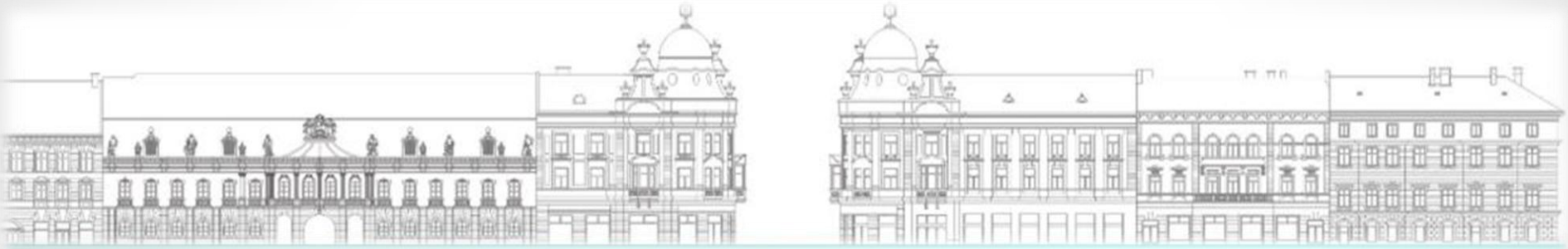
UMF UNIVERSITATEA DE MEDICINĂ ȘI FARMACIE IULIU HAȚIEGANU CLUJ-NAPOCA

IOCN Institutul Oncologic "Prof. Dr. Ion Chiricuță" Cluj-Napoca

SOCIETATEA ROMÂNĂ DE RADIOTERAPIE ȘI ONCOLOGIE MEDICALĂ SRROM

Noi abordări în managementul multidisciplinar al cancerului

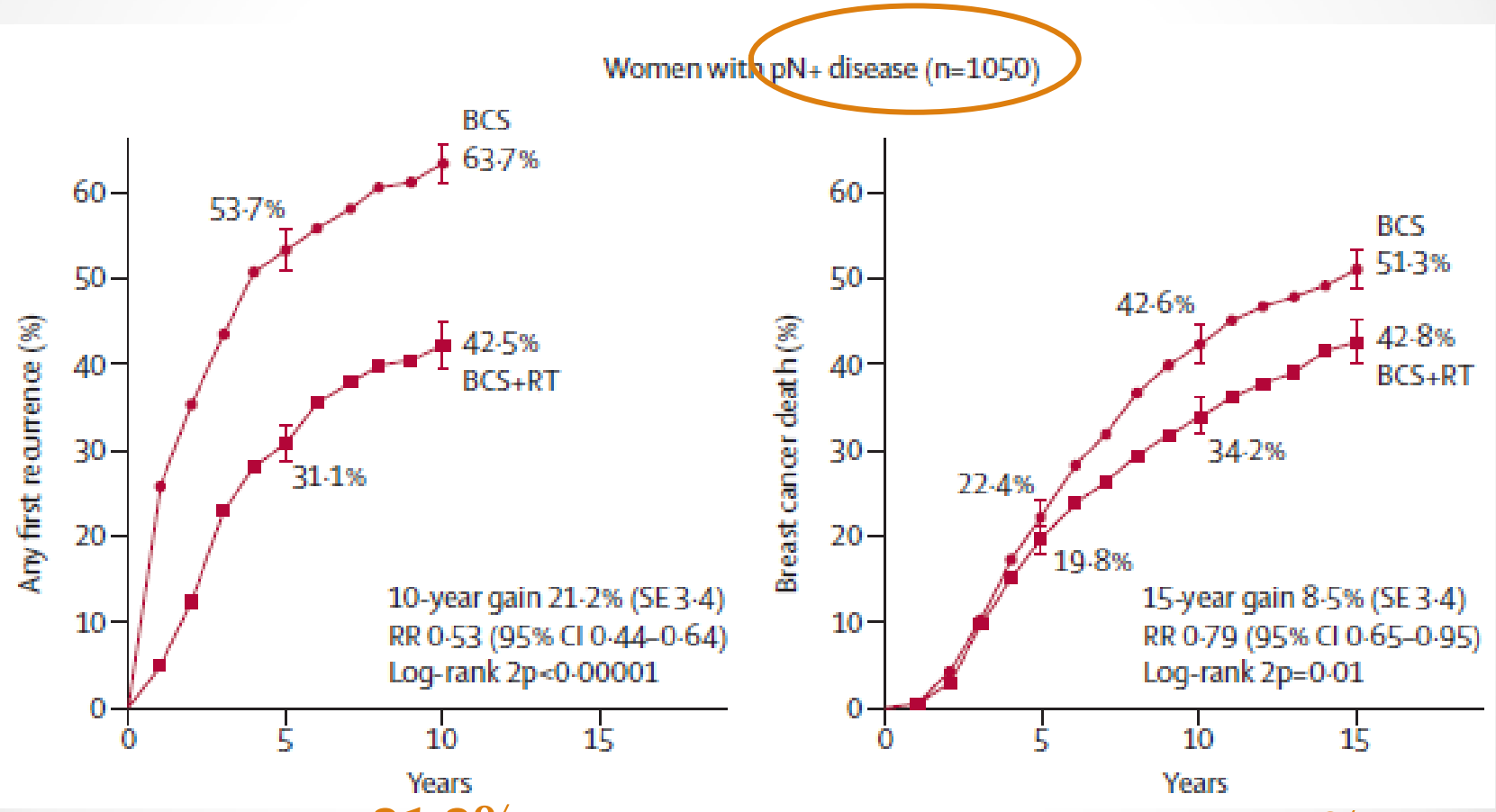
Al 12-lea curs postuniversitar



Provocări și perspective în radioterapia cancerului mamar

Daniela Martin

Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death

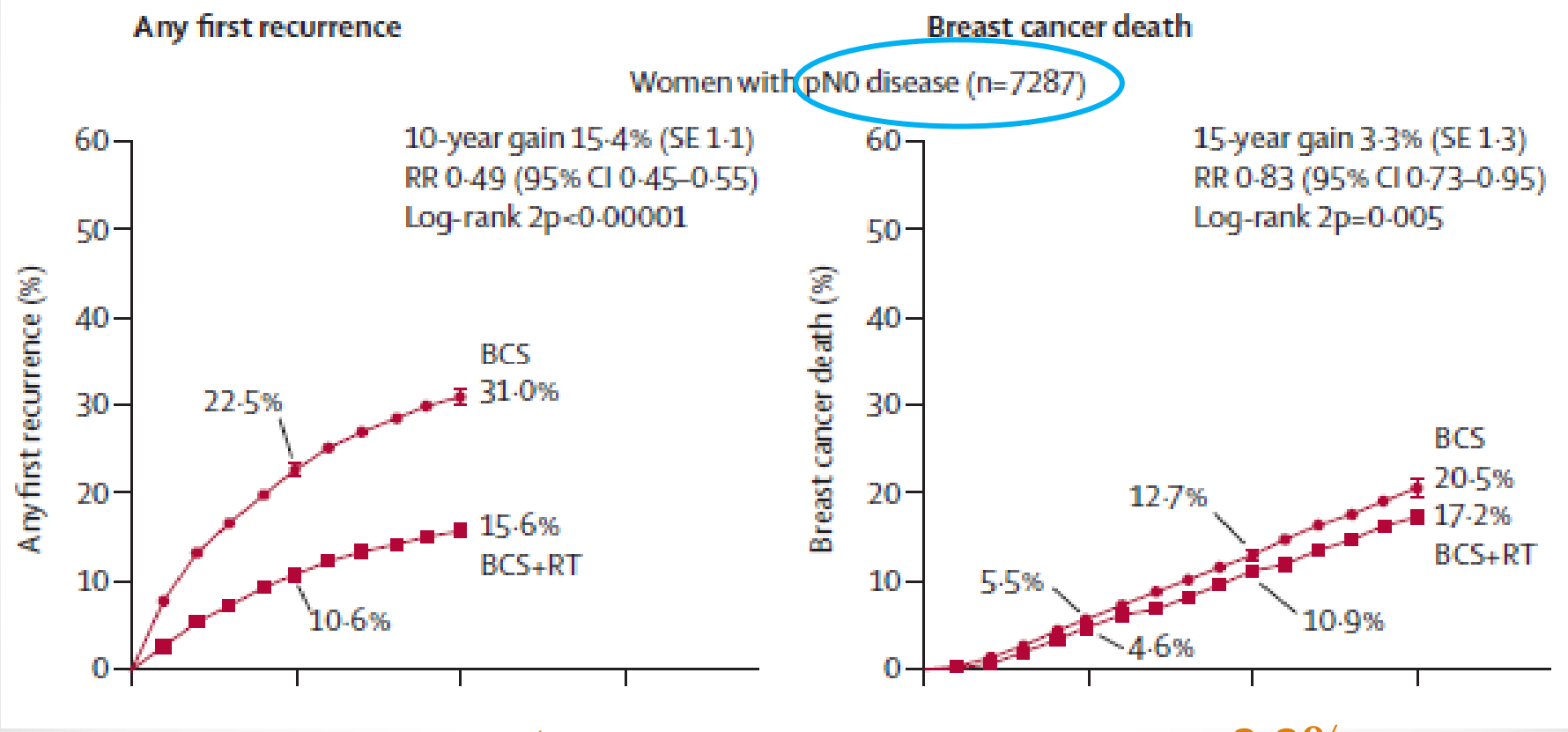


-21.2%

-8.5%

2.5:1

Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death



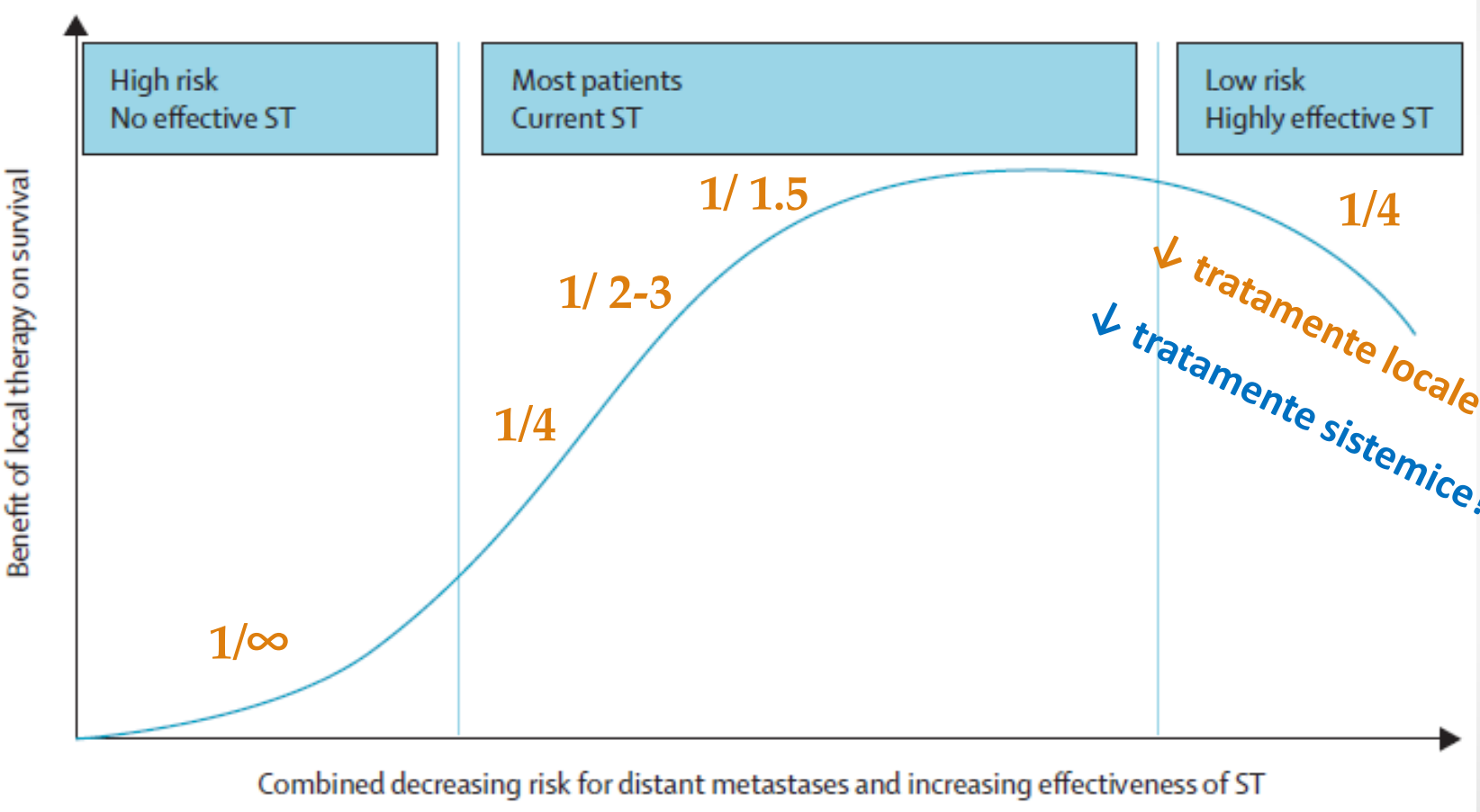
-15.4%

-3.3%

5:1

- EBCTCG Lancet 2011

Interacțiunea tt. locale & tt. sistemice



Combined hypothetical benefit of local tumour control on survival with increasing effectiveness of systemic therapy (ST) and decreasing risk of distant metastases of the primary tumour

- Poortmans P, Lancet 2014

RT după BCS în 2017

sân

- moderată
  - hipofracționare
  - APBI
- intensificată
  - utilizarea selectivă a supraimpresiunii
- deloc
  - fără RT

regiuni ganglionare

- moderată
  - axila
- intensificată
  - axila + GSC
  - axila + GSC+ GMI
- deloc
  - fără RT

CC. mamar operabil & fracționare

1 → 2 → 3 → 4 → 5 → 6 → 7 WBRT

1 → 2 → 3 → 4 → 5 WBRT, fără boost

1 → 2 → 3 hipofracționare +/- boost

1 APBI

1 IORT

fără RT

Hipo↓fracționare: ↓doză, ↓timp, ↓volum

- trialuri multicentrice prospective rand., 8000 p
- > 50 ani (75-79%), T< 2cm (70%), BCS (85-100%), RE+ (73-80%), N0 (80-100%)

- progrese în radiobiologie – model LQ, estimarea EQD2
- progrese în radioterapie
  - LINAC, energii mai mari
  - planning 3D, calcul doză 3D, distribuția dozei

