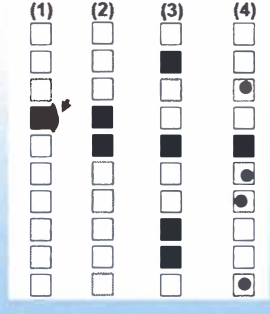




Spratt, Lancet Oncol, 2017

Indikacije za stereotaktično obsevanje

- Spinalni zasevki od C1-S
- Solitarni zasevki v vretencih (sl. 1)
- Zajetost največ dveh sosednjih vretenc (sl. 2)
- Največ tri ločene lokacije na hrbtenici (sl. 3)
- Ob prisotnosti več majhnih lezij po hrbtenici (sl. 4), zajetost manj kot 20% vretenca, ostale lezije asimptomatske



Protokol za obsevanje vretenc s tehniko SBRT, OI, v delu

Indikacije za stereotaktično obsevanje

- Oddaljenost roba tumorja od hrbtenjače ≥3mm v primeru kompresije
- Velikost paraspinalne lezije ≤5 cm
- Reiradiacija - >5 mesecev po EBRT
- Pooperativna SBRT - pri prizadetosti največ 2 nivoja, pri radiorezistentni bolezni in kot reiradiacija

Protokol za obsevanje vretenc s tehniko SBRT, OI, v delu

Fiksacijske podlage, pripomočki

- Wing-Board, vakuumska blazina, Body Fix System, različne podlage, fiksacijska maska za cervikalno in zgornjo torakalno hrbtenico
- Planiranje – VMAT, IMRT
- IGRT - CBCT pred in po vsakem obsevanju, ev. intrafrakcijsko, poravnava na kostne strukture

Protokol za obsevanje vretenc s tehniko SBRT, OI, v delu; Spratt, Lancet Oncol, 2017

Stereotaktično obsevanje hrbtenice

- SBRS pri hrbtenici dosega značilno boljšo lokalno kontrolo kot SBRT (2-5 fr.)
- Cca 3x večji odmerek obsevanja (BED)
- Optimalni odmerek in število frakcij?
  - 1x16 Gy, 1x18 Gy, 1x 20 Gy, 1x24 Gy
  - Reiradijacija: 1x16 Gy, 1x18 Gy, 1x 20 Gy
  - Pooperativno: 1x18 Gy, 1x 20 Gy, 1x24 Gy

Protokol za obsevanje vretenc s tehniko SBRT, OI, v delu; Spratt, Lancet Oncol, 2017

Stereotaktično obsevanje hrbtenice

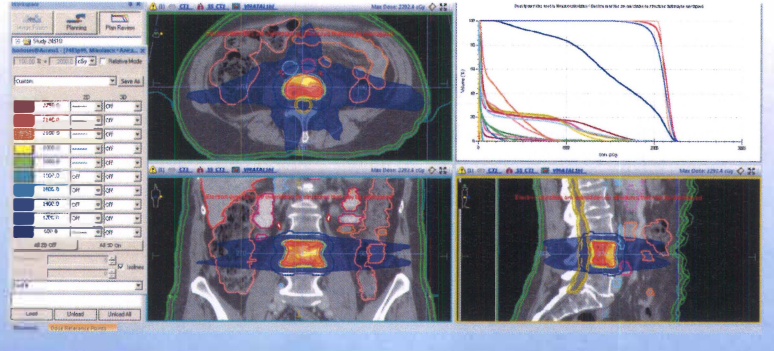
- 2-letna lokalna kontrola >85%
- Mediano celokupno preživetje >75 mesecev
- 2-letno preživetje 60-90%
- 5-letno preživetje cca 60%
- Insuficientna fraktura vretenca - 11-20%, povprečno po 3 mesecih
- Mijelopatija - 0.6%, povprečno po 6.3 mesecev

Ho, J Neurosurg Spine, 2016; Spratt, Lancet Oncology, 2017

SRS hrbtenice (L4)

- Gospa A.M., l. 1958
- Rak L dojke l. 1999: ILC, vel. 2 cm, gr. I, mit. I, brez LVI, ER poz. 2x2, PR poz. 2x2, HER-2 IHK 2+, st. bezg. 3/32
- QUAX, KT (4xAC, 3xCMF), RT, HT (Nolvadex)
- L. 2003 lokalni recidiv v L dojki: ILC, vel. 6 mm, gr. I, mit. I, brez LVI, ER 40% (šibko poz.), PR 50%, HER-2 neg.
- Ablacija dojke, HT (Arimidex) do l. 2010
- L. 2017 solitarni zasevek v L4, vel. 2 cm, ER 40%, PR 10%
- 12.4.2018 SRS s TD 1x20 Gy, HT (Arimidex)

SRS hrbtenice (L4)



SBRT jeter

- Gospa V.V., l. 1953
- Bilateralni rak dojk l. 2008: D - IDC, multicentrična žarišča, največje vel. 1.5 cm, gr. lll, mit. lll , brez LVI, ER 60-90%, PR 10-80%, HER-2 neg., st. bezg. 0/2
- L – invazivni, tubulolobularnega tipa, vel. 5 mm, gr. l, mit. L, ER > 5% (šibko poz.), PR < 80% (močno poz.), HER-2 neg./poz.
- D – MRM, L – ablacija + SNB, KT (4xEC), anti HER-2 (Herceptin), HT (Nolvadex) do 2013
- Februarja 2016 razsoj z zasevki v jetrih (3 zasevka): KT (8xDocetaxel), HT (letrozol), decembra 2016 in aprila 2017 RFA 2 jetrna zasevka, zasevek v 8. jetrnem segmentu je bil slabo dostopen
- Novembra 2017 progres zasevka v 8. jetrnem segmentu, HT (Faslodex)
- 19.-23.3.2018 SBRS s TD 3x18 Gy

SBRT jeter