Združenje za
senologijo Slovenije
Slovenian Senologic
Society

Spomladansko strokovno srečanje Združenja za senologijo 2017

Neoadjuvantno zdravljenje raka dojk

Ljubljana, 18. Maj 2017

Predavatelji:
Maja Ravnik, dr. med., Oddelek za onkologijo, UKC Maribor
Doc. dr. Cvetka Grašič Kuhar, dr. med., Oddelek za internistično onkologijo, Onkološki inštitut Ljubljana
Doc. dr.Andraž Perhavec, dr. med., Oddelek za onkološko kirurgijo, Onkološki inštitut Ljubljana
As. dr. Tanja Marinko, dr. med., Oddelek za radioterapijo, Onkološki inštitut Ljubljana

Urednica zbornika:
Simona Borštnar

Organizator in izdajatelj:
Združenje za senologijo pri SZD

Simpozij sta finančno omogočila podetja Roche in Novartis

Ljubljana, maj 2017

PROGRAM STROKOVNEGA SREČANJA:

16.30-16.50	**Rezultati neoadjuantnega zdravljenja raka dojk v UKC Maribor in izzivi za vnaprej** **Maja Ravnik,** Oddelek za onkologijo, UKC Maribor
16.50-17.10	**Izbor neoadjuvantnega sistemskega zdravljenja raka dojk, komu, kaj in kako dolgo** **Cvetka Grašič Kuhar,** Oddelek za internistično onkologijo, Onkološki inštitut Ljubljana
17.10-17.30	**Operacija po neoadjuvantnem sistemskem zdravljenju raka dojk** **Andraž Perhavec,** Oddelek za onkološko kirurgijo, Onkološki inštitut Ljubljana
17.30-17.50	**Radioterapija po neadjuvantnem sistemskem zdravljenju raka dojk** **Tanja Marinko,** Oddelek za radioterapijo, Onkološki inštitut Ljubljana
17.50-18.15	Razprava

REZULTATI NEOADJUVANTNEGA ZDRAVLJENJA RAKA DOJK V UKC MB

IN IZZIVI ZA NAPREJ

Maja Ravnik, Oddelek za onkologijo,

Nina Čas Sikošek, Oddelek za ginekološko onkologijo in onkologijo dojk,

Nejc Kozar, Oddelek za ginekološko onkologijo in onkologijo dojk

UKC MB

UKC MB

- Letno okoli 200 bolnic z rakom dojke v UKC MB
- Oddelek za ginekološko onkologijo in onkologijo dojk - večina
- Oddelek za torakalno kirurgijo – zelo malo

POT OBRAVNAVE BOLNIC

NATH V UKC MB

2008	2009	2010	2011	2012	2013	2014	2015	2016
9	13	10	9	8	15	27	42	32

NATH 2016

- Lokalno napredovali

T1	T2	T3	T4	N0	N+
4	21	1	6	11	21

- Vnetni rak dojke
- Kjer OP ni možna zaradi komorbidnosti (HT)

NATH 2016 - PODTIPI

	VNETNI	HER2 +	TNT	ostalo
N = 32	1	11	4	16

HER 2 +	HR +	HR-
N=11	8	3

HISTOLOGIJA

INVAZIVNI DUKTALNI	LOBULARNI
30	2

OPERATIVNO ZDRAVLJENJE

	MRM	TUMOREKTOMIJA
N=30 (2 bolnici OP na OI, ostale še niso zaključile s predoperativno TH)	5	12

2014-2015

- 51 bolnic prejelo NAKT
- Srednja starost 53 let (30 – 81 let)
- 2014-2016: srednja starost 54 let (30 – 81let)

2014-2016

T	T1	T2	T3	T4
N (%)	6 (8.1)	53 (71.6)	5 (6.8)	10 (13.5)

Nodusi	N0	N1	N2	N3
N (%)	19 (25.7)	28 (37.8)	26 (35.1)	1 (1.4)

Gradus	G1	G2	G3	Gx
N (%)	3(4.1)	37 (50.0)	33 (33)	1 (1.4)

2014-2016

	VNETNI	HER2+	TNT	ostalo
N= 73	5	29	20	26

KT sheme

SHEMA	N
ANTRACIKLINI (EC, d.d.EC)	42
TAKSANI (TCH)	18
KOMBINACIJE	14

Odgovori

- Povprečna UZ velikost tumorja pred KT: 3,9 cm
- Povprečna končna po KT: 1,7cm

- pCR (patološki popolni odgovor)

Odgovor T, N, G

T	T1	T2	T3	T4
N (%)	6 (8.1)	53 (71.6)	5 (6.8)	10 (13.5)
pCR	2 (33.3)	6 (11.3)	0	1 (10.0)

Nodusi	N0	N1	N2	N3
N (%)	19 (25.7)	28 (37.8)	26 (35.1)	1 (1.4)
	4 (21.1)	4 (14.3)	1 (3.8)	0

Gradus	G1	G2	G3	Gx
N (%)	3(4.1)	37 (50.0)	33 (33)	1 (1.4)
pCR	0	2(5.4)	7 (21.2)	0

Odgovori HR

ER	N	pCR
POZITIVNI	51 (68.9%)	6 (11.8%)
NEGATIVNI	23 (31.1%)	3 (13%)

PR	N	pCR
POZITIVNI	50 (68.9%)	7 (14.0%)
NEGATIVNI	24 (32.4%)	2 (13.0)

Odgovori HER2 in TNT

HER2	N	pCR
POZITIVNI	29 (39.5%)	6 (22.2%)
NEGATIVNI	47 (63.5%)	3 (6.4%)

	N	pCR
TNT	20 (27.0%)	1 (5.0%)

IZZIVI?

- Predpogoj: sodelovanje med člani konzilija!!
- Sodelovanje med inštitucijami (OI – UKC MB)
- DORA?

DORA 2016

- 20 bolnic poslanih na KT v UKC MB
- 1 bolnica primarno metastatska
- 7 bolnic z lokalno napredovalim rakom dojke – BREZ PREOPERATIVNEGA ZDRAVLJENJA

Primer B.D. 1966

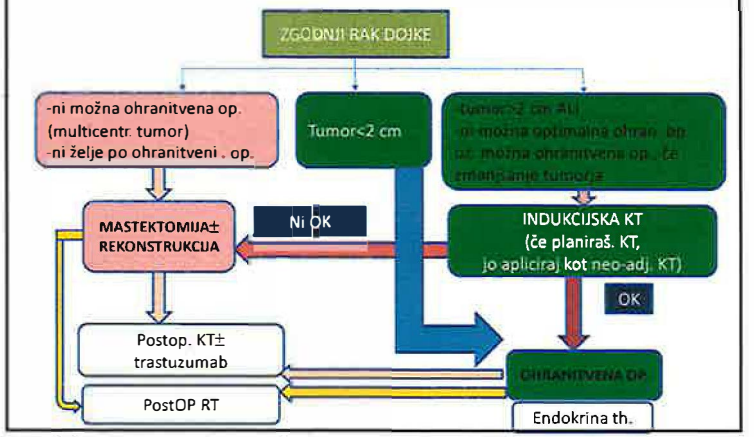
- St. po QUAX
- Primarni tumor: 7 cm
- Bezgavke:17/35, največji zasevek 2,2 cm, preraščanje kapsule
- G3, mitoze 3, vaskularna invazija in limfangioza
- ER80%, PR 70%, HER2 neg

HVALA

Izbor neoadjuvantnega sistemskega zdravljenja raka dojk: komu, kaj in kako dolgo

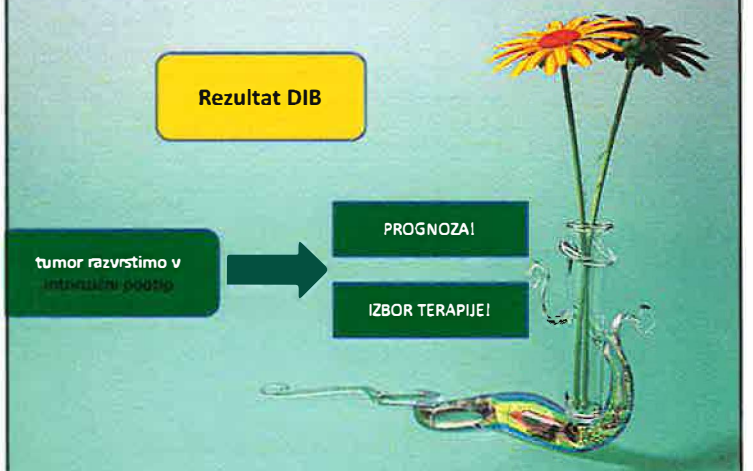
Cvetka Grašič Kuhar
Oddelek za internistično onkologijo
Onkološki inštitut Ljubljana

Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up
Annals of Oncology
Volume 26 | Supplement 5 | September 2015



Priporočene preiskave pred neoadjuvantno sistemsko terapijo

- Fizikalni pregled + laboratorij (hemogram, jetrna in ledvična funkcija, Ca, alkalna fosfataza)
- Dosedanje bolezni, familiarna anamneza raka, UZ srca, če bo th. z antraciklini, trastuzumabom
- Bilateralna mamografija
- Uz dojk + aksil
- Debeloigelna biopsija tumorja (histol., gradus, ER, PR, HER2, Ki-67)
- Citološka punkcija suspektnih bezgavk v aksili, scl
- MR dojk (ne rutinsko); MR dojk potreben,če:
  - BRCA-povezan hereditarni rak dojke
  - Implanti v dojkah
  - Lobularni rak
  - Sum na multifokalnost/multicentričnost
  - Velika diskrepanca med klinično velikostjo tumorja in velikostjo na mamografiji/UZ
  - Pred NAKT (če evaluiraš ODGOVOR NA TH)
  - Origo ignota z zasevki v pazduhi
- SNB pred NAKT?
- CT toraksa, Uz/CT abdomna, sken skeleta//PET CT pri lokalno napredovalem ca.