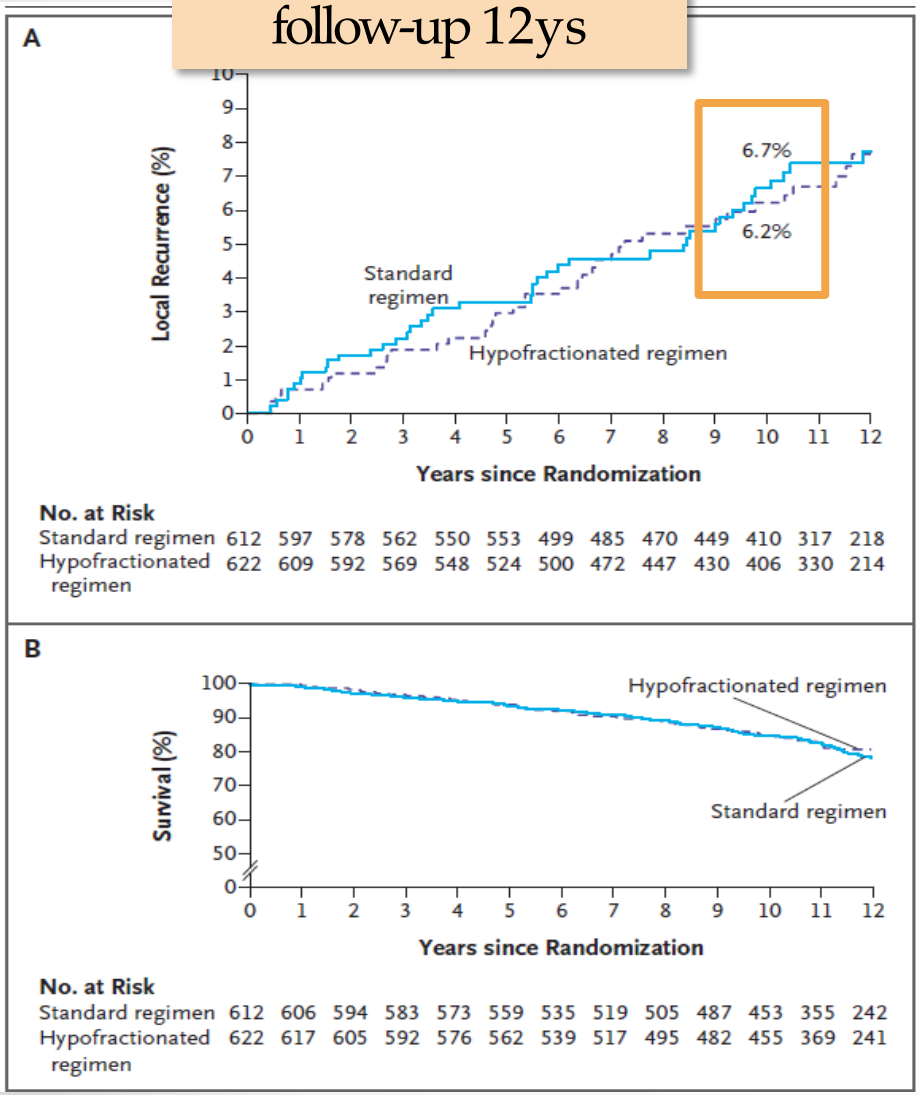
- follow-up (12ys Canadian, 9.9 ys Start B)

control local, Sv

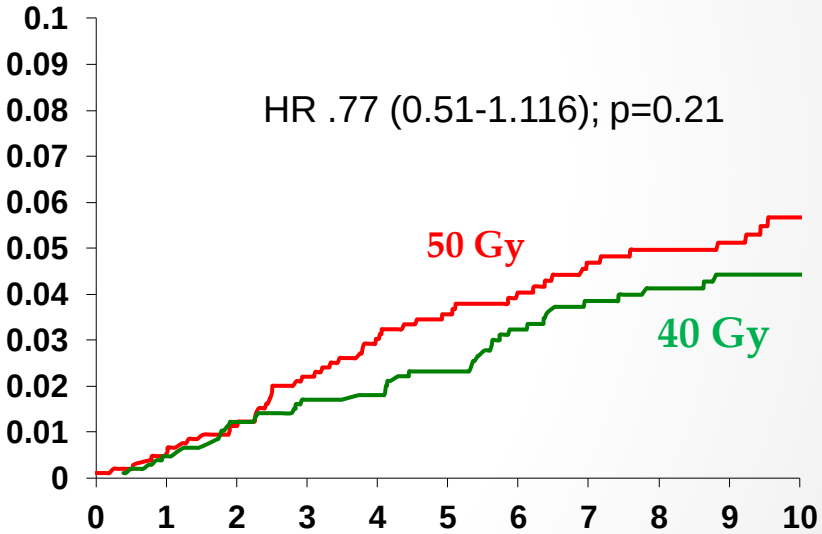
toxicitate

Hipofracționare: rezultate

Trial Canadian
follow-up 12ys



START B
follow-up 10 ys



Whelan et al NEJM 362 (6), 2010
Haviland JS et al. Lancet Oncology (14), 2013

Trial Canadian: toxicitate

DT= 42.5 Gy/ 16fr/ 3.2 săpt. , D/fr= 2.66Gy

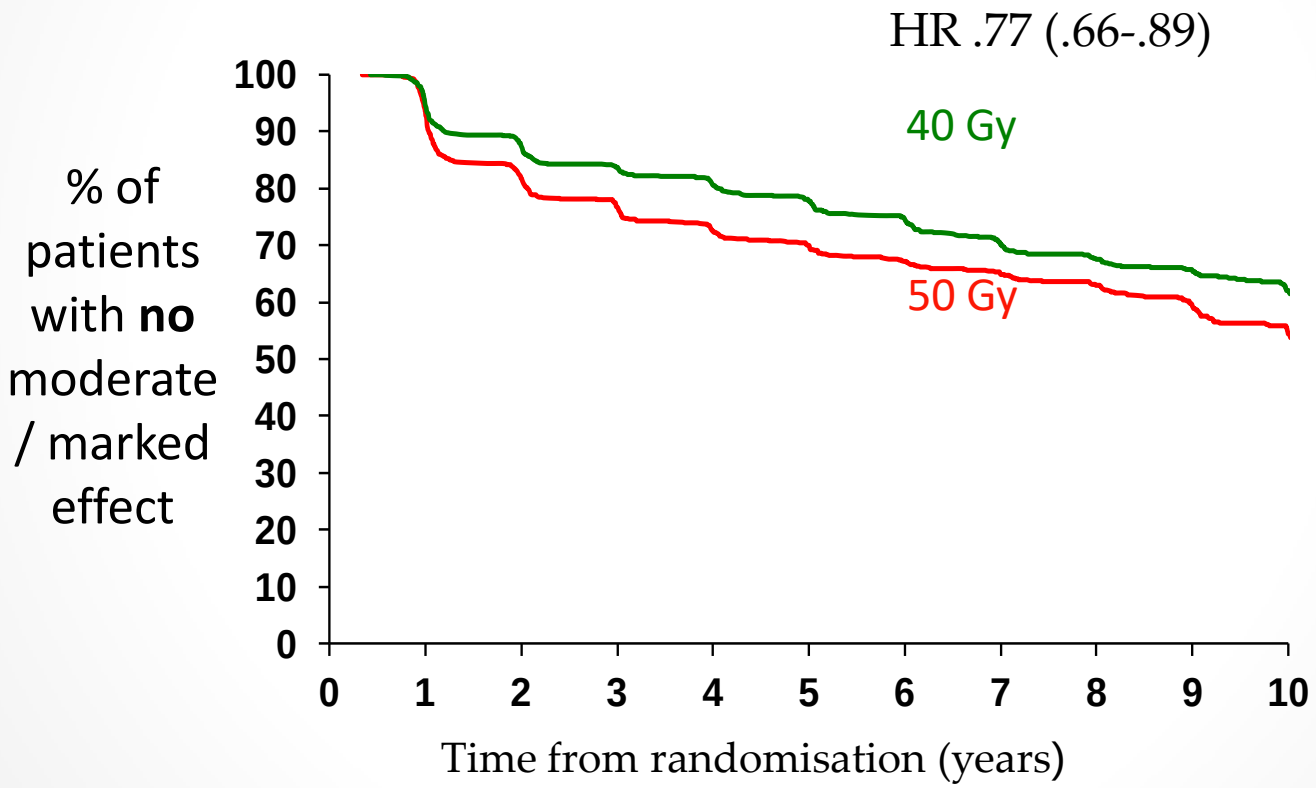
Site and Grade	5 Yr		10 Yr	
	Standard Regimen (N=424)	Hypofractionated Regimen (N=449)	Standard Regimen (N=220)	Hypofractionated Regimen (N=235)
	percent of patients			
Skin				
0†	82.3	86.1	70.5	66.8
1	14.4	10.7	21.8	24.3
2	2.6	2.5	5.0	6.4
3	0.7	0.7	2.7	2.5
Subcutaneous tissue				
0‡	61.4	66.8	45.3	48.1
1	32.5	29.5	44.3	40.0
2	5.2	3.8	6.8	9.4
3	0.9	0.9	3.6	2.5

- ✓ fără diferențe în toxicitatea cutanată/subcutanată
- ✓ fără diferențe în rezultatele cosmetice excelente la 5/ 10 ani

- Whelan TJ, NEJM 2010; 362:513-20

Start B: defecte cosmetice moderate/ semnificativ mai mici (urmărire 10 ani)

DT= 40 Gy/ 15 fr/ 3 săpt., D/fr= 2.67Gy



- Haviland JS et al. Lancet Oncology (14), 2013

Hipofracționarea: sigură și eficientă

- standard pentru majoritatea pacientelor cu chirurgie conservatoare
- control local, rezultate cosmetice și efecte tardive echivalente vs fracționarea standard
- rapidă, convenabilă, cost-eficientă
- QQL

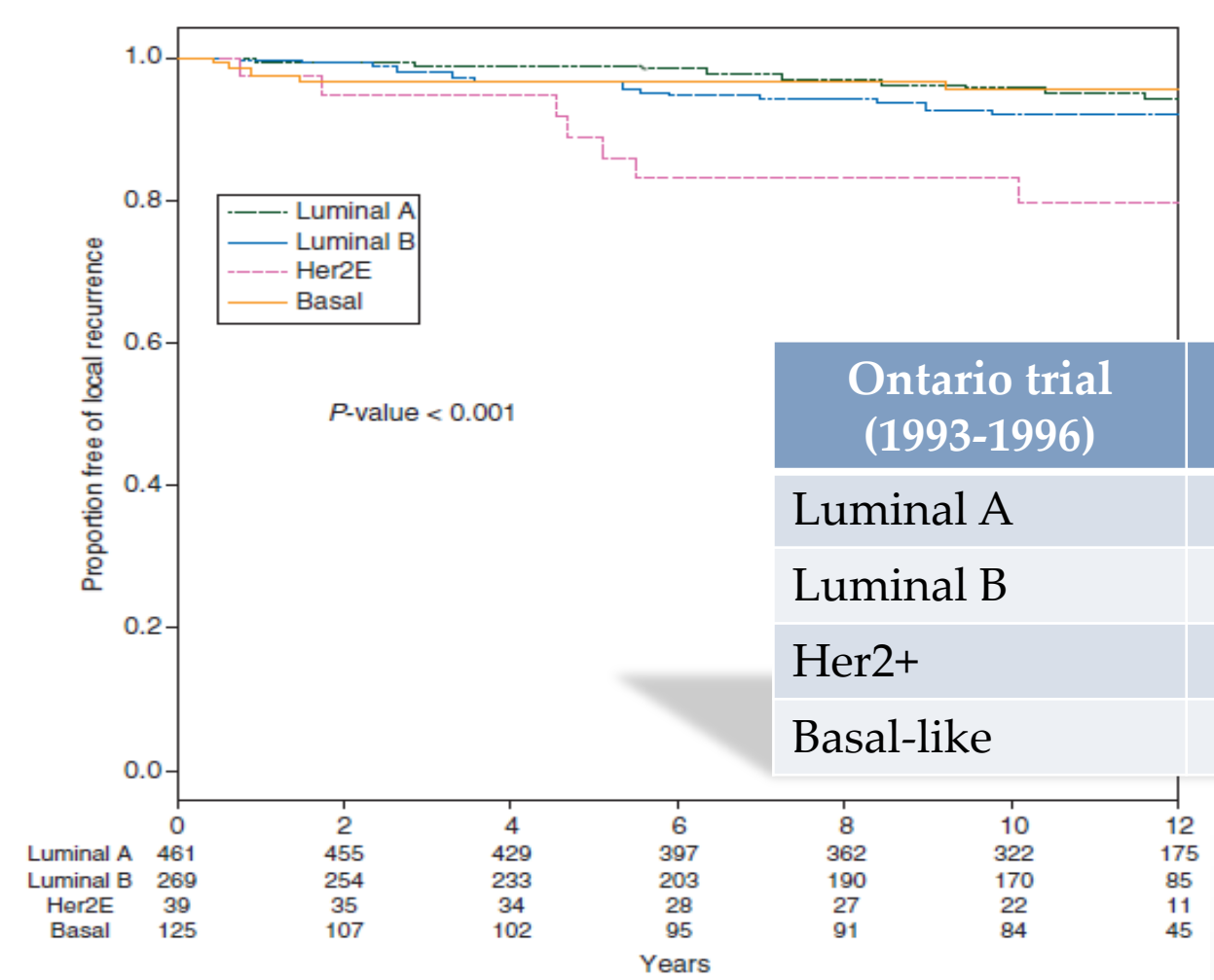
Întrebări...

- HF & biologia tumorală
  - TN, Her2+
  - DCIS (**TROG**, 1600p, 4 brațe)
- HF & PMRT
  - plexopatie brahială? Limfedem al brațului?
- toxicitate la pac. chimiotratați
- modalitatea de asociere a boostului
  - secvențial sau integrat

HF & trialuri în curs

- **RTOG 1005** (2354p)
  - 2 Gy x 25 fx + boost secv. **vs** 2.67 x 15 fx + boost concomitent
- **IMPORT High** (UK)
  - 2.4 Gy x 15 fx (boost integrat) **vs** 2.67 Gy x 15 fx (boost secvențial)
- **FAST** (UK)
  - 2 Gy x 25 fx **vs** 5.7 Gy x 5 fx **vs** 6 Gy x 5 fx
- **FAST – FORWARD**
  - 40.05 Gy/15 fr/3 sapt vs 27Gy/5fr/1 sapt. vs 26 Gy/5fr/1 sapt

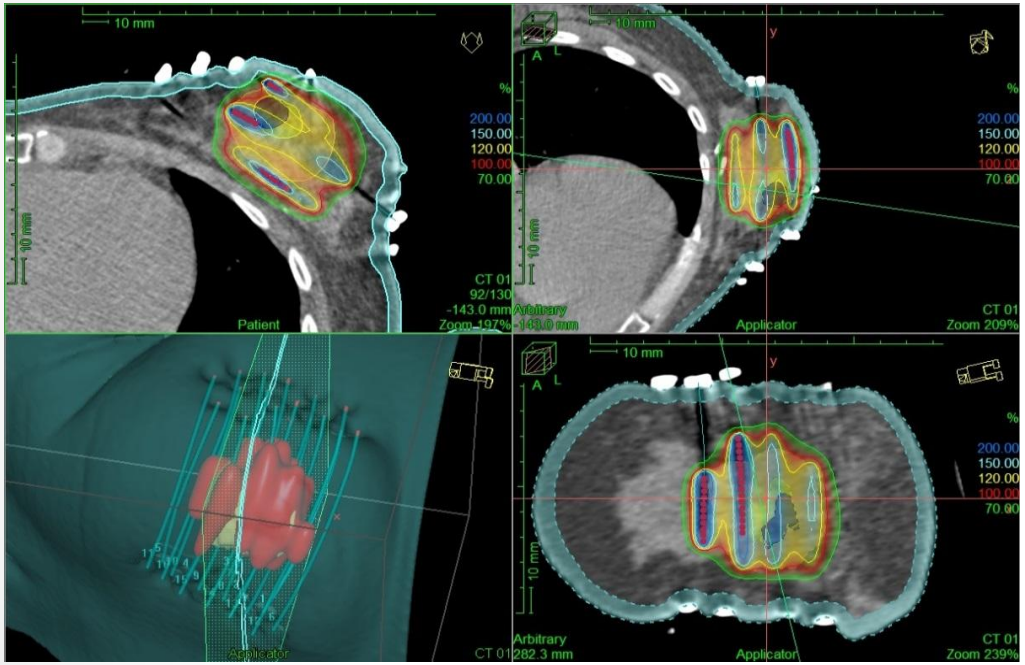
HF & biologia tumorală

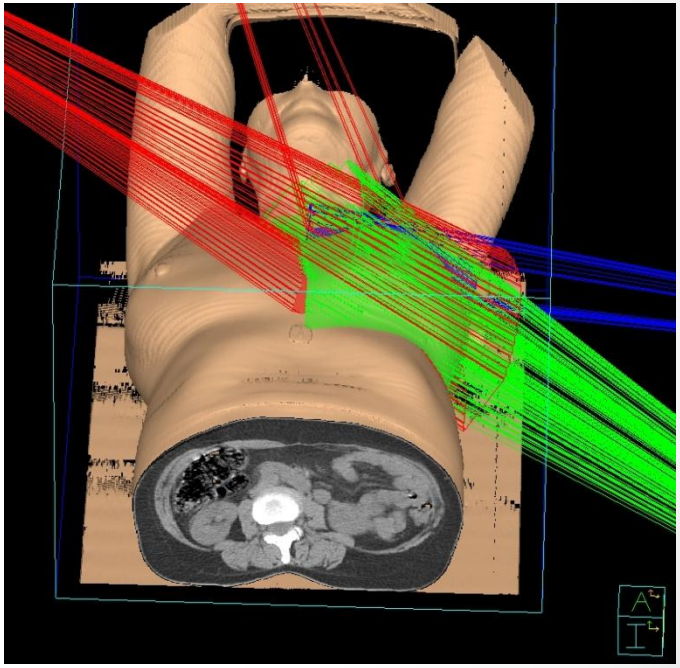


Ontario trial (1993-1996)	HR
Luminal A	1
Luminal B	1.71
Her2+	5.87
Basal-like	**0.90**

- Bane AL et al, Ann Oncol 2014

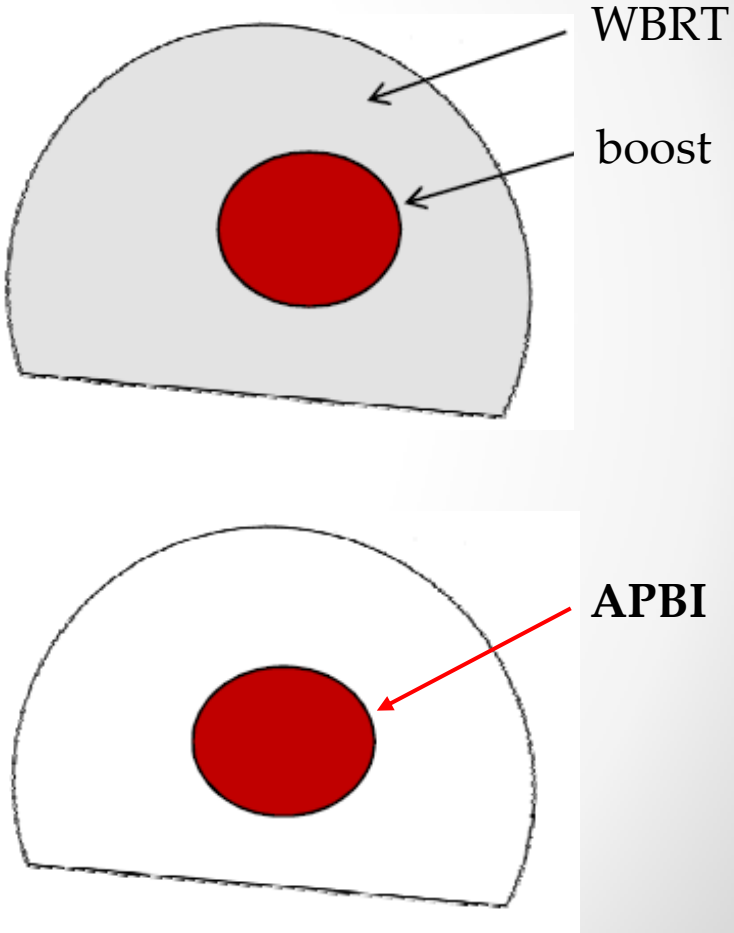
APBI vs WBRT


10 mm
Patient
Applicator
Arbitrary
CT 01
Zoom 209%
Zoom 239%
282.3 mm



APBI : DT↓, etalare↓↓, volum↓↓↓

- etalare scurtă 1 - 5 zile vs. 5-6 săpt.
- admninistrarea D mari în proximitatea cavității de sector
- evitarea iradierii axilei



APBI vs. WBI – trialuri fază III

Institution/trial	Trial design	N	Control arm	Experimental arm	LRR5%
NSABP B-39/RTOG 0413 [114]	Equivalence	4300 patients Lumpectomy Stage 0, I or II $T \leqslant 3.0$ cm pN1 neg margins any age	WBI 50–50.4 Gy, 1.8–2.0 Gy per fraction to whole breast followed by optional boost to 60–66 Gy	34 Gy in 3.4 Gy fractions using multi-cathether brachytherapy or MammoSite balloon catheter or 38.5 Gy in 3.85 Gy fractions using 3D CRT #	2x/zi, ef adv ↓
RAPID/Ontario Clinical Oncology Group[b] 2006- 7/2011	Equivalence	2128 patients Lumpectomy $\geqslant$40 years, DCIS, pT < 3 cm, pN0, non-lobular, No BRCA 1 or 2	WBI 42.5 Gy/16 f/22 days (small breasts), 50 Gy/25 f/35 days (large breasts). Optional boost of 10 Gy/4–5 f	3D CRT 38.5 Gy/10 f/5–8 days Minimum daily fraction separation 6–8	ef adverse 17 vs 29% **p<0.001**
GEC-ESTRO [115]	Non-inferiority, non-irrelevant, 3% difference	1170 patients, Lumpectomy $\geqslant$40 years, $T \leqslant 3$ cm, $\leqslant$1 micrometastasis in axilla, neg margins $\geqslant$2 mm ($\geqslant$5 mm for lobular or pure DCIS)	WBI, 50–50.4 Gy, 1.8–2.0 Gy per fraction to whole breast followed by optional boost to 60 Gy	Interstitial brachytherapy # 32 Gy/8 fractions HDR, 30.3 Gy/7 fractions HDR, 50 Gy PDR	0.9vs 1.4, **p= ns** 👍
IMPORT-LOW, UK 2007-2010	Non-inferiority	1935 patients Lumpectomy $\geqslant$50 years, pT $\leqslant$ 2 cm, pN0 (isolated tumor cells <0.2 mm allowed) non-lobular, grade I or II, neg margins $\geqslant$2 mm	WBI 40 Gy/15 f/3 weeks	ARM 1: 36 Gy/15 f (2.4 Gy/f) to low risk areas and 40 Gy/15 f (2.67 Gy/f) to region of primary tumor ARM 2: 40 Gy/15 f to region of primary tumor Based on IMRT and supine position	1.1vs 0.5, **p=ns** 👍
ELIOT, Milan [116] 2000-2007	Equivalence	824 patients Quadrantectomy Age >48 years, any invasive cancer $\leqslant$2.5 cm, pN0	WBI 50 Gy/ 25 fractions followed by optional boost 10 Gy	Intraoperative 21 Gy single fraction, electrons up to 9 MeV	0.4vs 4.4 **p<0.001**
TARGIT [111] multicentric trial 2000-2012	Equivalence	1600 patients "Pragmatic trial" where the treating institution judges the patient to be suitable. Non-lobular and no EIC (if EIC or ILC on final pathological report, WBI is added)	WBI according to institutional guidelines at the participating center	20 Gy low-energy X-rays 50 kV intraoperative single fraction	1.7vs 5.4 **p< 0.04**

B.V. Offersen et al, Rad Oncol 2009; Whelan T, St Gallen 2017; Orecchia R, St Gallen 2017

Concluzii APBI vs WBRT

- IORT
  - **RRL** ↑ Lum A =1.4%, Lum B= 4.9%, Her2+= 5.9%, TN= 18.9% (ELIOT)
  - date rezultate cosmetice indisponibile
- BT intestițială
  - control local echivalent (GEC-ESTRO)
  - rezultate cosmetice bune
- 3D-CRT
  - CL - date limitate (IMPORT LOW ✓, NSABP –B39…)
  - rezultate cosmetice – date contradictorii
- balloon catheter brachytherapy
  - na (TR)

SUPPLEMENTAL MATERIAL

Practical Radiation Oncology (2017)

Accelerated Partial Breast Irradiation: Update of an ASTRO Evidence-Based Consensus Statement

Candace Correa, MD,[1] Eleanor E. Harris, MD, [2] Maria Cristina Leonardi, MD,[3] Benjamin D. Smith, MD,[4] Alphonse G. Taghian, MD, PhD,[5] Alastair M. Thompson, MD,[6] Julia White, MD,[7] Jay R. Harris, MD[8*]

Criterii eligibilitate APBI 2017

Factor	*Criterion*
Patient Factors	
Age	**≥ 50 y**
BRCA1/2 mutation	not present
Pathologic factors	
Tumor size	≤2 cm*
T stage	**Tis** or T1
Margins	Negative by at least 2 mm
Grade	Any
LVSI	No†
ER status	Positive
Multicentricity	Unicentric only
Multifocality	Clinically unifocal with total size ≤2 cm‡
Histology	Invasive ductal or other favorable subtypes§
Pure DCIS	**Allowed if screen-detected, low to intermediate nuclear grade, ≤ 2.5 cm size, and resected with margins negative at ≥ 3 mm**
EIC	Not allowed
Associated LCIS	Allowed
Nodal factors	
N stage	pN0 (i-,i+)
Nodal surgery	SN Bx or ALND‖
Treatment factors	
Neoadjuvant therapy	Not allowed

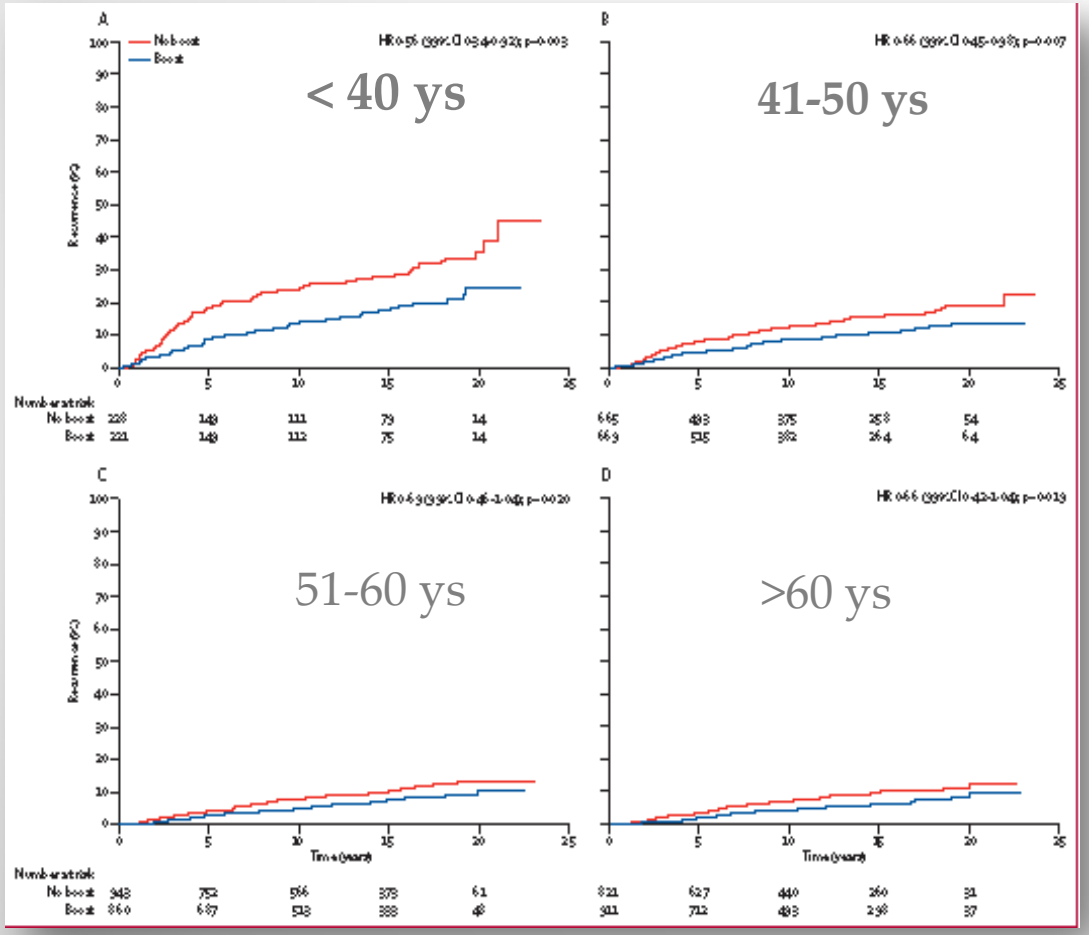
- Correa C et al, *Practical Radiation Oncology (March 2017)*

RT după BCS

- moderată
  - hipofracționare
  - APBI
- intensificată
  - utilizarea selectivă a supraimpresiunii
- deloc
  - omiterea RT

Boost- no boost: follow-up 20 ani

EORTC 22881/10882 “boost vs no boost”, 5318p.)



- **reduce rata recidivelor loco-regionale** (LRR) , p< 0.001
- **scăderea ratei mastectomiei** de salvare cu 35%
- beneficiu mai modest la pac. în vârstă fără factori de risc
- rezultate cosmetice mai modeste (14 vs 29%), **fibroza severă** crește de la 1.8% la 5.2%

Bartelink, Poortmans, Horiot et al. Lancet Oncol 2015;16: 47-56, Whelan T, St Gallen 2017

Risc recidivă & componenta CDIS
Efectul boost

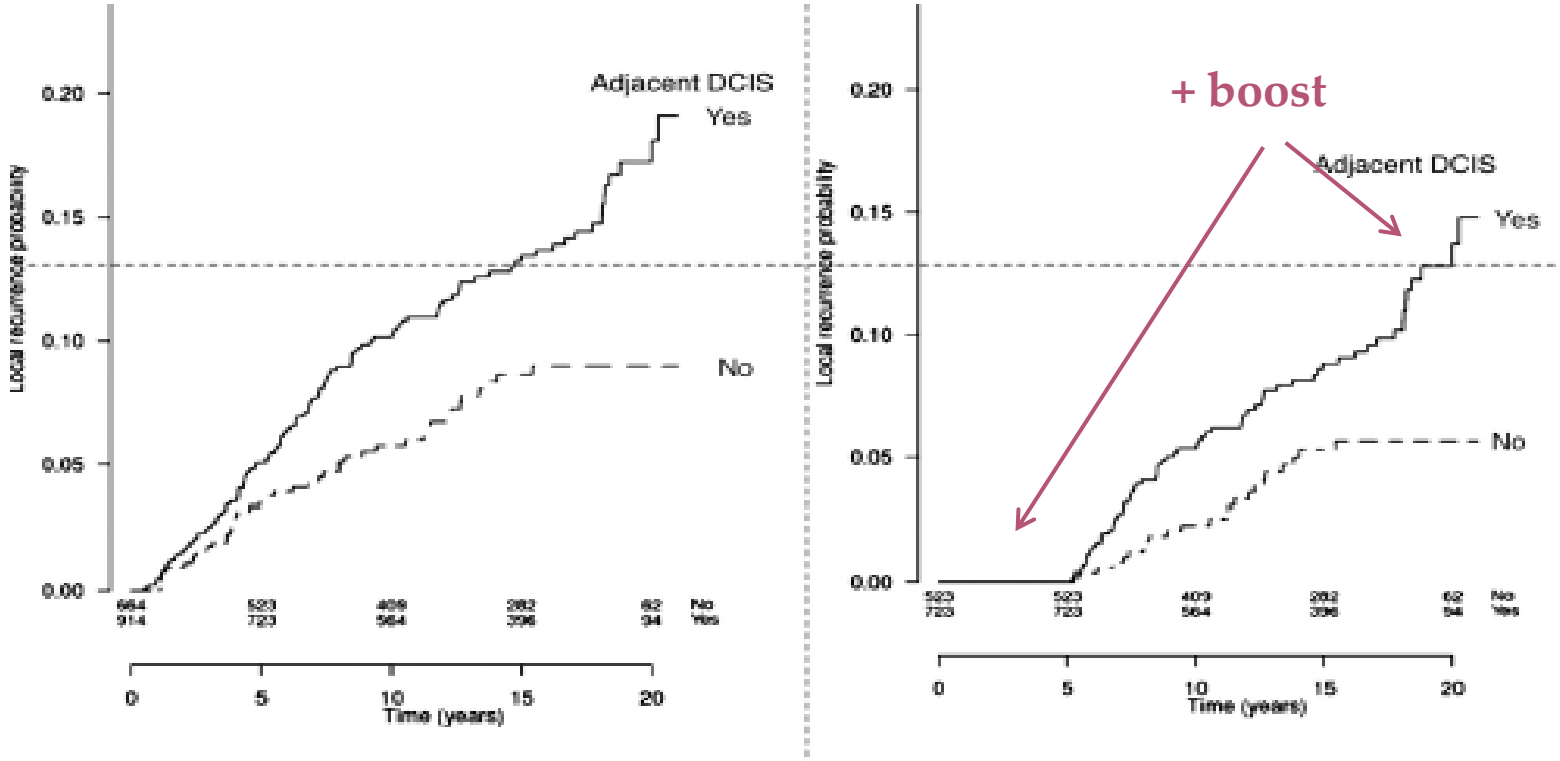


Fig. 5. Local recurrence in patients with invasive breast cancer in and adjacent DCIS. Adapted from Ref. [16].