INTRINZIČNI PODTIPI RAKA DOJK

PODTIP	značilnosti
Luminalni A	ER+, HER2-, PR visok (>20%), Ki-67 nizek (<10%), molekul. podpis: nizek riziko
Luminalni B, HER2-	ER+, HER2-, PR nizek (<20%) ali Ki-67 visok (>30%), molekul. podpis: visok riziko
Luminalni B, HER2+	ER+, HER2+, katerikoli PR, Ki-67
HER2+ (neluminalni)	HER2+ ER-, PR-
Bazalni (trojno negativni duktalni)	HER2- ER-, PR-

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

Genski ekspresijski profili

GENSKI PODPIS	Št. genov	Prognostičen za ponovitev bolezni	Prediktiven za dobrobit dopolnilne KT pri lumA,B	Odobren s strani	Prognostičen za pozne ponovitve (po 5. letih)
Mammaprint	70	+	+	St. Gallen	-
Oncotype DX	21	+	+	St. Gallen, NCCN, ASCO	+
Prosigna	50	+	+	St. Gallen, NCCN, ASCO	+
Endopredict	12	+	+	St. Gallen, ASCO	+
Breast Cancer Index	7	+	+	St. Gallen, ASCO	(dobrobit dop. HT po 5. letih)
BluePrint PROSIGNA	80 50	GENOMSKA KLASIFIKACIJA RAKA (parafin)			

OncotypeDCIS test- benefit dopolnilne RT pri DCIS

CILJi NAST (internistični, kirurški)

- pCR
- Čim manjši ostanek tumorja (↓ residual cancer burden)
- Spremljanje učinka KT (FDA, EMA: registracija novih substanc na podlagi ↑pCR med NAKT; potrebne še potrditvene adjuvantne študije)

- ↑ operabilnost pri lokalno napredovalem raku
- ↑ delež konzervirajočih operacij pri operabilnem raku
- ↓ velikost odstranjenega tumorja

- SNB namesto ALND

- Rezidualni rak po NAST je močan prognostični dejavnik za ponovitev bolezni

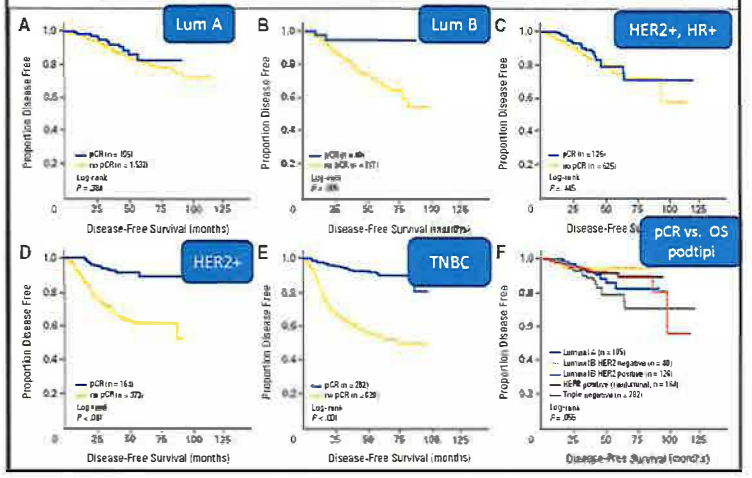
PATOLOŠKA KOMPLETNA REMISIJA (pCR)

pCR vs. no pCR je prognostična za daljši EFS, OS,

vendar samo pri HER2+ in trojno negativnem podtipu raka dojk

Vpliv pCR po NAKT na prognozo bolezni

Minckwitz et al, JCO 2012. Meta-analiza 7 nemških študij, n=6377)



Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis

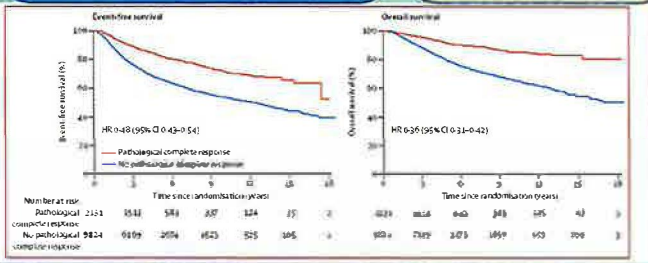
Lancet 2014; 384: 164–72

Collaborative Trials in Neoadjuvant Breast Cancer

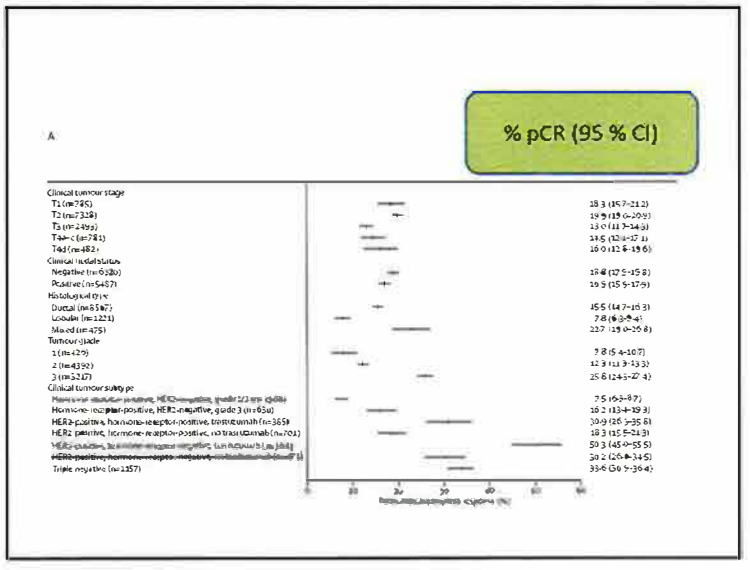
EFS
ypT0 ypN0: HR 0·44 (95% CI 0·39–0·51)
ypT0/Is ypN0: HR 0·48 (95 CI 0·43–0·54)
OS
ypT0 ypN0: HR 0·36 (0·30–0·44)
ypT0/Is ypN0: HR 0·36 (0·31–0·42)

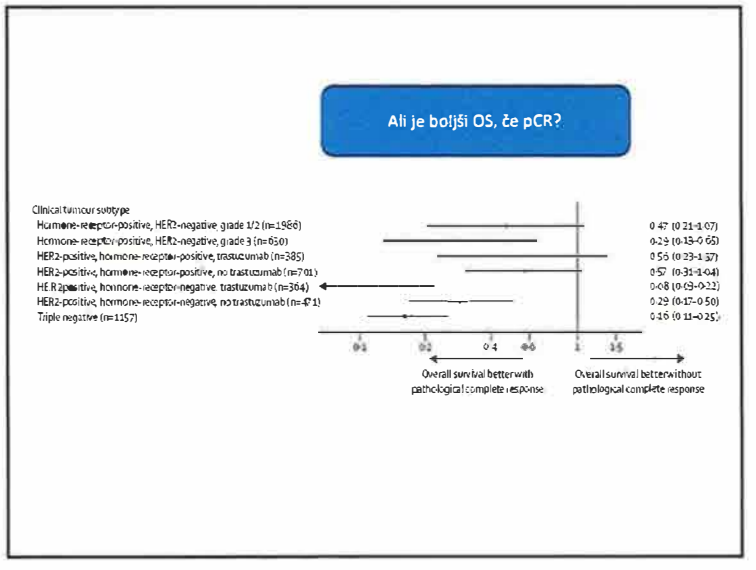
12 neoadj. medn. raziskav
12.000 bolnic

AGO 1 (n=668), ECTO (n=1355) EORTC 10994/BIG 1-00(n=1856) GeparDuo (n=907), GeparQuattro (n=1495), GeparTrio (n=2072), GeparTrio-Pilot (n=285), NOAH (n=334), NSABP B-18 (n=1523), NSABP B-27 (n=2411), PREPARE (n=733), TECHNO