H. Bartelink The changing landscape in radiotherapy for breast cancer: Lessons from long term follow-up in some European breast cancer trials, R&O, 2016

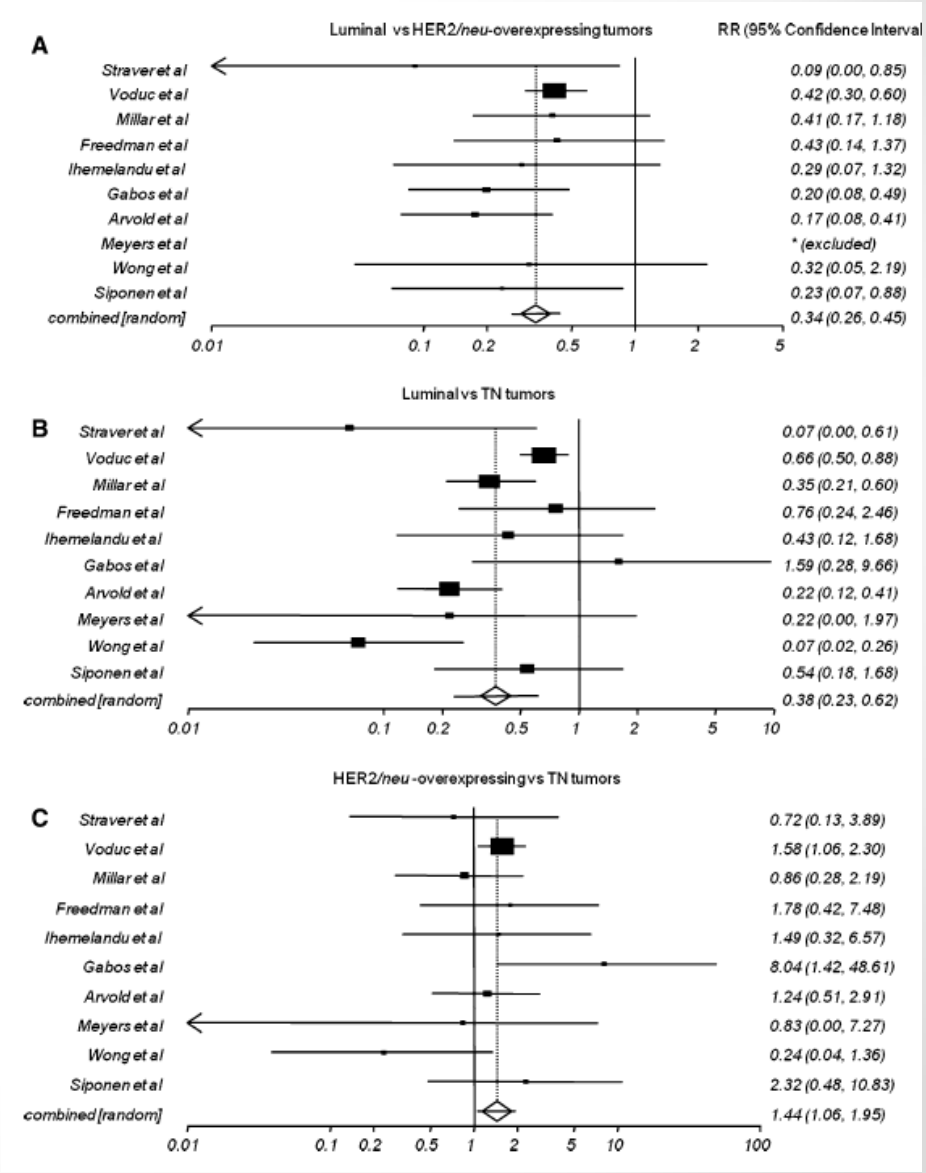
LRR după BCS & subtip biologic

- RISC↓ pt. Luminal

  A). vs Her2, RR:0.34, p=0.0001

  B). vs TN, RR:0.38, p=0.0001

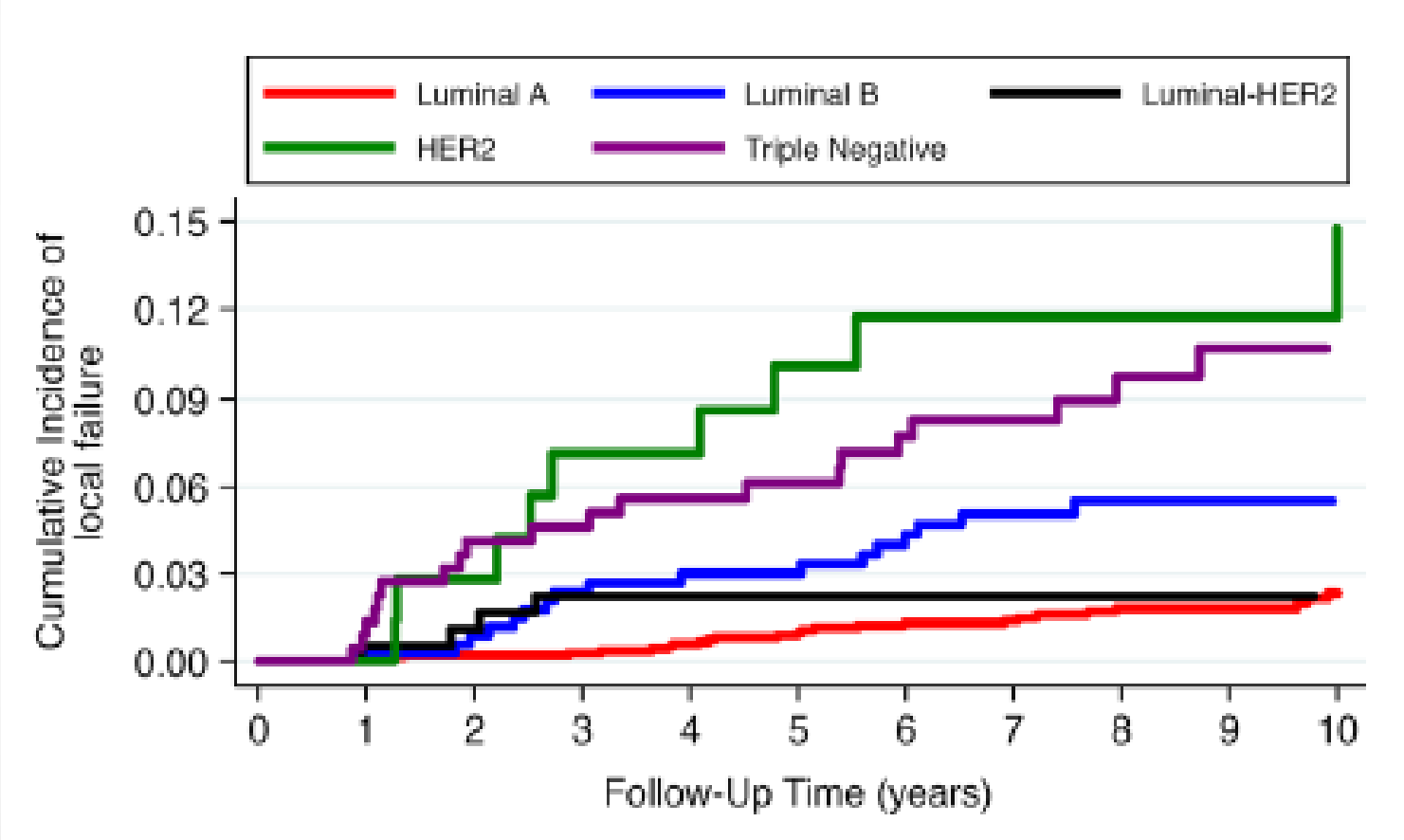
- RISC↑ pt. Her2+ vs TN
  - RR=1.44, p=0.02



- Lowery et al, Breast Cancer Res Treat (2012)

LRR după BCS & subtip biologic

2233 p, 1998-2007



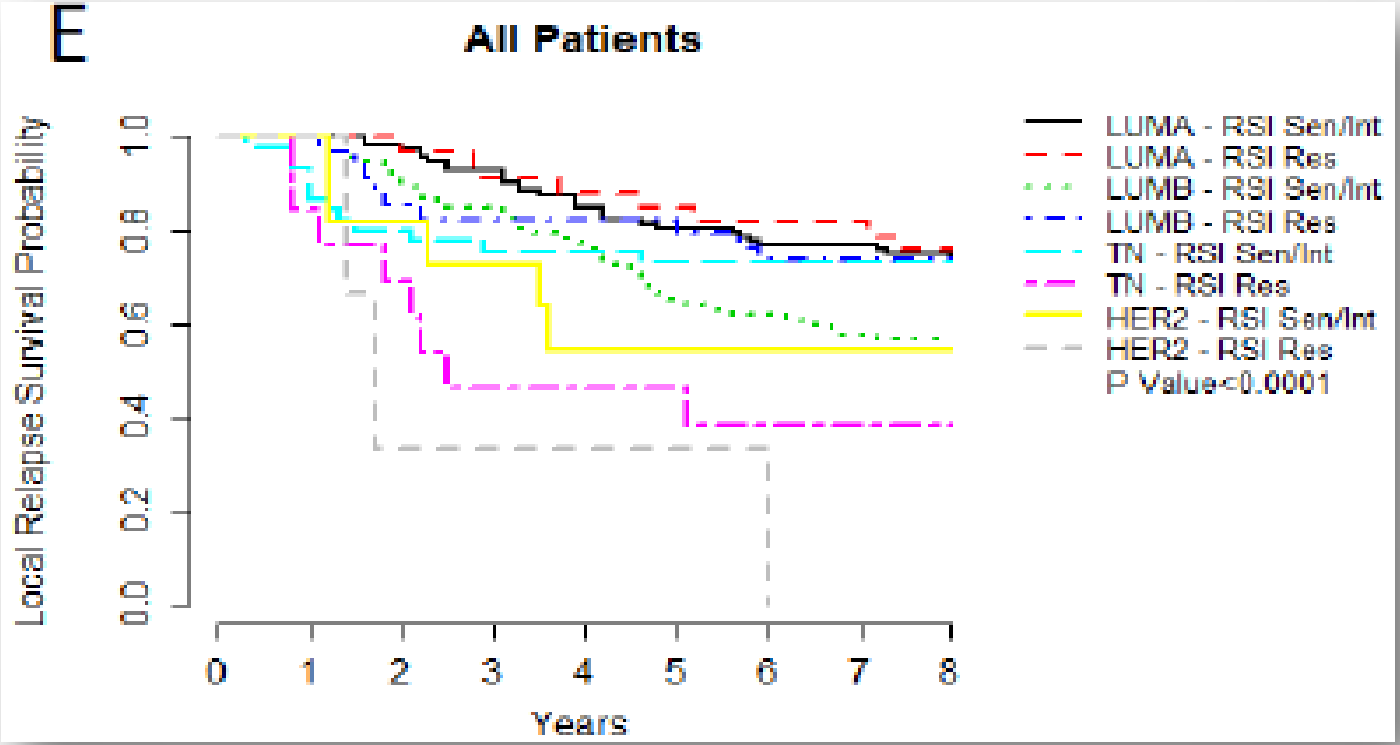
- Braunstein et al, Breast Cancer Res Treat 2017

LRR după BCS & biologie, vârstă, N+

	analiza multivariată	
	HR	P value
Subtype		
Luminal-A	1	
Luminal-B	2.64	0.001
Luminal-HER2	0.93	0.90
HER2	5.42	<0.001
TNBC	4.32	<0.001
Age		
≤50	1	
>50	0.56	0.01
# Positive lymph nodes	1.06 per node	0.004

- Braunstein et al, Breast Cancer Res Treat 2017

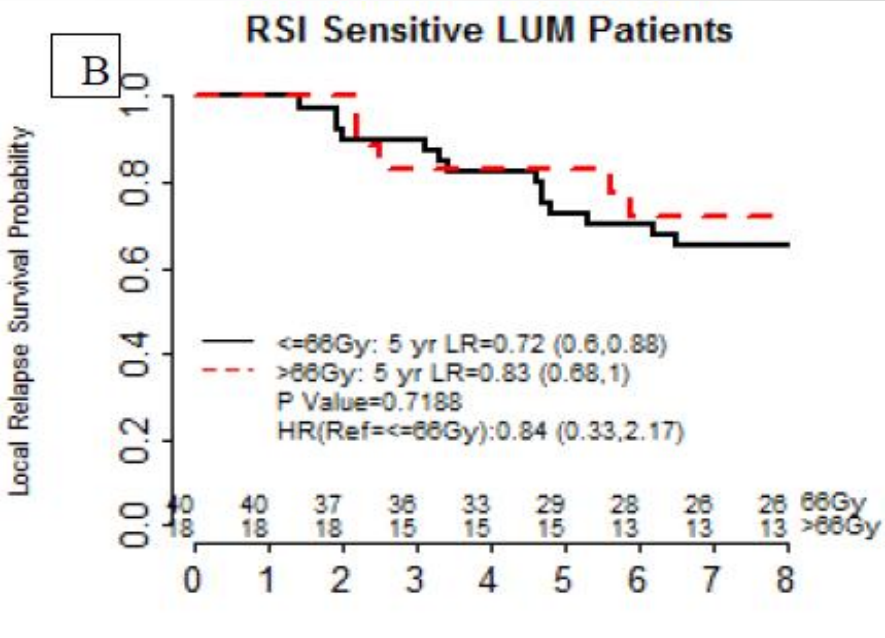
Integration of a Radiosensitivity Molecular Signature Into the Assessment of Local Recurrence Risk in Breast Cancer

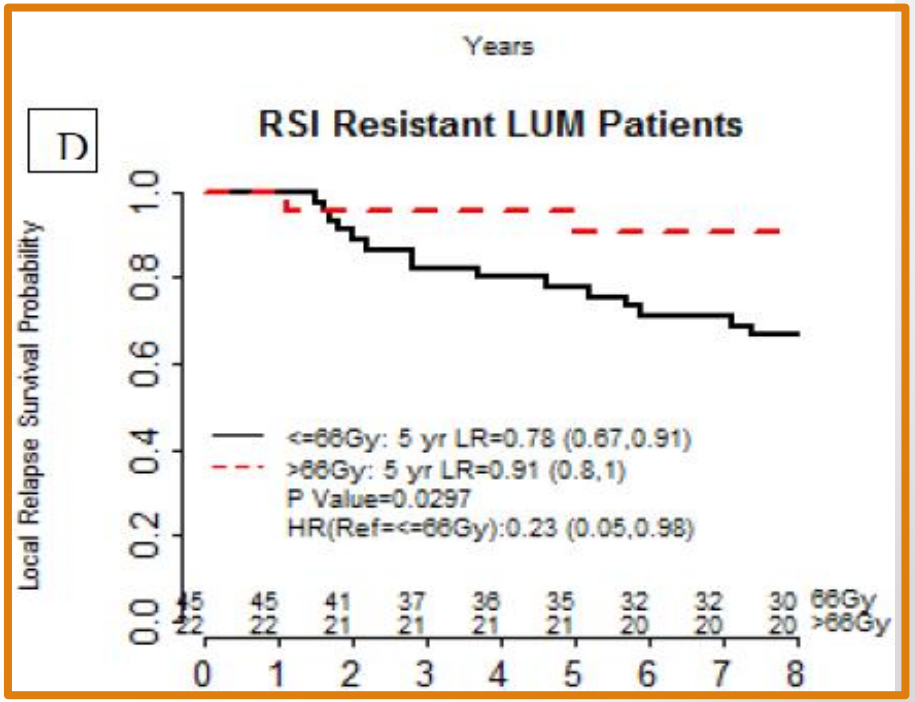


- obiectiv: (re)definirea clasificării RRL în funcție de combinarea RSI cu subtipul molecular
- identificarea pac. care beneficiază de escaladarea D

Torres-Roca J et al, IJROBP 2015

Integration of a Radiosensitivity Molecular Signature Into the Assessment of Local Recurrence Risk in Breast Cancer

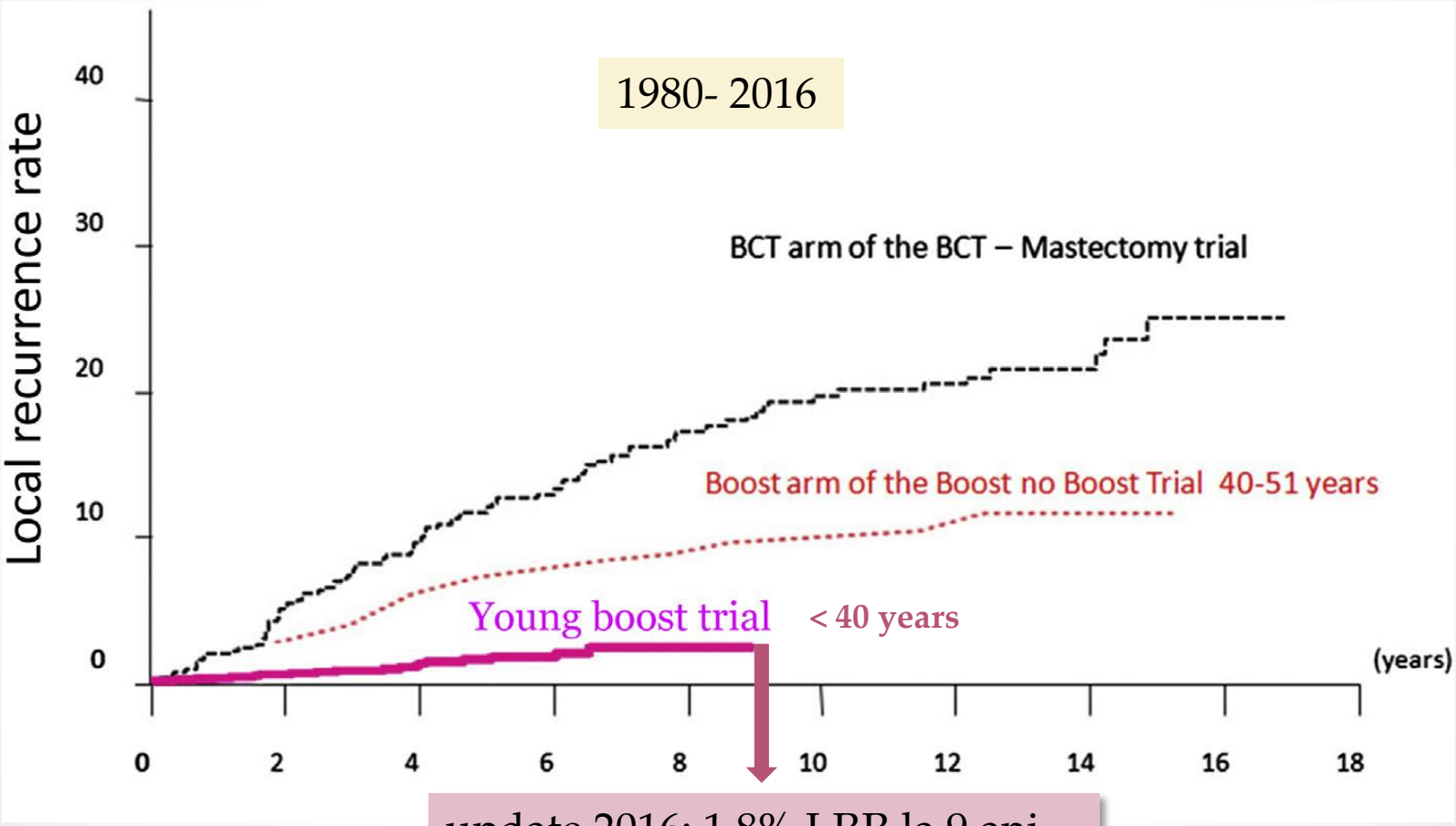




- rata RL **Luminal** în functie de subtipul RSI pt. 343 p. cu BCT ± boost 45-72 Gy
- **DT> 66Gy** vs < 66 Gy **reduce semnificativ LRR la pac Luminal RSI – R** (p=0.02)

- Torres-Roca J et al, IJROBP 2015

Recidiva locală & BCT



update 2016: 1.8% LRR la 9 ani

Poortmans P et al, The Breast 31 (2017) 295-302
Bartelink H, R&O, 121 (2016) 348–356

Administrarea selectivă a supraimpresiunii (10-16 Gy)

- cine beneficiază?
  - < 50 ani
  - G3
  - TN, Her2+
  - CDIS extensiv
  - invazia sp. limfovascular (LVI)
  - margini apropiate

➢ ghid ASTRO pentru WBRT 2017/2018

RTE & risc

>> WBRT

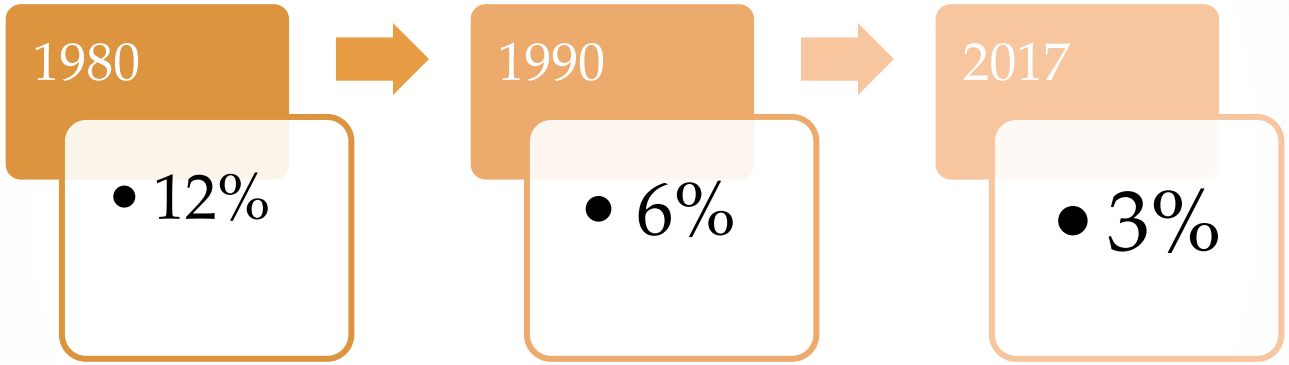
- risc înalt de recidivă loco-regională

<< WBRT

- risc scăzut de recidivă locală

~~WBRT~~ ?

- scăderea RRL10



- screening mamar/ progrese în chirurgie/ progrese în tt. sistemice adjuvante

EBCTCG by Age

	Number Allocated BCS+RT/BCS	10-year risk of a locoregional or distant recurrence (%)		
		BCS+RT	BCS	Absolute Reduction with RT (95% CI)
a.) Entry Age (years)				
< 40	189/174	36.1	60.7	24.6 [13.2 to 36.0]
40-49	576/582	20.8	41.4	20.6 [15.1 to 26.1]
50-59	1093/1028	15	29.7	14.7 [10.8 to 18.6]
60-69	1138/1167	14.2	28.3	14.1 [10.4 to 17.8]
70+	679/661	8.8	17.7	8.9 [4.0 to 13.8]

Early Breast Cancer Trialists' Collaborative Group, Lancet 2011 Nov 12; 378(9804):1707-1716

Radiation for Older Women with Early-Stage Breast Cancer: To treat or not?

Trial (n)	Inclusion criteria	IBTR w/o RT	IBTR w/ RT	P-value	Survival different?
CALGB (686)	≥70 years HR+/unk T1	10% @ 10 years	2% @ 10 years	<0.001	NS
PMH (749)	≥50 years HR+/unk T1/T2	17.6% @ 8 years	3.5% @ 8 years	<0.001	NS
PRIME II (1326)	≥ 65 years T<3cm HR+	2.7% @ 5 years	0.6% @ 5 years	0.002	NS
ABCSG (869)	Post-meno T<3cm HR+	5.1% @ 5 years	0.4% @ 5 years	<0.001	NS

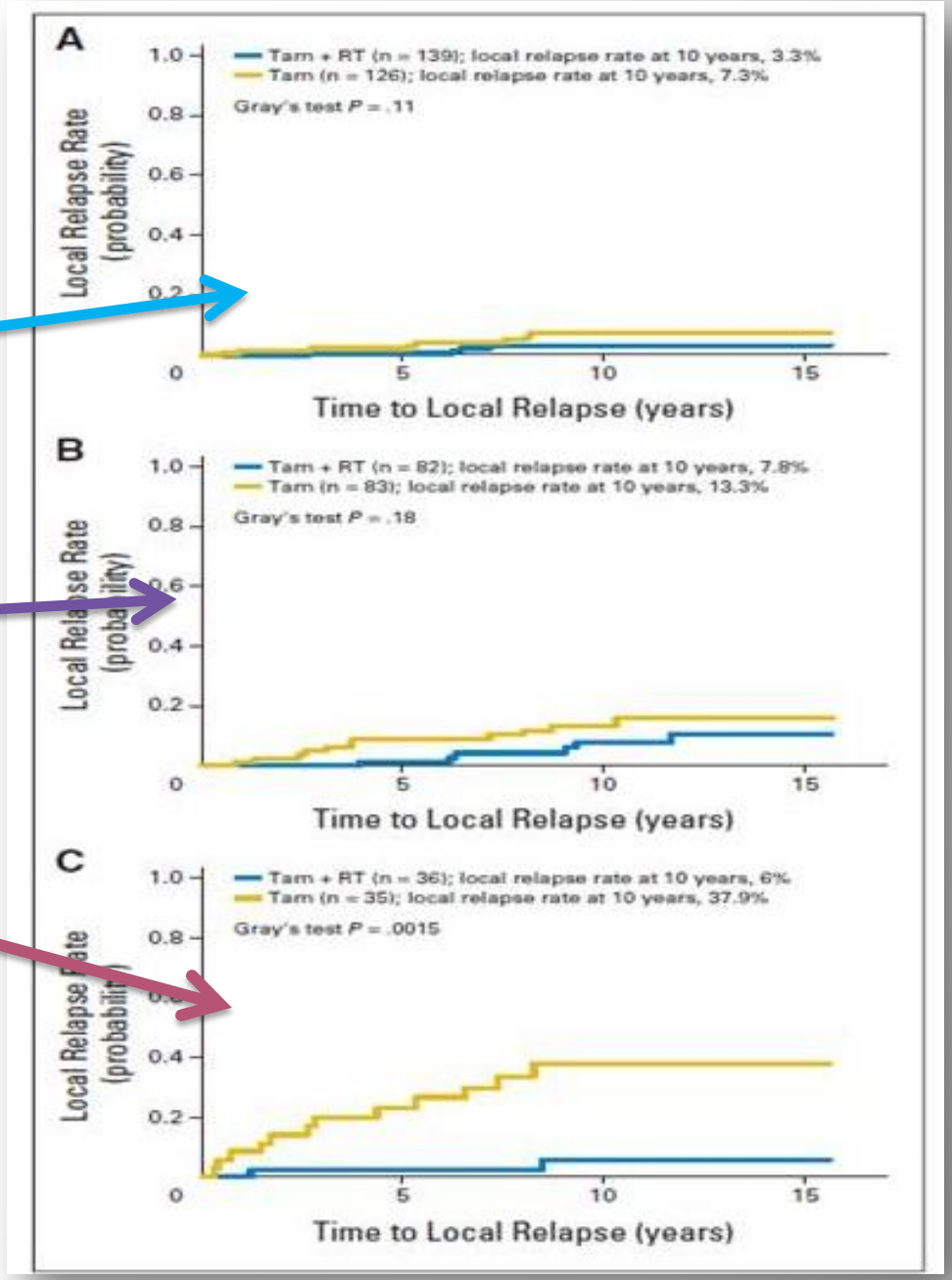
RT for all?

cT1-2N0, Tam vs Tam +RT

A. Luminal A
(+/+/-, Ki67<14%) & Gr I/II

B. Luminal B
(+/+/-, Ki67>14%)

C. High-risk
(her2+, basal, -/-/-)



Liu F-F et al JCO 2015;

~~WBRT~~ ?

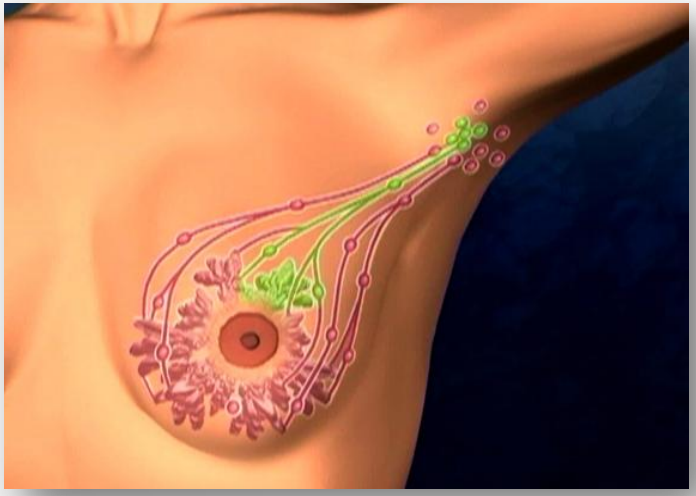
- >70 ani, Lum A
  - recidive *tardive*
  - RRL fără WBRT 4% la 5 ani, 8% la 10 ani
  - fără prejudiciu pentru Sv
  - opțiune pt. pac cu HT

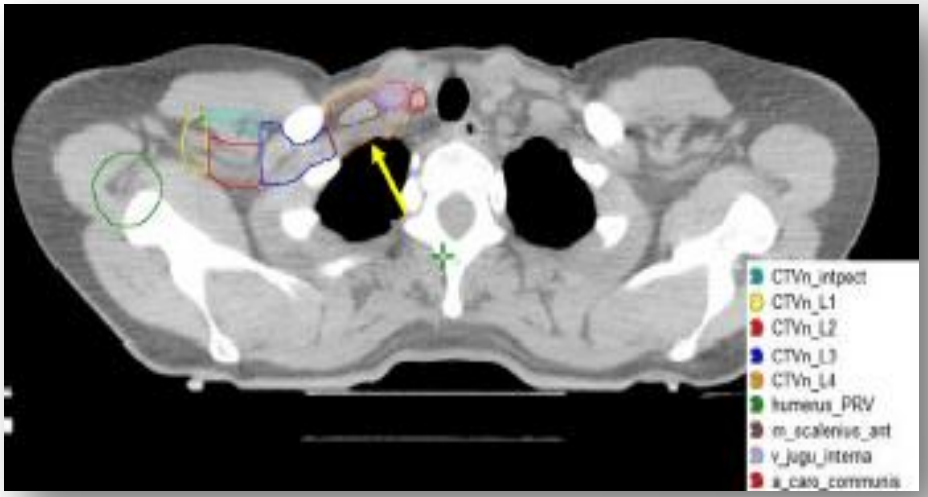
- Biomarker low risk trials
  - Luminal A p., > 55 ani ,T1N0 – fără RT?
    - OCOG - Lumina
    - U of M – IDEA (oncotype<18)
    - DFCI/BWH – PRECISION (PAM-50)

RT & strategie adaptată riscului

- < 50 ani
  - HF+ boost secvențial
  - fracționare standard cu boost secvențial sau integrat
- >50 ani
  - risc scăzut: HF (40.05Gy/15 fr sau 42.5 Gy/16 fr)
  - risc crescut: idem ca pt pac. < 50 ani
- pac. în vârstă
  - opțiune – omiterea RT in funcție de riscul individual, evaluare geriatrică
- orice vârstă & arii ganglionare
  - RT fracționare standard

Tratamentul regiunilor ganglionare





less surgery more radiotherapy

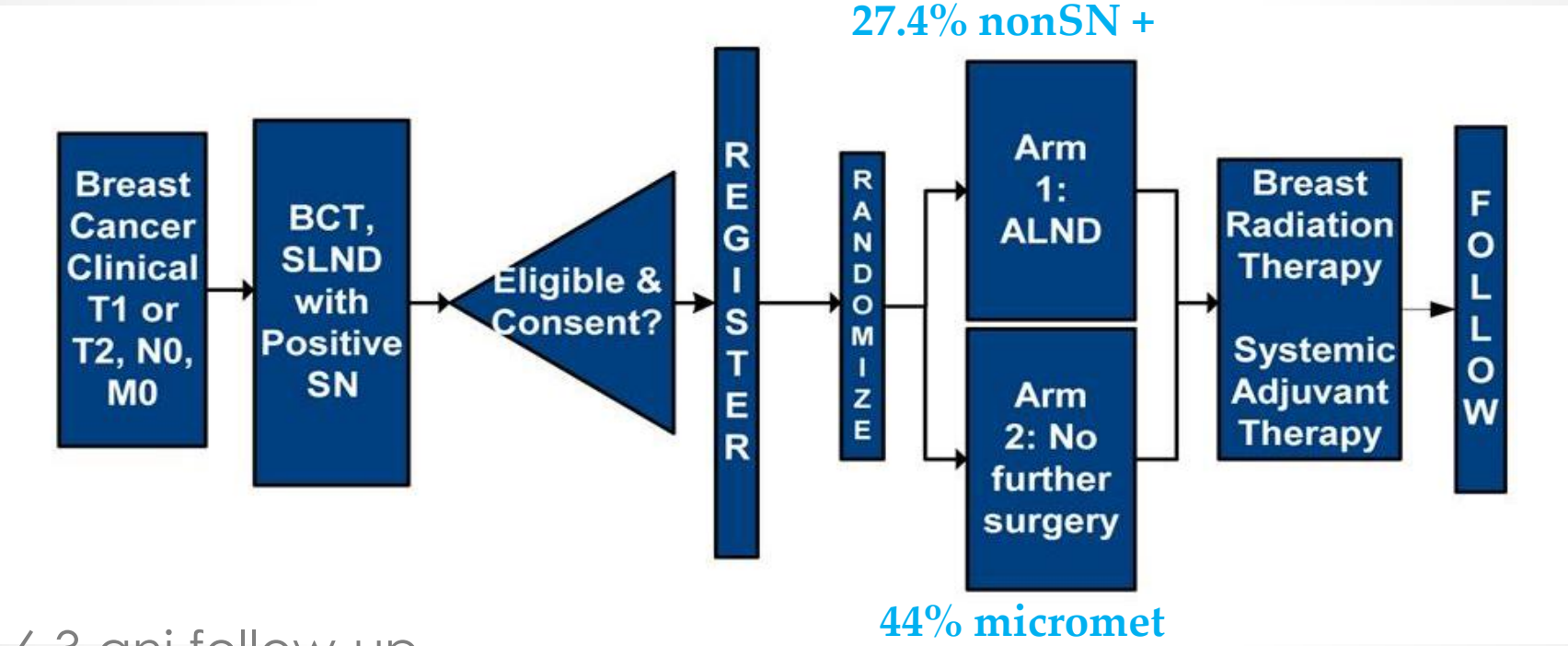
Caz 1

- 62 ani, cT2N0M0, st II A, Lum A
- sector+SNB, pT1cN1snL0V0, SNB+1/2, fără ECE

?