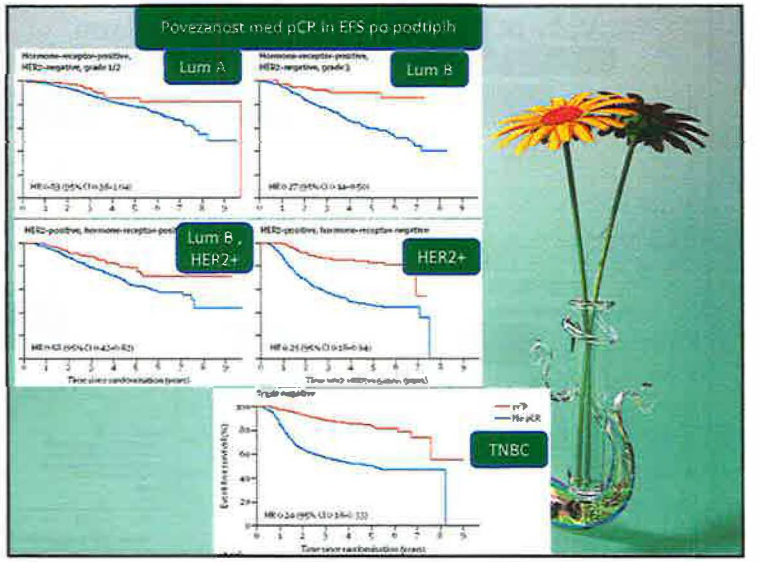


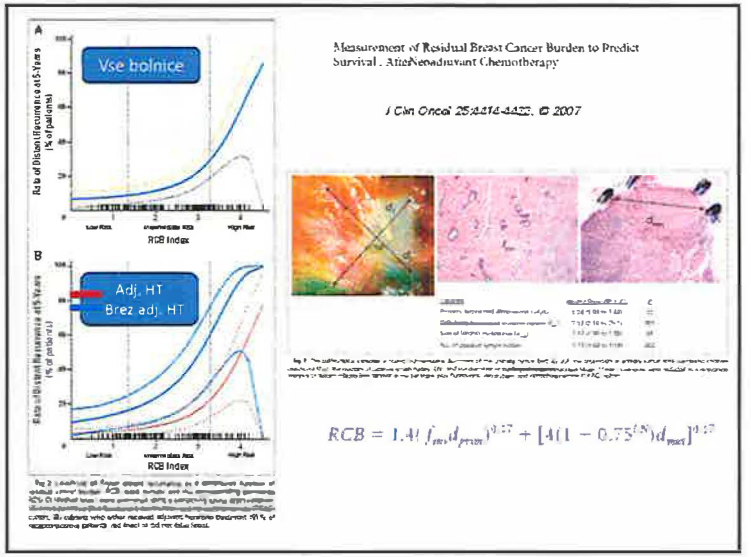
Our pooled analysis could not validate pCR as a surrogate endpoint for improved EFS and OS

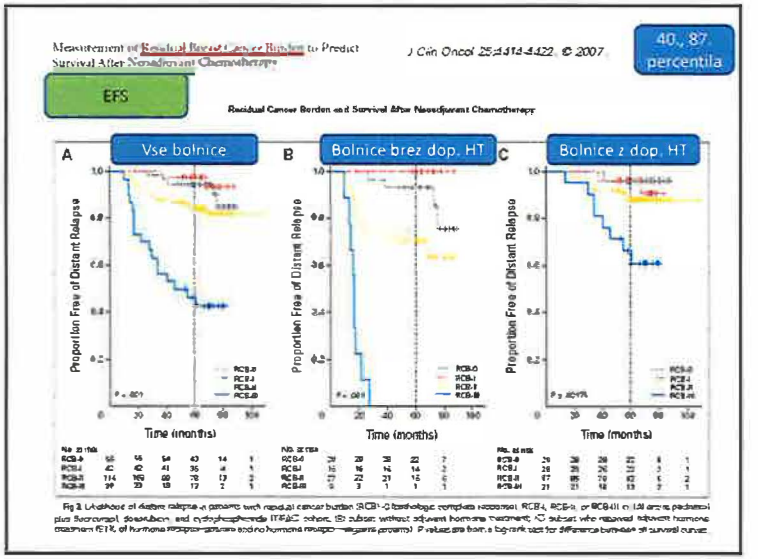




Podtip raka dojk	n	% pCR	pCR korelira z OS
HR+, HER2-, gradus I/II	1986	7,5 (6,3-8,3)	0,47 (0,21-1,07)
HR+, HER2-, gradus III	630	16,2 (13,4-19,3)	0,29 (0,13-0,65)
HER2+, HR+, brez trastuzumaba	701	18,3 (15,5-21,3)	0,57 (0,31-1,04)
HER2+, HR+, s trastuzumabom	385	30,9 (26,3-35,8)	0,56 (0,23-1,37)
HER2+, HR-, brez trastuzumaba	471	30,2 (26,0-34,5)	0,29 (0,17-0,50)
HER2+, HR-, s trastuzumabom	364	50,3 (45,0-55,5)	0,08 (0,03-0,22)
Trojno negativni	1157	33,6 (30,9-36,4)	0,16 (0,25)







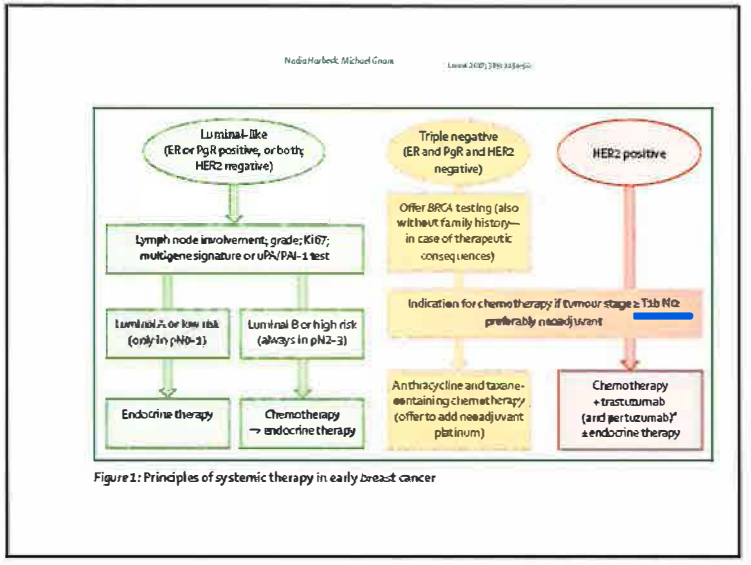


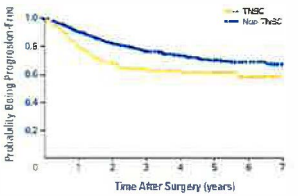
Figure 1: Principles of systemic therapy in early breast cancer

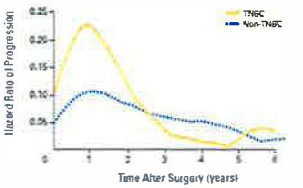
Trojno negativni rak dojk

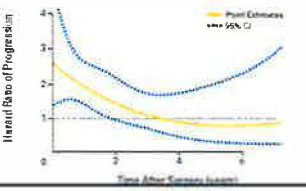
Response to Neoadjuvant Therapy and Long-Term Survival in Patients With Triple-Negative Breast Cancer

J Clin Oncol 26:1275-1281. © 2008

MDA, n=1118 pts, NAKT 1985-2004







Vrsta KT pri trojno negativnem raku dojk

- Standard: sekvenčno antraciklini in taksani

- Dodatek BEVACIZUMABa: rezultati raziskav so heterogeni, zato ni standardno zdravljenje
- Dodatek KARBOPLATINA: VEČJI pCR (Gepard Sixto study, CALGB 40603), vendar ni večji EFS pri CALGB, zato različna mnenja v Evropi in Ameriki
- Dobrobit karboplatina na pCR je ne glede na BRCA mutacijo
- Nab-paklitaksel: boljši od paklitaksela (Gepard Septo study: ↑pCR pri TNBC), vendar ETNA študija tega ni potrdila
- Brez antraciklinov: TC, Nab-paklitaksel+Carbo 12x tedensko (boljše od Nab-pakli+Gem): ADAPT study

Standardno zdravljenje je sekvenčno antraciklini, taksani (Liedke , JCO 2008)

OS kot funkcija odgovora na NAKT

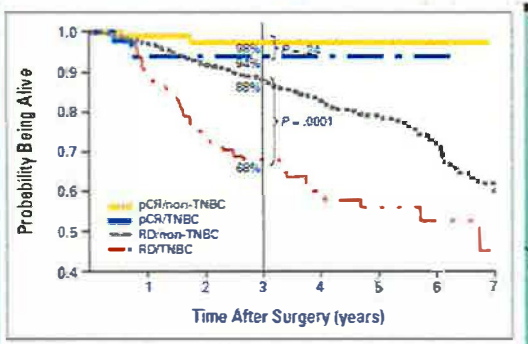
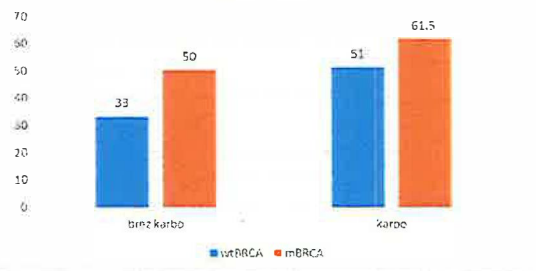


Fig 2. Overall survival as a function of response to chemotherapy (pathologic complete response [pCR] v residual disease [RD]) and triple-negative status (triple-negative breast cancer [TNBC] v non-TNBC).