1. LA, WBRT
2. WBRT, fără RT bazei axilei
3. WBRT+ RT bazei axilei
4. WBRT+ GSC+axila I,II,III

ACOSOG Z0011, cT1,2N0, 1,2 SNB+



6.3 ani follow-up

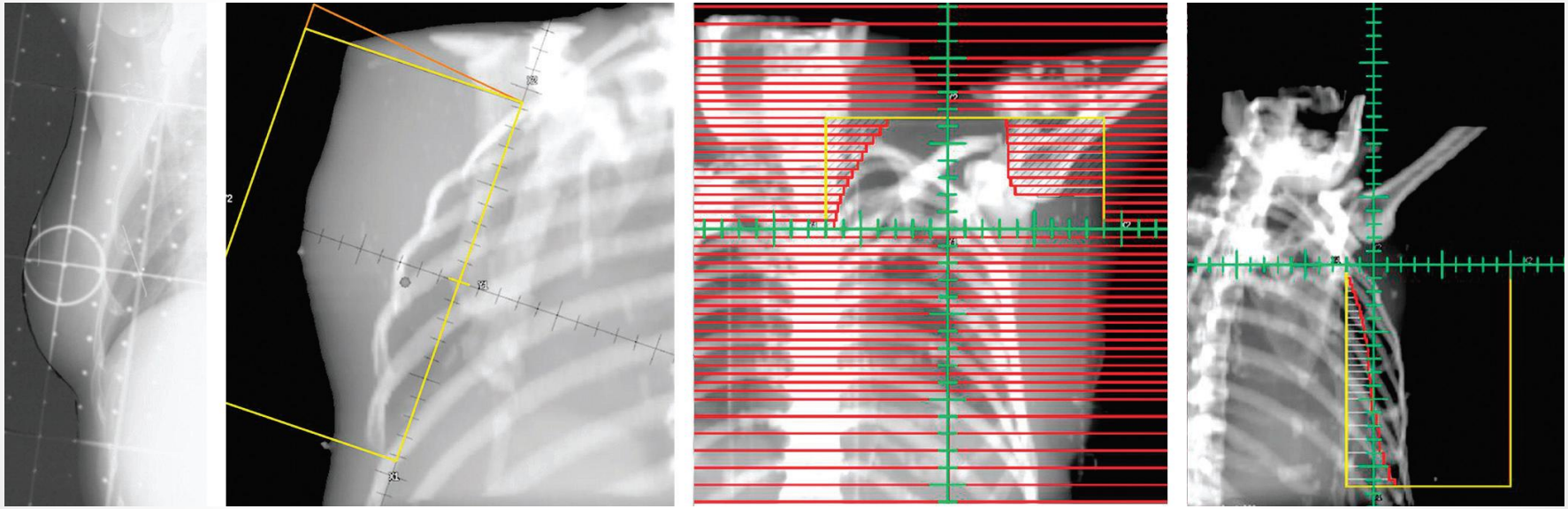
- fără diferențe în recidivă
- fără diferențe în DFS și OS
- morbiditate semnificativ mai scăzută în brațul SN

Giuliano A JAMA 2011;305:589

ACOSOG Z0011 & critici

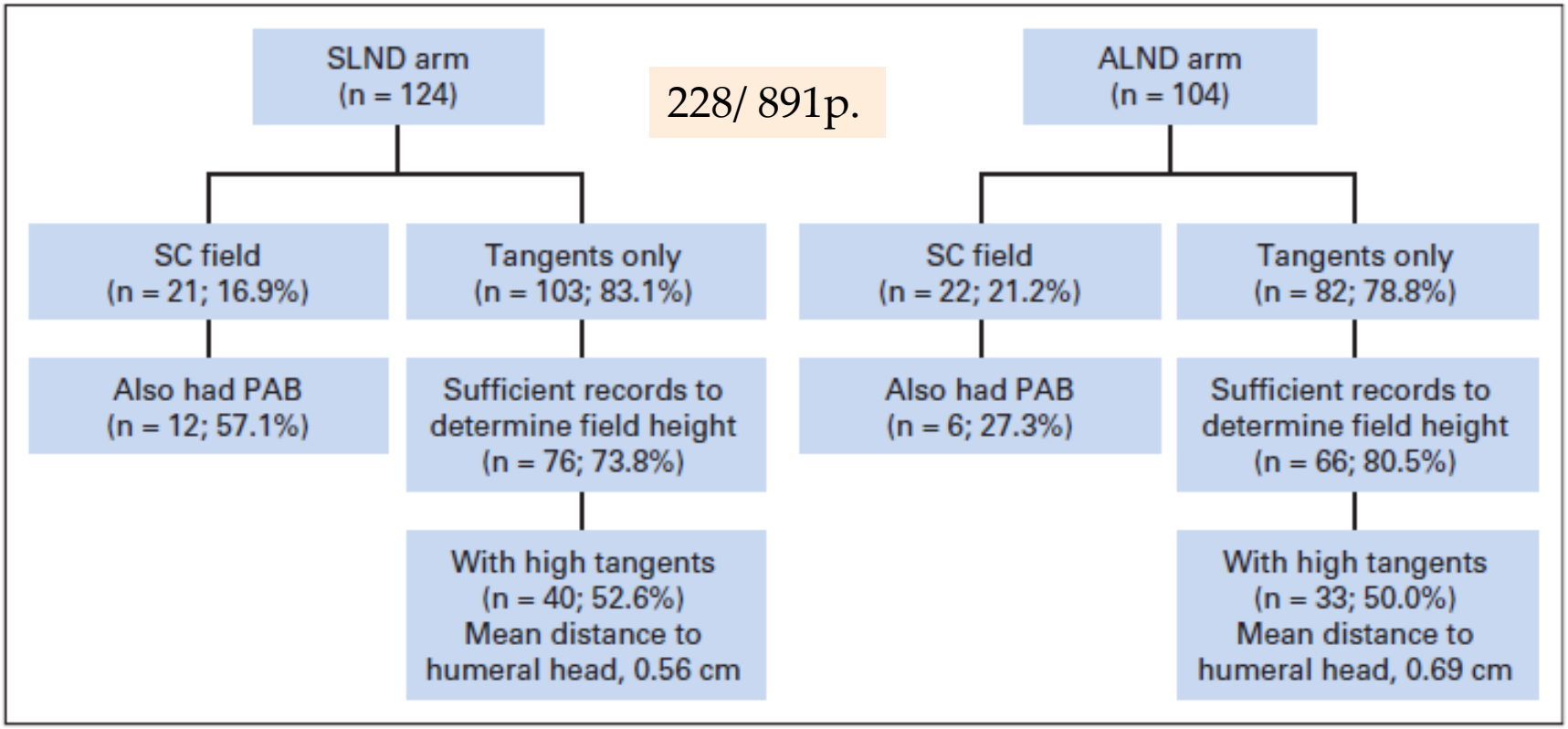
- date pacienți
  - planificați 1900 , randomizați 891
  - rata scăzută a evenimentelor
- urmărire scurtă
  - pac RE+ la risc pentru recidive tardive
- pac supraselectate, factori prognostici favorabili
  - 65% - > 50 ani
  - 69% T1
  - 85% RE+
- **QA pentru RT?**
  - analizarea centrală a planurilor pentru 228 p **(25%)**
  - fără RT - 15%, ↑ **LR p=0.004**

Radiation Field Design ACOSOG Z0011



- Jagsi R et al.JCO 2014; 32:3600-3606

Radiation Field Design in the ACOSOG Z0011



44% micromet

27% ggl +non SN
14% > 4N+

ACOSOG Z0011& med follow-up=9.3 ys

Outcome	SLND N=436	ALND N=420	P-value
10-yr local recurrence	12 (3.8%)	19 (5.6%)	0.13
10-yr regional recurrence	5 (1.5%)	2 (0.5%)	0.28
Total LR recurrence	17 (5.3%)	21 (6.2%)	0.36

Outcome	SLND N=436	ALND N=420	P-value
10-yr DFS	80.2%	78.2%	0.44
10-yr OS	86.3%	83.6%	0.72

- Giugliano A, Ann Surg 2016;264:413

Rată ↓ a RLL
less surgery **more radiotherapy**

- ✓ status cN
- ✓ tip chirurgie
- ✓ status RE, RP, Her2

- boala LumA răspunde la HT adj
- N+ eradicată de tt. sistemic
- N+ este biologic nerelevantă ? -
- N+ eradicată de WBRT cu tangente înalte

ACOSOG Z11, cN0, **1,2 SNB+**

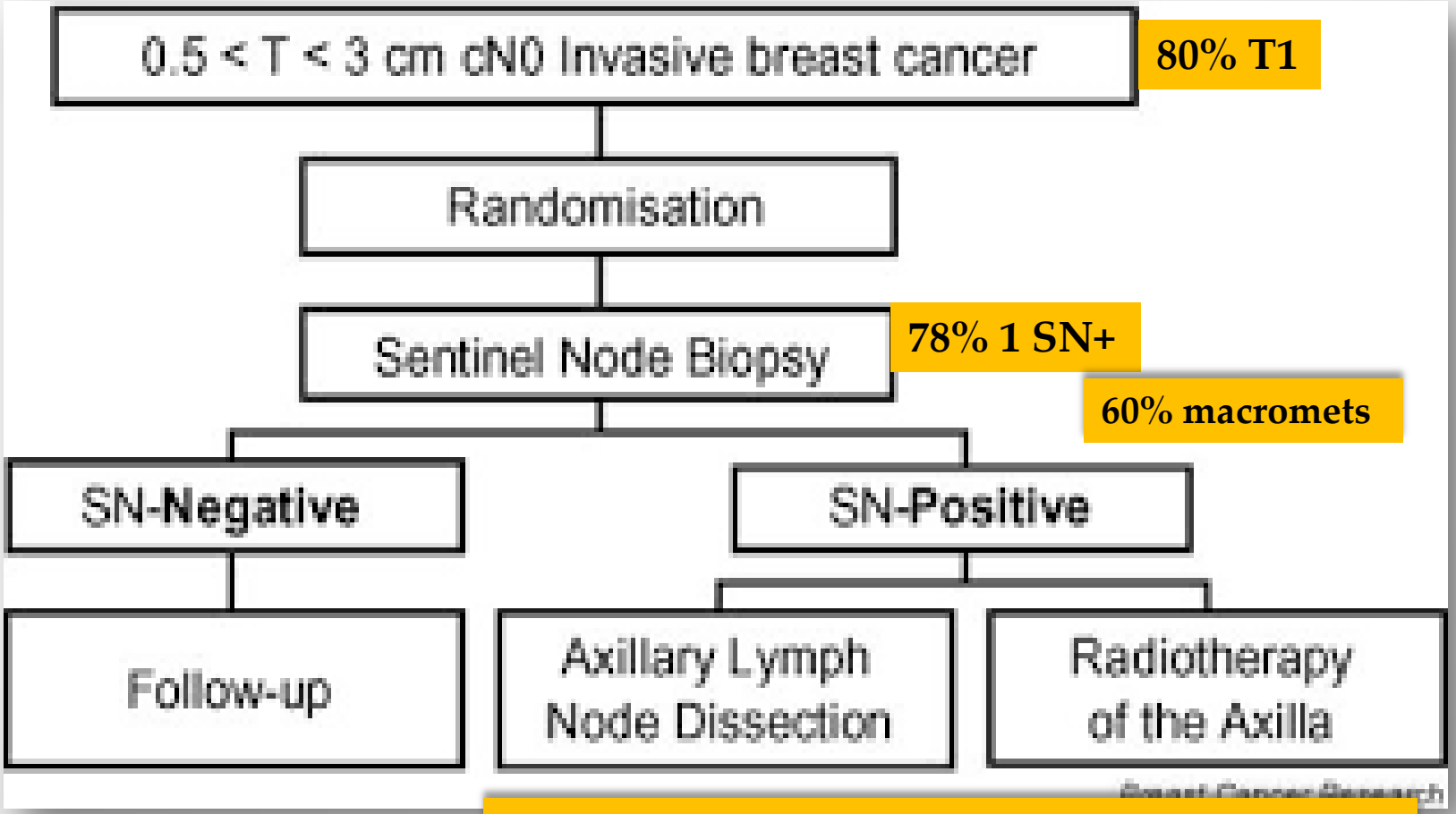
- cT1,2N0
- RE+, menopauză
- BCS
- tratam. sistemic adjuvant
- ***WBRT (+ baza axilei)***

- cN+
- EEC
- mastectomie
- APBI
- tratam. sistemic neoadjuvant

NCCN guidelines 2017

SNB+: radioterapia axilei sau limfadenectomie?

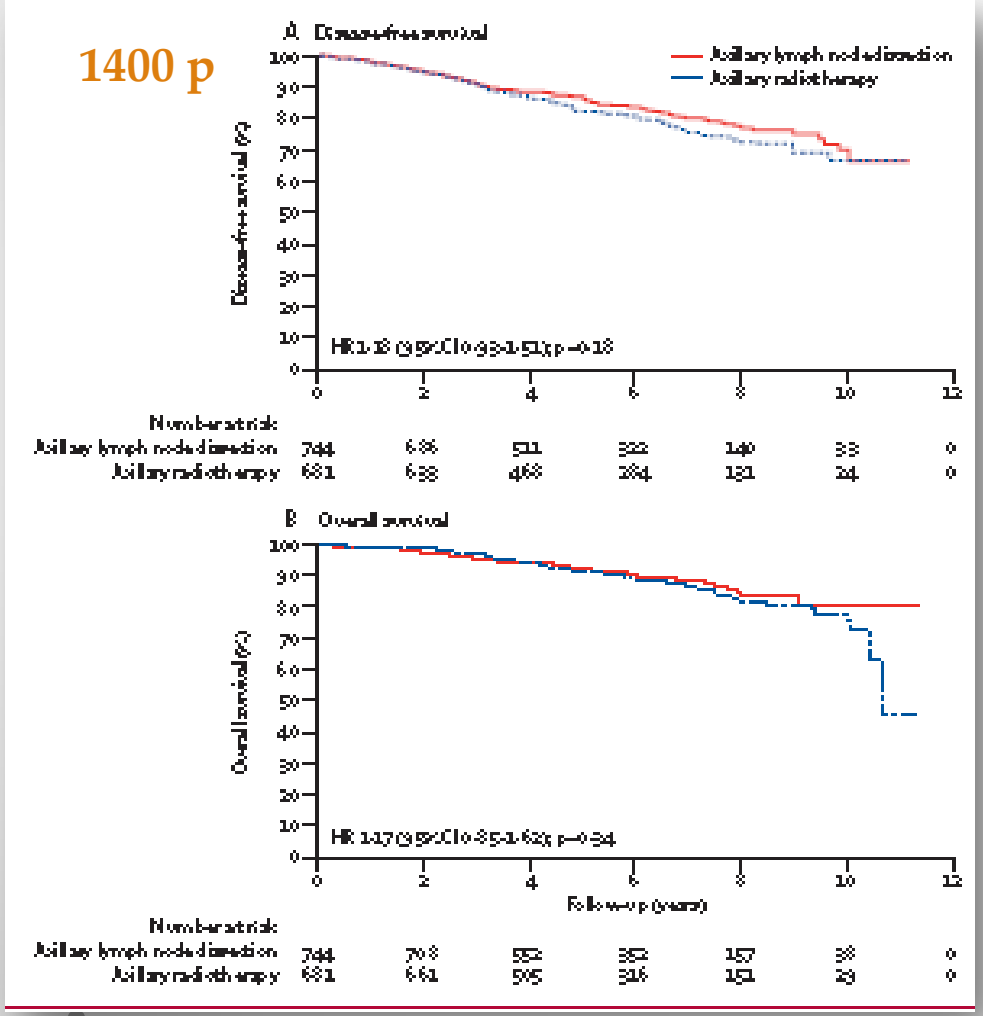
EORTC 10981-22023 AMAROS



60% menopauza, 80% T= 0.5-1.5cm, G I,II=76%

- Dunker M, et al., Lancet Oncol 2014;15:1303-10

AMAROS:
LA sau radioterapia axilei?



- urmărire mediană 6.1 ani
- fără diferențe semnificative în DFS/OS
- recidive axilare <1.5%
- fără beneficiu pt DMFS (doar 10% cu RT GMI)
- OS – separarea curbelor la 10 ani
  - efect diferit al controlului sistemic?
  - distributia factorilor prognostici moleculari?