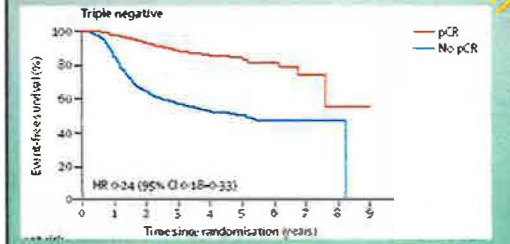
GeparSixto study

18x tedensko pakli+liposomalni doxo ± karboplatin AUC 1,5

Komu koristi KARBOPLATIN?
Ni odvisno od BRCA mutacije!

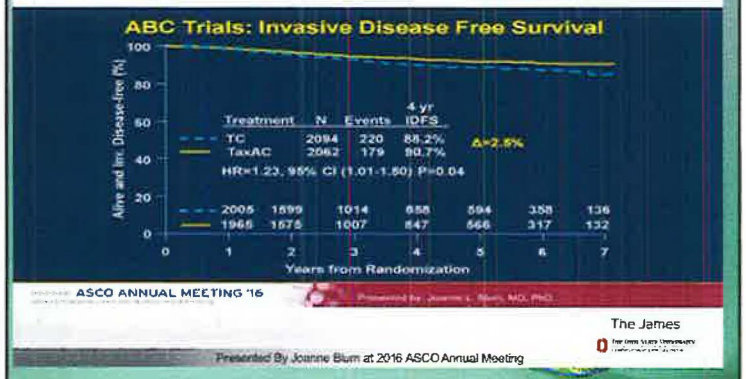


TNBC: pCR kot vmesni marker učinkovitosti: dober, ne idealen



15-20% s pCR relapsira oz. umre
50 % non-pCR ne relapsira

Ne-antraciklinski režim (ni dosežena non-inferiority; pri 'high-risk' ne moreš izpustiti antracikline)



Post neoadjuvantna KT, če ni pCR

CREATE X

Does capecitabine improve DFS after pre-op chemo?

Capecitabine 2,500 mg/m2/day po Day 1-14 in a 21-day cycle x6 cycles
** Safety interim analysis after N=50, IDMC recommended 8 cycles of tx

HER2-

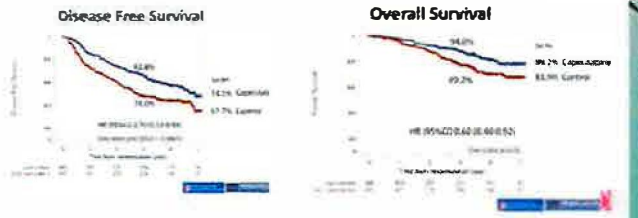
NAC → Surgery → Pathology Non-pCR or node + → R (n=900)
- Control: Standard therapy
- Standard therapy + Capecitabine

Stratification factors:
ER, Age, NAC, ypN,
SFU and institution

Standard therapy:
HR+: Hormone therapy
HR-: No further systemic treatment

Lee S-J, Toi et al. SABCS 2015

Capecitabine improves DFS/OS following pre-operative chemotherapy



5% improvement in overall survival!
Across all subsets
42% improvement if TNBC

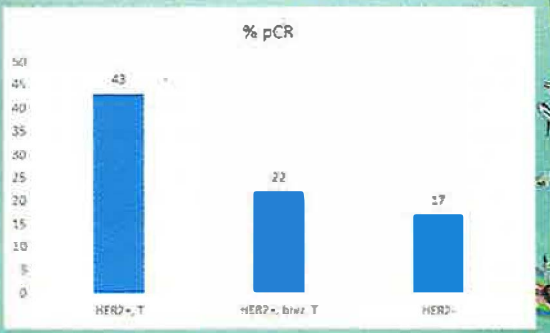
Lee S-J, Toi et al; SABCS 2015

NAST pri HER2+ raku

Gianni, Lancet 2010

Raziskava NOAH

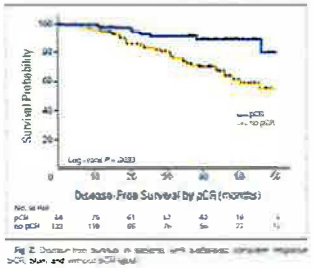
Dodatek trastuzumaba pri th HER2+ raka podvoji pCR

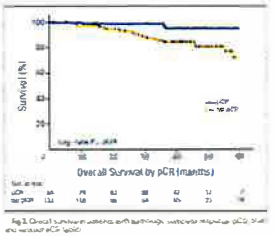


pCR po NAKT z antraciklinih je prognostičen faktor za DFS, OS

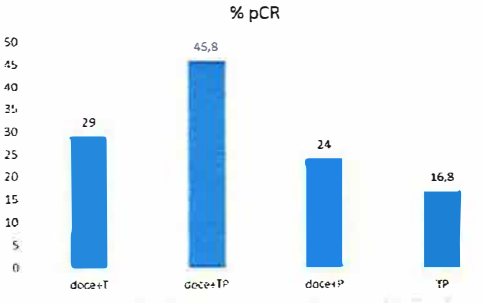
3EC→3paklit/3t+trastuzumab...

Untch, JCO 2010

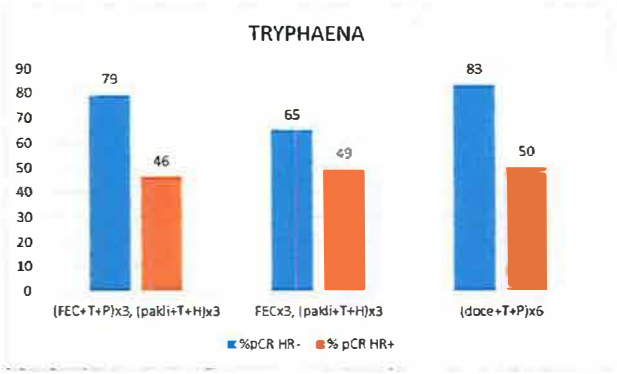




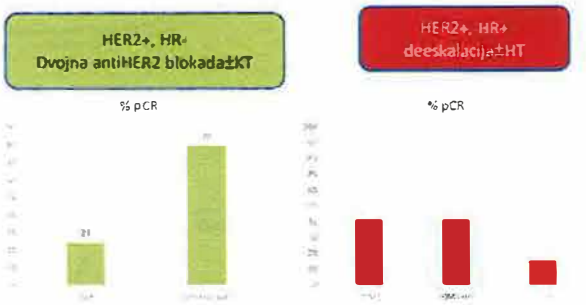
Raziskava NEOSHERE: dvojna antiHER2 blokada; trastuzumab, pertuzumab