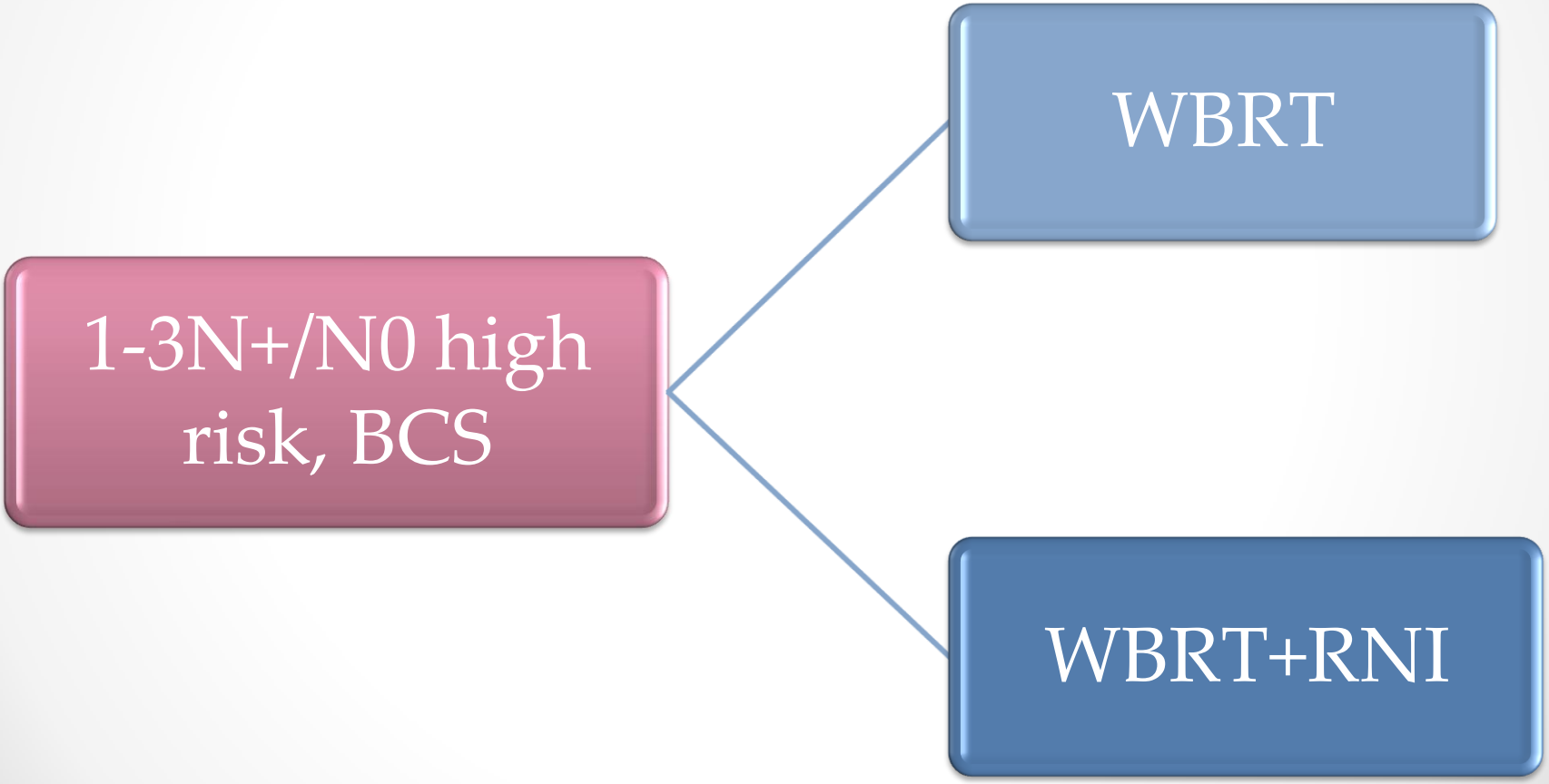
Caz 2

- 44 ani, cT2N0M0, st IIA, cadran intern, TN, sector+SNB, **pT1cN1snL1V0R0**, +2/3 SN+, 4.5 mm inv, fără EEC
- chimio

?

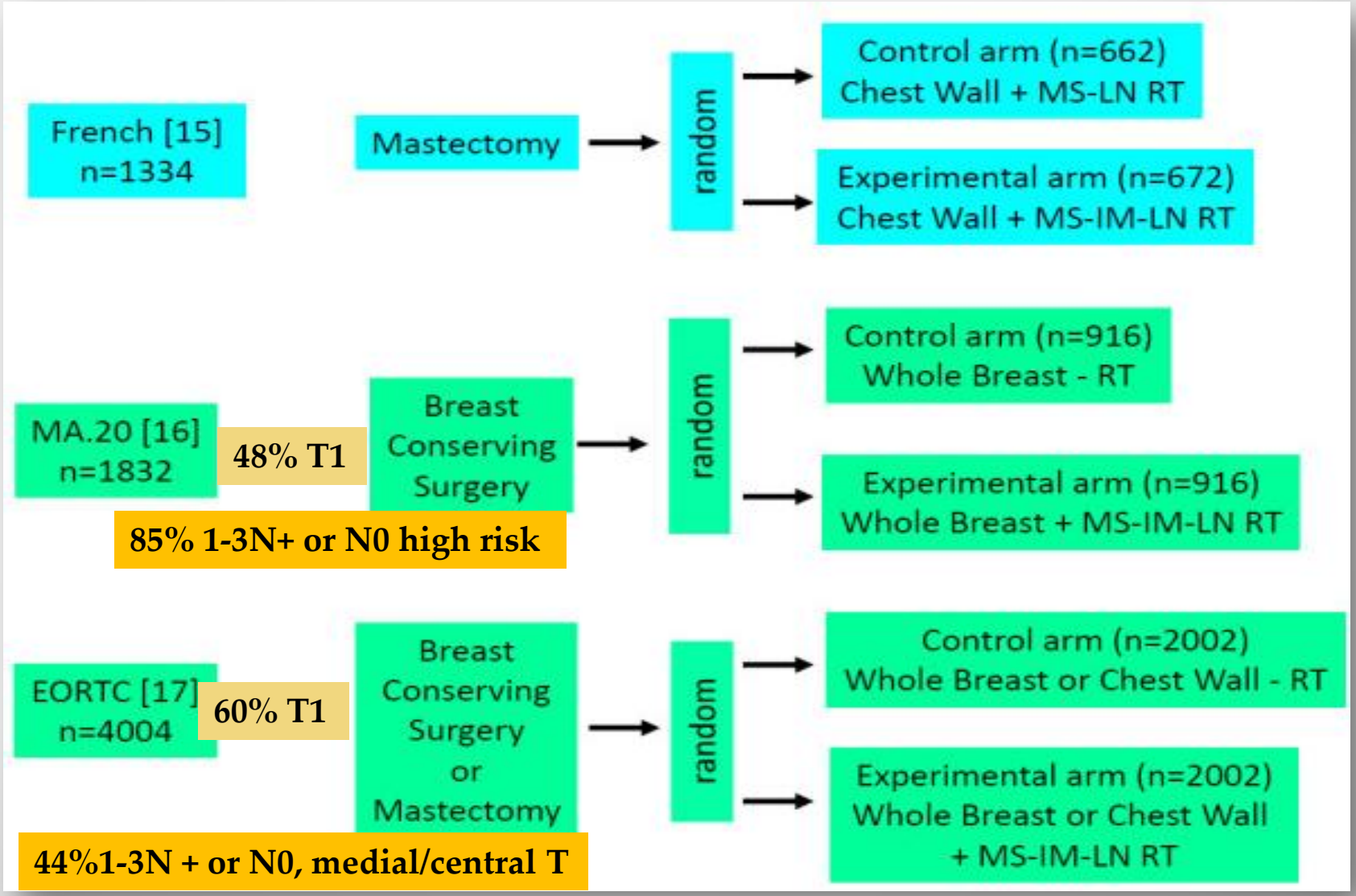
1. LA, WBRT
2. WBRT, fără RT bazei axilei
3. WBRT+ RT bazei axilei
4. WBRT+ GSC+axila III + GMI ± LA/RT bazei axilei

Regional RT (RNI)
NCIC-MA 20 WBRT ± RNI



- **Whelan et al, ASCO 2011**

RT adjuvantă a regiunilor ganglionare –metaanaliza

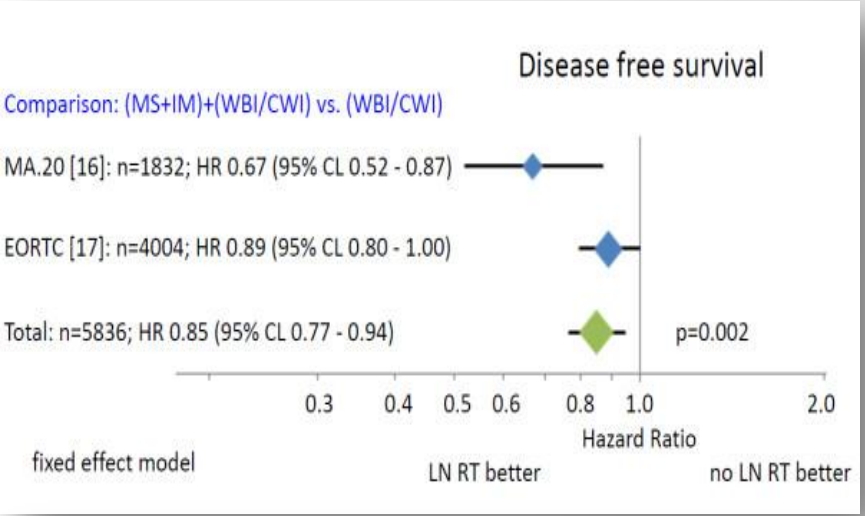


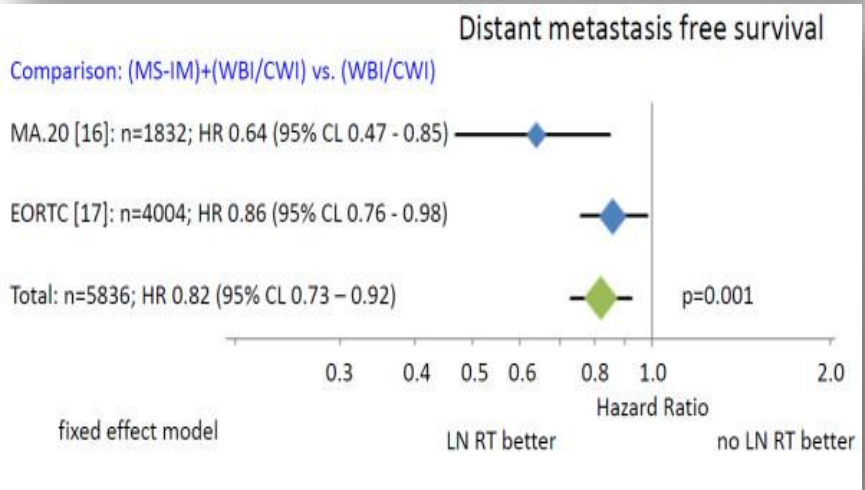
Budach W, Radiation Oncology 2013, 8:267

Radioterapia regiunilor ganglionare 👍

NCI Canada: **MA20 și EORTC 22922/10925**

- beneficiu în **DFS, DMFS și OS** pentru pacienții cu stadii I-III, 1-3 N+ și N0, risc înalt, pentru care s-a făcut iradierea sânului și a ariilor ganglionare *inclusiv* ***GMI***
- ! efect mai important la p. cu risc scăzut, dar cu tt. sistemic adjuvant
- toxicitate limitată





Budach W, Radiation Oncology 2013, 8:267

MA20 și EORTC 22922/10925 & implicații clinice

- toți pac. 1-3 N+ beneficiază de RNI, **GMI**?
  - 1-3N+ → risc GMI+ =20%
  - 4-6N+ → risc GMI+ =30-47%(Huang, 2008)

- cele 2 TR reprezintă pac. modern?
  (MA20 2000-2007, EORTC 1996-2004)
  - majoritatea pac. au avut LA
  - progrese tratam chirurgicale
    - tehnica SNB
    - secțiuni seriate SNB → +10-33% pac. cN0→ pN+ ; IHC: + 10-15% N+
  - progrese tratam. sistemice

- biologia tumorală neexplorată în cele 2 TR

Concluzii & RNI

- DFS10 ani
  - ↑ cu RNI
- DMFS10 ani
  - ↑ cu RNI
- OS10ani
  - tendință de îmbunătățire cu RNI
- breast cancer specific survival 10 ani
  - ↑ cu RNI
- efecte tardive10 ani cu RNI
  - pulmonare, cutanate
  - cele mai multe < gr 2
  - fără creșterea toxicității letale

Caz 1&2 → Stadiul II = heterogen

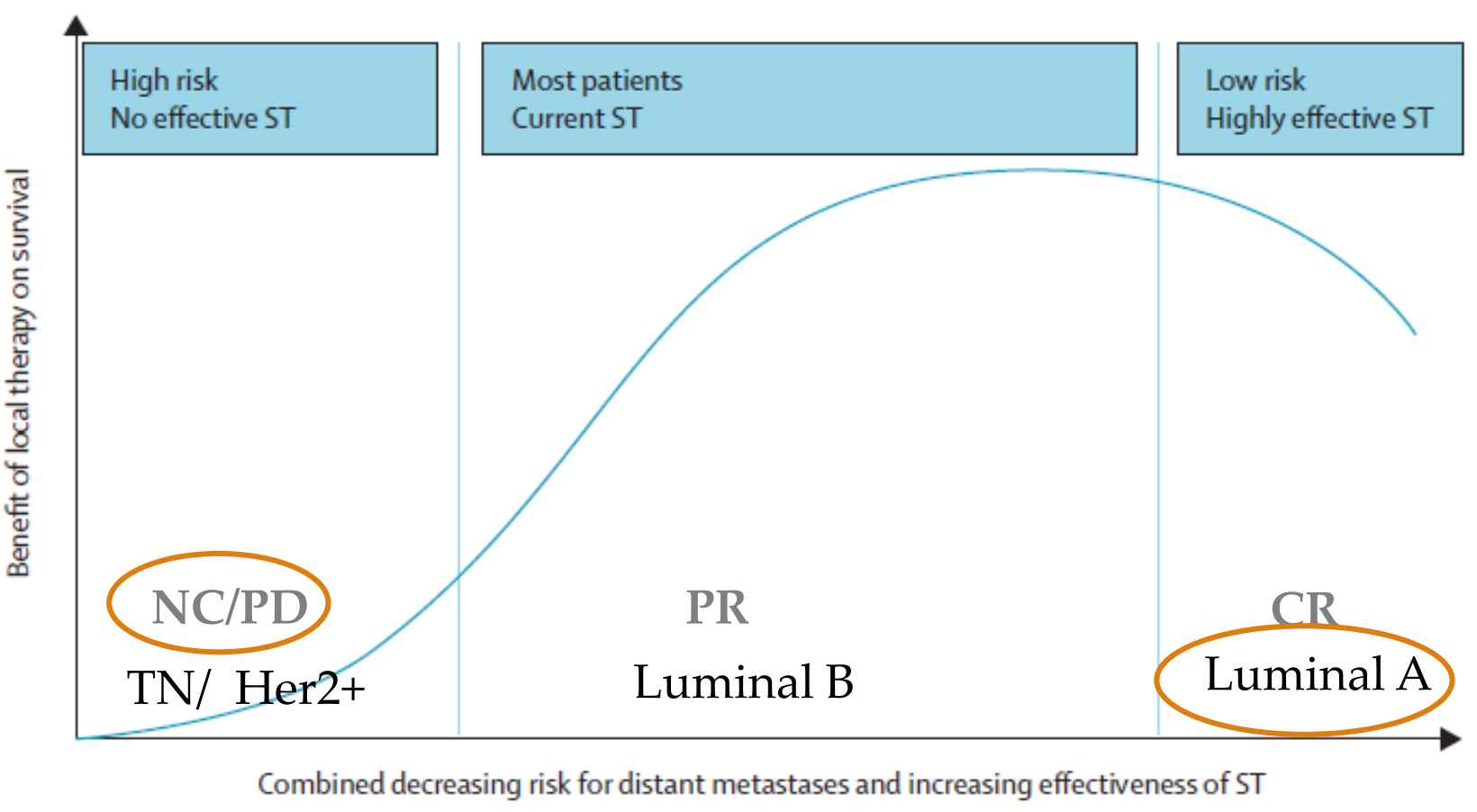
- prognostic favorabil
  - dg. screening, cN0, imagistic N0
  - Luminal A
  - SNB cu micromet sau ICT (volume ggl. mici metastatice)