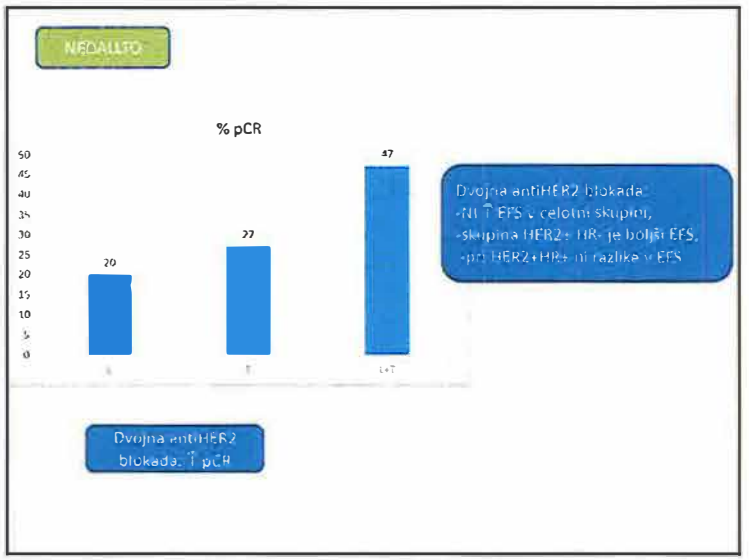


-dodatek antiHER2 th. k antraciklinom
-pCR glede na HR



Raziskava ADAPT





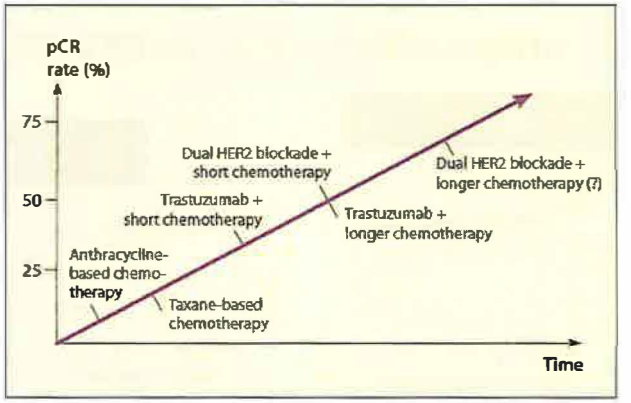


Figure 1: Incremental Improvement in Pathologic Complete Remission (pCR) Rates by Optimizing Systemic Neoadjuvant Treatment of HER2-Positive Breast Cancer.

http://www.cancernetwork.com/sites/default/files/cn_import/2016211.png

Zaključki:

- NAKT je standard za **TNBC in HER2+ rak dojk**
- Evidence-based NAST se razlikuje od adjuvantnih
- pCR korelira z izidom bolezni; ne-pCR: potekajo raziskave

- TNBC: Antraciklini in taksani so standard
- Bevacizumab: konfliktni podatki+dodatna toksičnost
- Platina: ↑ pCR neodvissno od BRCA statusa
- Obetajoči režimi brez antraciklinov (taksani+karbo)

- HER2+: standard antraciklini in taksani vs. Taksani + karbo
- 'high risk': dvojna antiHER2 blokada
- 'low risk': adjuvantno ted. Pakli+trastuzumab

Izzivi

- Personalizirana terapija, ne 'one size fit all therapy'
- -deeskalacija NAKT
- pCR: kakšno adj. Th?
- Kaj pri non-pCR?
- Inkorporacija molekularnih podtipov in 'molecular imaging'
- -HER2+ rak dojk: poiskati koncept zdravljenja pri luminalnih in neluminalnih

Operacija po neoadjuvantnem sistemskem zdravljenju raka dojk

Andraž Perhavec

18.5.2017

PREDNOSTI

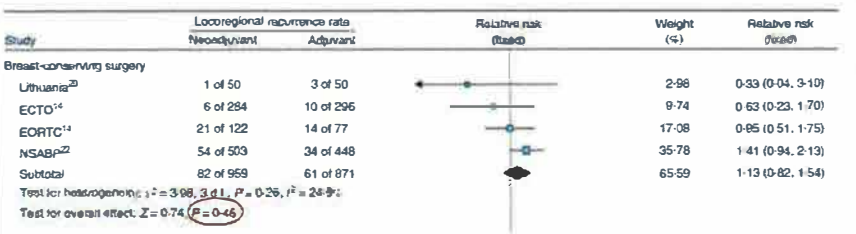
- 40% več ohranitvenih operacij dojk[1]
- 40% manj disekcij pazdušnih bezgavk[2]
- 60% manj reoperacij[3]

[1]Golshan, BCRT, 2017
[2]Alvarado, Ann Surg Oncol, 2012
[3]Landercasper, Ann Surg Oncol 2017

- **Kirurgija dojke**
- Kirurgija pazduhe

VARNOST OHRANITVENE OPERACIJE

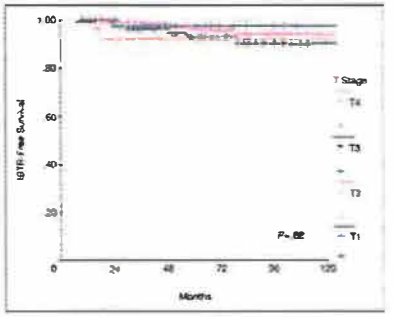
- Metaanaliza (n=4198)



Mieog JSD et al. Br J Surg, 2007

VARNOST OHRANITVENE OPERACIJE – velikost tumorja

Retrospektivna raziskava (MD Anderson)
n=403

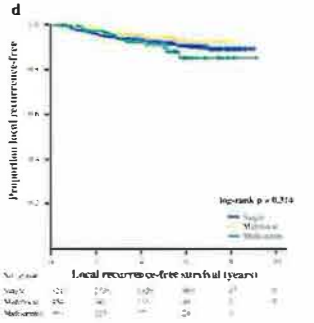


Chen et al. JCO, 2004

VARNOST OHRANITVENE OPERACIJE – glede na fokalnost PRED NAKT

Fokalnost pred NAKT	10-letno LRFS (%)
Unifokalen	92
Multifokalen	95
Multicenričen	90

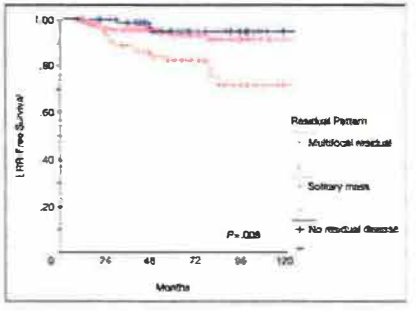
Conclusion. Breast conservation is feasible for clinically multifocal or multicentric breast cancer patients who undergo NACT without worsening LRFS if tumor-free margins can be attained or if patients achieve a pCR.



Ataseven et al. Ann Surg Oncol, 2015

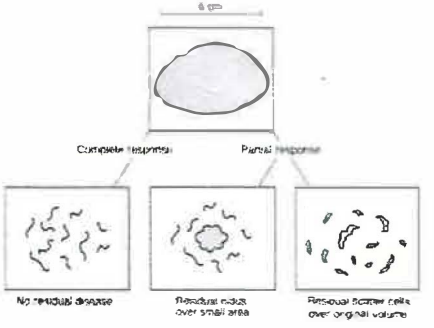
VARNOST OHRANITVENE OPERACIJE – glede na fokalnost PO NAKT

Multifokalna bolezen (histološko) po neoadjuvantni KT poveča verjetnost za lokalni recidiv



Chen et al. JCO, 2004

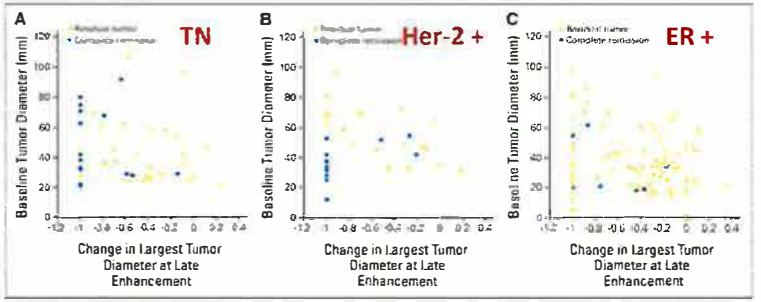
Tip odgovora na NAKT



TN, Her-2 + **ER+**

Diagnostika rezidualne bolezni - MRI

MRI dobro korelira s patološkim ostankom bolezni pri neluminalnih rakih



Loo et al. JCO, 2011

Delež reoperacij glede na podtip

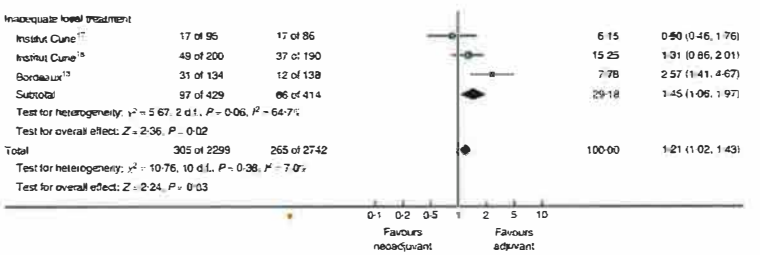
n= 71627 (12157 NAKT)

Podtip	Brez NAKT (%)	NAKT (%)	OR (95% CI)
Luminal A	23.6	20.0	0.84 (0.76-0.93)
Luminal B	20.3	12.8	0.64 (0.56-0.74)
Luminal Her-2+	21.4	10.6	0.49 (0.42-0.57)
TN	14.0	6.4	0.47 (0.41-0.55)
Her-2+	22.7	7.3	0.34 (0.27-0.43)

Landercasper et al. Ann Surg Oncol, 2017

Je operacija sploh potrebna?