WBRT± axila nivel I,II

- prognostic nefavorabil
  - cN1
  - TN
  - 3 N+ vs 1-2 SN+

WBRT+ RNI

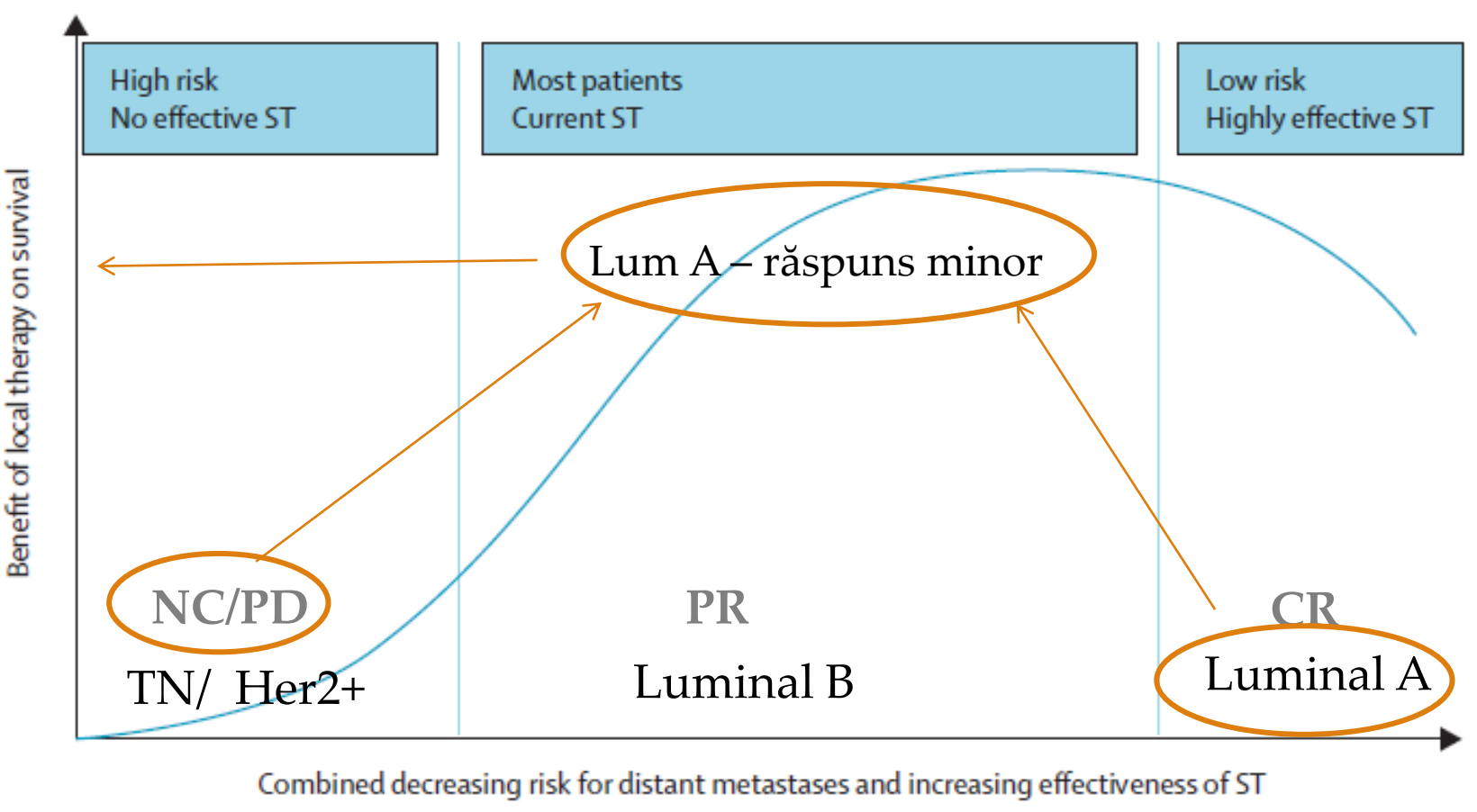
Interacțiunea tt. locale & tt. sistemice



Combined hypothetical benefit of local tumour control on survival with increasing effectiveness of systemic therapy (ST) and decreasing risk of distant metastases of the primary tumour

- **Poortmans P, Lancet 2014**

Interacțiunea tt. locale & tt. sistemice



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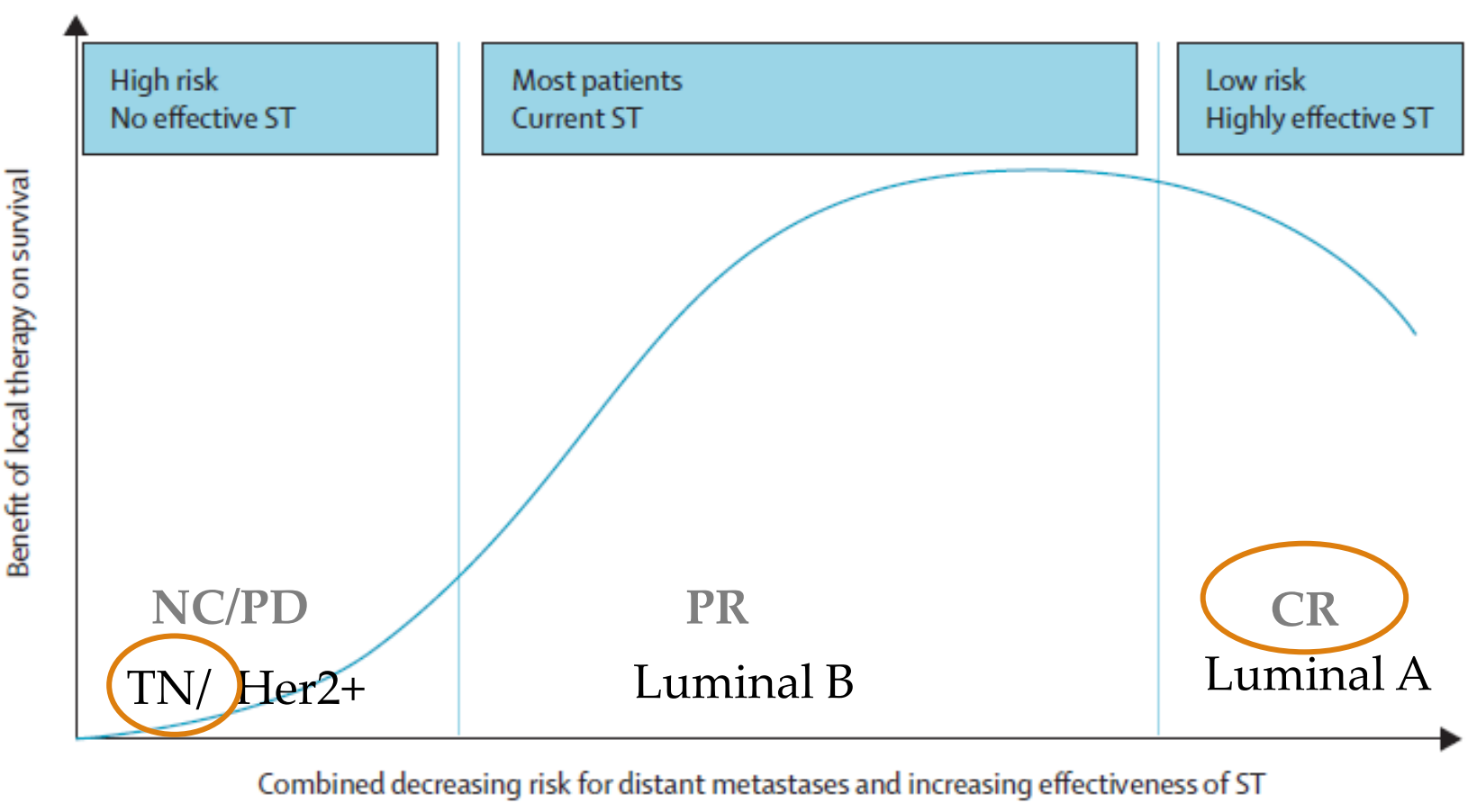

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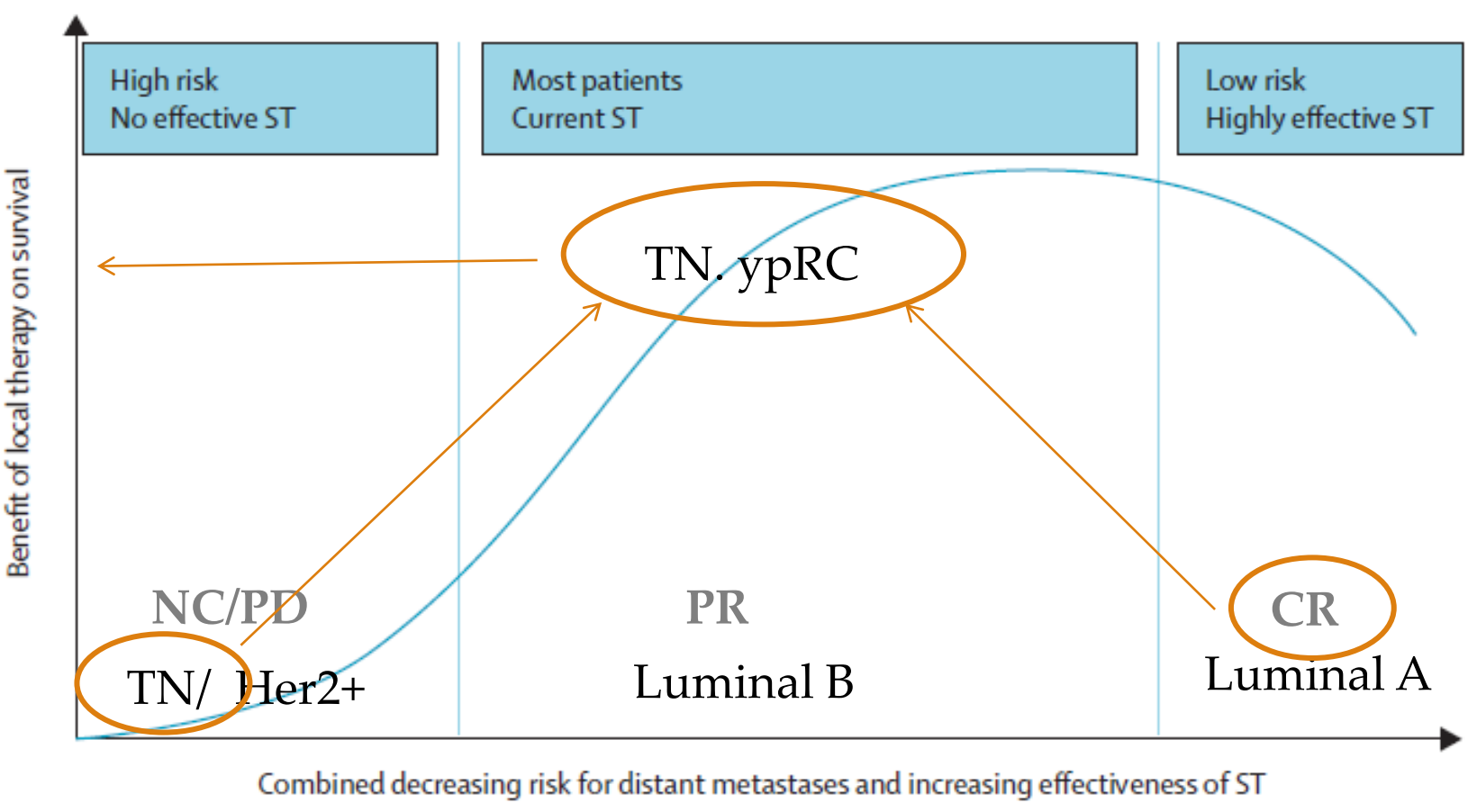

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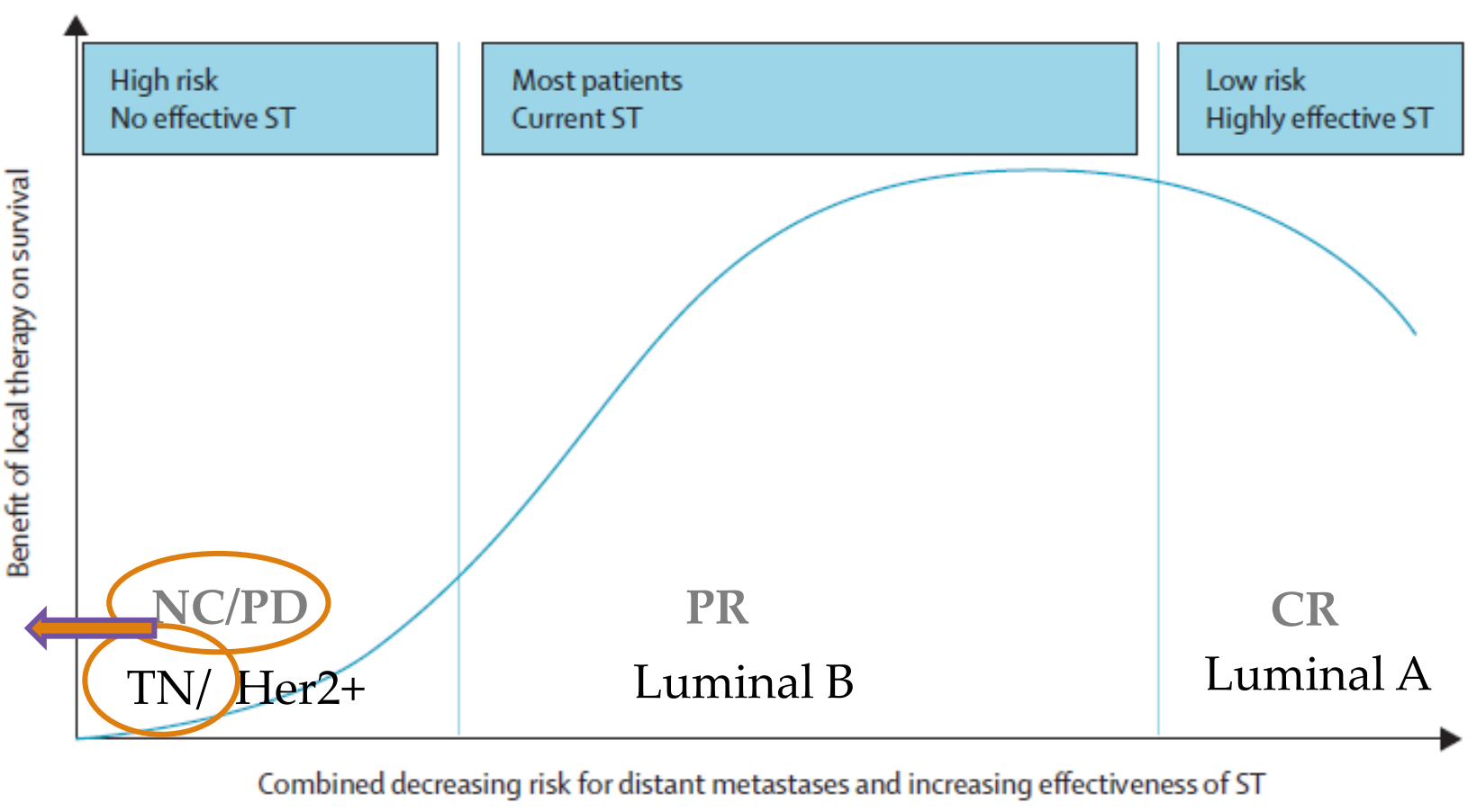

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- Poortmans P, Lancet 2014

RT & biologia tumorală

- Luminal A
  - radiosensibilitate înaltă
  - RRL scăzută
  - tip eșec: recidivă locală
  - trat.: hipofracționare, APBI, omiterea RT

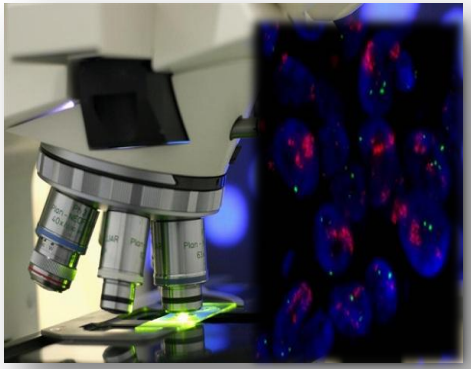
- Luminal B
  - radiosensibilitate intermediară
  - rata moderată a RRL
  - tip eșec: recidivă locală, regională
  - trat.: escaladarea D, RNI

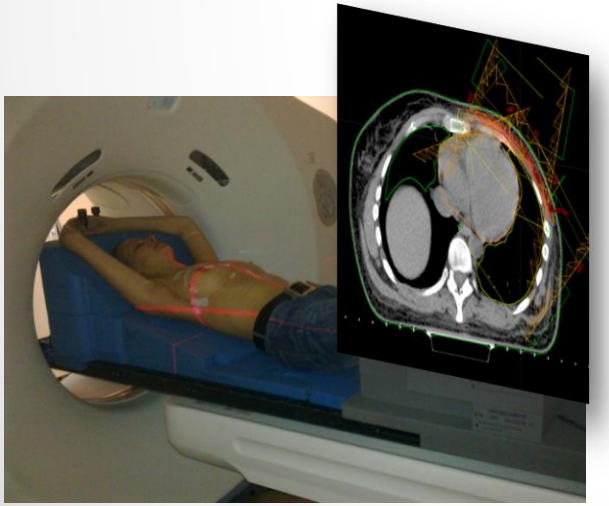
RT & biologia tumorală

- Her2+
  - radiosensibilitate scăzută
  - rata RRL: intermediară/ ridicată (post/preTranstuzumab)
  - tip eșec: recidivă locală, regională, la distanță
  - trat.: escaladarea D, RNI

- TN
  - radiosensibilitate foarte scăzută
  - rata RRL: ridicată
  - tip eșec: recidivă locală, regională, la distanță
  - trat.: escaladarea D, RNI, radiosensibilizatori, hipofracționare

Echipa multidisciplinară





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