Večja verjetnost lokalnih recidivov, če kirurgija nezadostna po neoadjuvantni KT v primerjavi z adjuvantno KT



Mieog JSD, et al. Br J Surg, 2007

Je operacija sploh potrebna?

- klinično dober ali popoln odgovor na NAKT (n=50)
- reprezentativna biospija pred operacijo (n=38)

	Biopsija – rezidualni tumor	Biopsija - pCR	Skupaj
Kirurški preparat – rezidualni tumor	20	1	21
Kirurški preparat - pCR	0	17	17
Skupaj	20	18	38

LN = 4.8%

Heil J et al. EJC, 2016

Zaključki – kirurgija dojke

- Ohranitvena operacija po neoadjuvanti KT
  - varna ne glede na izhodiščno velikost tumorja
  - varna ne glede na fokalnost pred neoadjuvantno KT
  - previdnost pri patološko multifokalni bolezni (ER+)
- MRI slabo napove rezidualno bolezen pri ER+, bolje pri TN in Her-2 +
- NAKT zmanjša delež reoperacij po ohranitveni operaciji
- Kirurgija po NAKT je zaenkrat potrebna v vsakem primeru
  - veliko obeta debeloigelna biopsija v primeru cCR

Kirurgija dojke

- **Kirurgija pazduhe**

Klinično negativna aksila pred NAKT (cN0)

	SNB upfront	SNB po neoadj KT	p
Število pacientk	3171	575	
T2-T3 tumorji	18.8%	87.3%	<0.0001
Uspešnost SNB	98.7%	97.4%	0.017
Delež lažno negativnih	4.9%	5.9%	NS
Delež pozitivnih SN			
T1	19%	12.7%	NS
T2	36.5%	20.5%	<0.0001
T3	51.4%	30.4%	0.04
Regionalna ponovitev (F/U 47 mes)	0.9%	1.2%	NS

„SLN surgery after chemotherapy is as accurate for axillary staging as SLN surgery prior to chemotherapy, SLN surgery after chemotherapy results in fewer positive SLNs and decreases unnecessary axillary dissections."

Hunt KK et al. Ann Surg, 2009.

Delež bolnic s pCR v aksili (cN+ → ypN0)

Raziskava	n	pCR v bezgavkah
ACOSOG Z1071 (2014)	694	41%
SN FNAC (2015)	145	35%
Mamtani (2016)	195	49%

Boughey J. JAMA, 2014
Boileau J. JCO, 2015
Mamtani A. Ann Surg Oncol, 2016

Varnost SNB pri bolnicah s popolnim odgovorom na NAKT (cN+→cN0)

Table 3 | False-negative rates for SLNB after conversion to clinically node-negative disease following NACT

Prospective trial	Overall false-negative rate		Stratified by number of SLNs			Stratified by SLN-detection technique	
			1 (%)	2 (%)	≥3 (%)	Single agent (%)	Dual agent (%)
SENTINA (treatment arm C)[39]	14.2	(95% CI 9.9–19.4)	24.3	18.5	7.3	16.0[a]	8.6
ACOSOG Z1071[40,41]	12.6	(95% CI 9.9–16.1)	31.5	21	9.1	20.3[b]	10.8
SN FNAC[42]	8.4%	(95% CI 2.4–14.4)	18.2	4.9[b]	NR	16.0[a]	5.2

Nesentinel bezgavka ni nadomestek za sentinel bezgavko

King TA, Morrow M. Nat Rev Clin Oncol, 2015

Pomen zasevkov v sentinel bezgavki po NAKT

- SN FNAC
  - Ni povezave med velikostjo zasevka v SB in številom poz. non-SB
  - ypN0i+ smatramo kot poz. → FN 8.4%
    ypN0i+ smatramo kot neg. → FN 13.3%
- Z1071 (vsaj 2 odstranjeni SB)
  - ypN0mi smatramo kot poz. → FN 8.7%
    ypN0mi smatramo kot neg. → FN 11.3%

Boileau JF et al. JCO, 2015
Boughey JC et al. Poster No P2-01-02. San Antonio Breast Cancer Symposium, 2014

Pomen zasevkov v sentinel bezgavki po NAKT

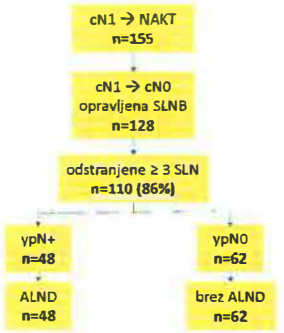
- Pomen zasevkov (tudi mikro in ITC) drugačen kot pri „upfront" SNB
- Imunohistokemija!
- i+ → pozitivna sentinel bezgavka → ALND

Jatoi I et al. *Lancet Oncology*, 2016

Kolikim bolnicam z cN1 lahko z NAKT prihranimo ALND?

- Pogoj:
  - Identifikacija ≥ 3 SLN
  - pCR v sentinel bezgavkah (ypN0)

Kolikim bolnicam z cN1 lahko z NAKT prihranimo ALND?



62/155 (40%)

Mamtani A. Ann Surg Oncol, 2016

pCR v bezgavkah glede na izražanje receptorjev

Status receptorjev	n	%
Vsi	96/195	49%
ER+ / Her2-	15/73	21%
ER- / Her2-	26/55	47%
ER+ / Her2+	26/37	70%
ER- / Her2+	29/30	97%

$p < 0,0001$

Mamtani A. Ann Surg Oncol, 2016

Bezgavke vs. primarni tumor: različen odgovor na NAKT

Status receptorjev	pCR v bezgavkah	pCR primarnega tumorja	P
Vsi	**49%**	**37%**	**≤ 0.0001**
ER+ / Her2-	21%	10%	0.003
ER+ / Her2+	70%	59%	0.3
ER- / Her2+	97%	70%	0.3
ER- / Her2-	47%	40%	< 0.0001

Mamtani A. Ann Surg Oncol, 2016

Targeted axillary dissection (TAG)

Odstranitev sentinel bezgavk in s klipom označenih prizadetih bezgavk

- UZ pazduhe → UZ-ABTI najbolj sumljive bezgavke → vstavitev klipa v patološko bezgavko → neoadjuvantna KT
- Pred operacijo lokalizacija s klipom označene bezgavke z ^{125}I *seed*
- Odstranimo s klipom označene bezgavke in običajne sentinel bezgavke
- Odstranjene bezgavke slikane → identifikacija s klipom označenih bezgavk

Caudle AS et al. *JCO*, 2016

Targeted axillary dissection (TAG)

	FN (%)
SNB	10,1
S klipom označene bezgavke	4,2
SNB + s klipom označene bezgavke (TAD)	2

- Pri 23% bolnicah s klipom označena bezgavka ni bila sentinel bezgavka
- Povprečno 2,7 sentinel bezgavk, dvojna metoda samo v 55%
- Dislokacija klipa (5-10%), kompleksnost izvedbe

Caudle AS et al. *JCO*, 2016

Optimalni pristop za zmanjšanje deleža ALND?

cN+

NAKT (40%)

cN0

„upfront" kirurgija (Z0011) ali NAKT?

Optimalni pristop za zmanjšanje deleža ALND?

- cT1-2 N0

Deleži ALND

Podtip raka	Najprej OHRANITVENA operacija (n=669)	NAKT (n=271)	p
ER+ / Her2-	15%	34%	< 0.01
Her2+	13%	8%	0.26
TN	14%	7%	0.26

Pilewskie M. SSO, 2017

Optimalni pristop za zmanjšanje deleža ALND?

- cT1-2 N0

Deleži ALND

Podtip raka	Najprej MASTEKTOMIJA (n=1004)	NAKT (n=271)	p
ER+ / Her2-	37%	34%	0.62
Her2+	36%	8%	<0.001
TN	25%	7%	0.001

Pilewskie M. SSO, 2017

Optimalni pristop za zmanjšanje deleža ALND?

- n=1980

	podtip	HR za ALND
Najprej NAKT vs ohranitvena op	ER+ / Her2-	3.4 (p<0.001)
Najprej NAKT vs mastektomija	Her2+	0.19 (p<0.001)
Najprej NAKT vs mastektomija	TN	0.25 (p=0.007)

Multivariatna analiza (starost, cT stadij, LVI)

Pilewskie M. SSO, 2017

Zaključki – kirurgija pazduhe

- SNB po NAKT je varna pri
  - cN0
  - cN1 → cN0, če odstranimo vsaj 3 sentinel bezgavke in uporabimo dvojno metodo ali če opravimo TAD
- ALND pri N1, N1mi in N0itc
- Optimalni vrstni red zdravljenja z namenom zmanjšanja možnosti za ALND je odvisen od kliničnega statusa bezgavk, tipa operacije in statusa receptorjev

Radioterapija po neoadjuvantnem sistemskem zdravljenju raka dojk

Tanja Marinko
Oddelek za radioterapijo
Onkološki inštitut Ljubljana
Maj 2017

Vloga neoadjuvantne sistemske terapije (NAST)

The original impetus for neoadjuvant chemotherapy was to improve survival in women with breast cancer beyond the benefits seen with adjuvant therapy. To date, preoperative treatment has not achieved that goal. However, **modification of locoregional therapy has emerged as a clear and compelling benefit from preoperative chemotherapy.**

Jennifer R Bellon, Julia S Wong, Harold J Burstein. Should Response to Preoperative Chemotherapy Affect Radiotherapy Recommendations After Mastectomy For Stage II Breast Cancer? JCO, 2012

National Comprehensive Cancer Network

NCCN Guidelines Version 2.2017
Invasive Breast Cancer

NCCN Guidelines Index
Table of Contents
Discussion

Preoperative Systemic Therapy:
In patients treated with preoperative systemic therapy, indications for radiation therapy and treatment fields should be based on the maximum stage from the pre-therapy clinical stage, pathologic stage, and tumor characteristics.

1. vse bolnice po ohranitveni operaciji dojke
2. vedno po mastektomiji če je tu > 5 cm oz če so pozitivne > 3 bezgavke
3. Pri vnetnem raku vedno obsevamo mamarno regijo in perikl. bzg.

- Ne glede na vrsto operacije pri > 3 pozitivnih bezgavkah poleg dojke/prsne stene obsevamo še periklavikularne bezgavke
- Pri 1-3 pozitivnih bezgavkah se odločamo individualno:
  RT pri večjem tveganju za LRR
  (mlajše bolnice, ER-, GIII, LVI+)

Ker se za pooperativno obsevanje odločamo glede na izhodiščni stadij

je za radioterapevta zapis pregleda pred uvedbo NAST odločilnega pomena!

Zapis naj vsebuje:

- Velikost tumorja (T), prizadetost kože
- Prizadetost bezgavk (N)
- izvid UZ pregleda pazduhe
- citološki oz. histološki izvid tumorja in pregledanih bezgavk

Zakaj potrebujemo zapis?

- **Prizadetost kože:**

  → da določimo potrebno dozo na koži
  (ev. uporaba bolusa,če je bila prizadeta koža...)

- **Prizadetost bezgavk:**

  → **po ohranitveni operaciji:** da postavimo indikacijo za obsevanje periklavikularnih bezgavk (prizadete več kot tri ??)

  → **po mastektomiji:** da postavimo indikacijo za obsevanje

Vloga pooperativne RT po NAST

- Retrospektivne študije:

  dobrobit dopolnilne RT tudi če pCR po NAST:

  Ring A et al. Jclin Oncol 2003;
  Huang EH et al. J clin Oncol 2004;
  Panades M et al. J Clin Oncol 2005;
  McGuire SE et al. Int J Radiat Oncol Biol Phys 2007;

primer *: NAST → mastektomija / mastektomija + RT
LRR po 10 letih: 22% / 11%
tveganje za smrt zaradi raka dojke po 10 letih: HR 0,5

* Buchholz TA et al. Predictors of local-regional recurrence after neoadjuvant chemotherapy and mastectomy without radiation. J Clin Oncol 2002; 20:17.

Ali lahko glede na odgovor na NAST napovemo, kakšno je tveganje za LRR?

- Podatki iz kombinirane analize * dveh velikih ameriških študij
- n > 3000
- NSABP B-18 : 1988-1993
- NSABP B-27: 1995-2000
- potekali še pred dobo zdravljenja s trastuzumabom
- B-18 – brez hormonske terapije
- B-27- HT glede na starost, ne pa glede na hormonski status tu
- Izključene bolnice s T4 ali N2
- Odgovor na NAST ni bil gradiran, ampak opredeljen samo kot ostanek tumorja ali pCR

* Mamounas EP, Anderson SJ, Dignam JJ et al. Predictors of locoregional recurrence after neoadjuvant chemotherapy: results from combined analysis of National Surgical Adjuvant Breast and Bowel Project B-18 and B-27. J Clin Oncol 2012; 30: 3960

- **Ugotovitve:**

Dejavniki, ki so povezani z večjim tveganjem za LRR :

- Starost < 50 let (≥ 50 let *vs* < 50 let : HR 0,78)

- T > 5 cm pred NAST (HR 1,5)

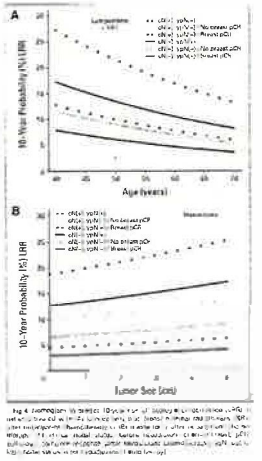
- klinično tipne bezgavke pred NAST (cN(+) *vs* cN(-): HR 1,6)

- prisotnost rezidualnega raka v dojki
(ypN(-)in ostanek v dojki *vs* ypN(-) in pCR v dojki : HR 1,5)

-prisotnost rezidualnega raka v bezgavkah
(v dojki pCR, ypN(+) *vs* ypN(-) : HR **2,7**)

Predvidevanja

- Podatki analize kažejo, da bi morda iz odgovora na NAKT lahko napovedali kolikšna je verjetnost za LRR v 10 letih.
- Če bi izračun pokazal **< 10%** se za poop. RT ne bi odločili.
- → izdelava **nomogramov** je v teku, vendar še niso za klinično uporabo



- Glede na podatke iz NSABP študij kaže, da imajo zelo nizko tveganje za LRR (≤ 5%) bolnice z rakom dojke **stadija II (N1) brez ostanka tumorja v bezgavkah po NAST**

→ Pri teh bolnicah obsevanje po mastektomiji morda ni potrebno, čeprav so imele pred pričetkom NAKT pozitivne bezgavke.*

UICC Stage	TMN Classification
1	T1, N0, M0
2	T2, N0-1, M0 T1, N1, M0
3	Any T, N2-3, M0 T3 or 4, any N, M0
4	Any T, any N, M1

N1- premakljiva(-e) bzg., nivo I/II
NE ZRAŠČENE med seboj!

* Jennifer R Bellon, Julia S Wong, Harold J Burstein. Should Response to Preoperative Chemotherapy Affect Radiotherapy Recommendations After Mastectomy For Stage II Breast Cancer? JCO, 2012

JOURNAL OF CLINICAL ONCOLOGY — ONCOLOGY GRAND ROUNDS

Should Response to Preoperative Chemotherapy Affect Radiotherapy Recommendations After Mastectomy for Stage II Breast Cancer?

Harvard (indikacije za RT po NAKT in mastektomiji):

Stadij III- vse bolnice

Stadij I ali II - RT vedno, če je ostanek v bezgavkah
-če je ostanek v dojki- odločitev o RT glede na ostale dejavnike za LRR

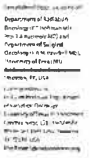
-če pCR: brez RT

klinični primer iz članka:

- Trojno negativni rak dojke, IDC, G III, LVI
- 38 letna bolnica, začetni stadij T2 **N1** (UZ: ena 2 cm velika bezgavka)
  = STADIJ II
- DIB tumorja :trojno negativni rak dojke, IDC, G III, LVI +
- " dramatičen odgovor " na predop.KT- pri operaciji: brez ostanka v bezgavki, v dojki pa do 0,3 cm veliki fokusi rezidualnega IDC
- **Odločitev o poop RT ???**
- zaradi starosti (<40 let), GIII, LVI+, trojno negativne bolezni so se odločili za postop RT ne glede na odličen odgovor na KT.

Personal View

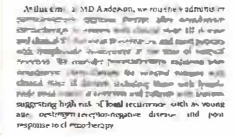
Optimising radiation treatment decisions for patients who receive neoadjuvant chemotherapy and mastectomy



MD Anderson- klinična praksa (indikacije za RT po NAST in mastektomji):

•vse stadij III

• stadij II s pozitivnimi bezgavkami pri operaciji
• stadij II pri večjem tveganju za LRR (mlade bolnice, ER -, slab odgovor na KT)



Ann Oncol. 2016 May;27(5):819-27. doi: 10.1093/annonc/mdw026. Epub 2016 Feb 9

The impact of postmastectomy and regional nodal radiation after neoadjuvant chemotherapy for clinically lymph node-positive breast cancer: a National Cancer Database (NCDB) analysis.

Rutter CE[1], Park HS[2], Corso CD[3], Kim AW[4], Kozak MM[5], Allen AM[6], Yu JB[7], Decker RH[8], Wilson LD[9], Kim SS[10], Yashar CM[11]

+ Author information

Abstract

BACKGROUND: Following neoadjuvant chemotherapy (NAC), the optimal strategies for postmastectomy radiotherapy (PMRT) and regional nodal irradiation (RNI) after breast-conserving surgery (BCS) are controversial. In this analysis, we evaluate the impact of these radiotherapy (RT) approaches for women with clinically node-positive breast cancer treated with NAC in the National Cancer Database (NCDB).

PATIENTS AND METHODS: Women with cT1-3 cN1 M0 breast cancer treated with NAC were divided into four cohorts by surgery (Mastectomy (Mast) versus BCS) and post-chemotherapy pathologic nodal status (ypN0 versus ypN+). Overall survival (OS) was estimated using the Kaplan-Meier method and RT approaches were analyzed using the log-rank test, multivariable Cox models, and propensity score-matched analyses.

RESULTS: From 2003 to 2011, 16 315 cases were identified including 3040 Mast-ypN0, 7243 Mast-ypN+, 2070 BCS-ypN0, and 3962 BCS-ypN+ patients. On univariate analysis, PMRT was associated with improved OS for both Mast-ypN0 ($P = 0.019$) and Mast-ypN+ ($P < 0.001$) patients. On multivariate analyses adjusted for factors including age, comorbidity score, cT stage, in-breast pathologic complete response, axillary surgery, ypN stage, estrogen receptor status and hormone therapy, PMRT remained independently associated with improved OS among Mast-ypN0 [hazard ratio (HR) = 0.729, 95% confidence interval (CI) 0.566-0.939, $P = 0.015$] and Mast-ypN+ patients (HR = 0.772, 95% CI 0.689-0.866, $P < 0.001$). No differences in OS were observed with the addition of RNI to breast RT for BCS-ypN0 or BCS-ypN+ patients. Propensity score-matched analyses demonstrated identical patterns of significance. On subset analysis, OS was improved with PMRT in each pathologic nodal subgroup (ypN0, ypN1, and ypN2-3) (all $P < 0.05$).

CONCLUSIONS: In the largest reported analysis of RT for cN1 patients treated with NAC, PMRT was associated with improved OS for all pathologic nodal subgroups. No OS differences were observed with the addition of RNI to breast RT.

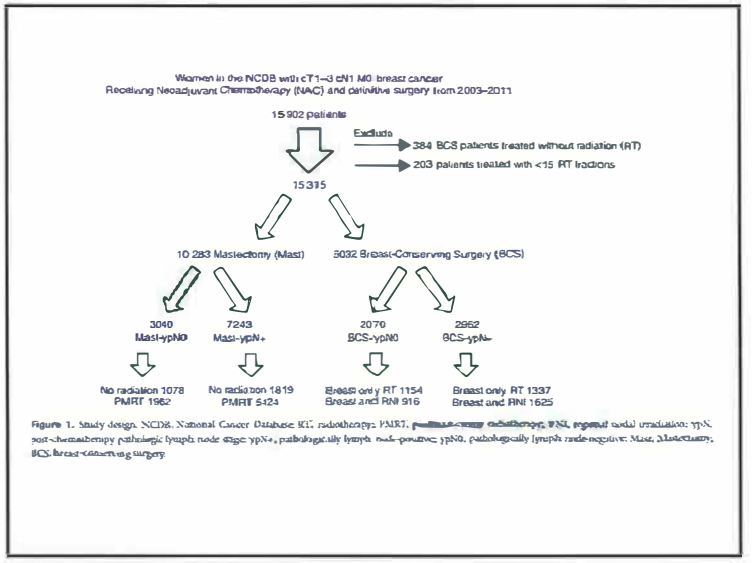


Figure 1. Study design. NCDB, National Cancer Database; RT, radiotherapy; PMRT, postmastectomy radiotherapy; RNI, regional nodal irradiation; ypN, post-chemotherapy pathologic lymph node stage; ypN+, pathologically lymph node-positive; ypN0, pathologically lymph node-negative; Mast, Mastectomy; BCS, breast-conserving surgery.

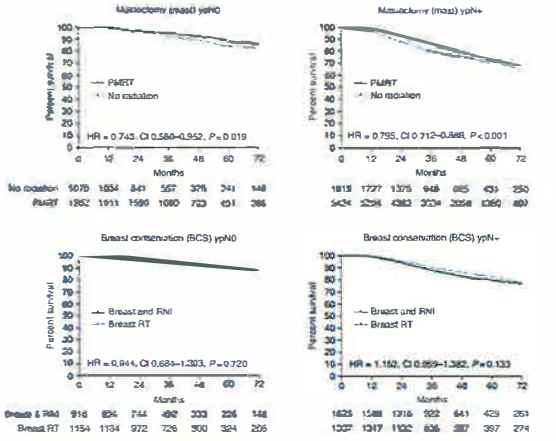


Figure 2. Kaplan–Meier survival curves. RT, radiotherapy; PMRT, postmastectomy radiotherapy; RNI, regional nodal irradiation; ypN, post-chemotherapy pathologic lymph node stage; ypN+, pathologically lymph node-positive; ypN0, pathologically lymph node-negative; Mast, Mastectomy; BCS, breast-conserving surgery.

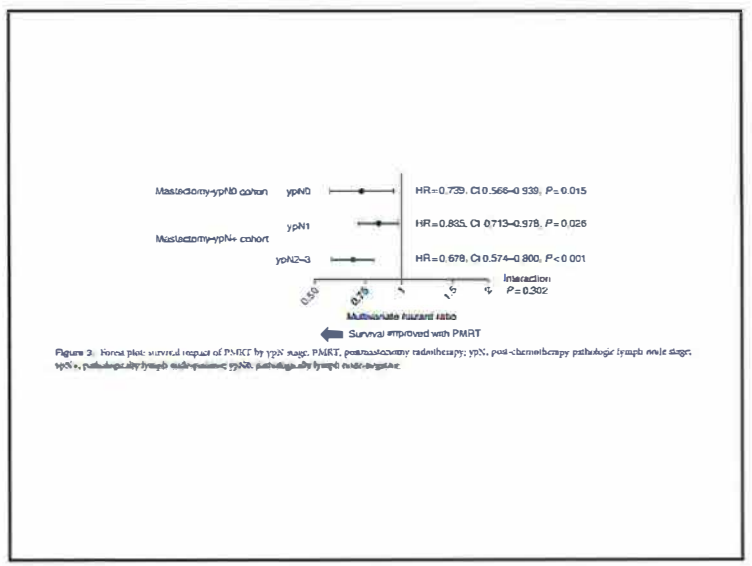


Figure 3. Forest plot: survival impact of PMRT by ypN stage. PMRT, postmastectomy radiotherapy; ypN, post-chemotherapy pathologic lymph node stage; ypN+, pathologically lymph node-positive; ypN0, pathologically lymph node-negative.

Post-mastectomy radiotherapy after neoadjuvant chemotherapy in breast cancer patients: a review (Bernier J. critical Rew in Oncol/Hematol, 2015)

4. Conclusions

The current literature review confirms that, following neoadjuvant chemotherapy, post-mastectomy irradiation has to be delivered selectively. Patients with locally advanced disease, especially those achieving incomplete response to chemotherapy in the primary tumour and/or lymph nodes should be irradiated postoperatively. Patients aged >40 years with clinical stages I–IIA and oestrogen-receptor positive disease do not need postmastectomy irradiation when a complete pathologic response to neo-adjuvant chemotherapy is achieved. The use or omission of post-mastectomy irradiation in the presence of 0–3 positive nodes remains poorly defined. Current and future prospective studies should allow a more precise determination of the exact risk of local regional recurrence in individuals especially in patients presenting with Stages IIB and IIIA disease achieving complete pathologic response. There are nevertheless still unresolved issues regarding the exact place of radiotherapy in the management of breast cancer patients treated by neoadjuvant chemotherapy and mastectomy. This is mainly due to the fact that so far most recommendations have been based on data retrieved from retrospective studies. Whether postmastectomy radiotherapy has to be delivered to chest wall and/or lymphatic drainage areas has to be decided on the basis of both the pre- and post-NAC status. Likewise controlled studies will enable

Zaključek

Za pooperativno RT po NAST se odločamo glede na stadij in značilnosti tumorja pred uvedbo NAST ter glede na patološki izvid po NAST. Upoštevamo najvišji stadij.

Pooperativno obsevamo vse bolnice po ohranitveni operaciji dojke, po mastektomiji pa vse lokalno napredovale rake dojke (stadij III), pri 1-3 pozitivnih bezgavkah se odločamo individualno