

TUMORE DELLA MAMMELLA: ATTUALITA' IN RADIOTERAPIA

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**Focus sul rientro a screening mammografico dopo follow up
e aggiornamenti sul trattamento dei tumori mammari**
Webinar 30 marzo 2021

RT in early stage breast cancer: *Introduction*



RT in early stage breast cancer: *RT & BCT*

Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomised trials

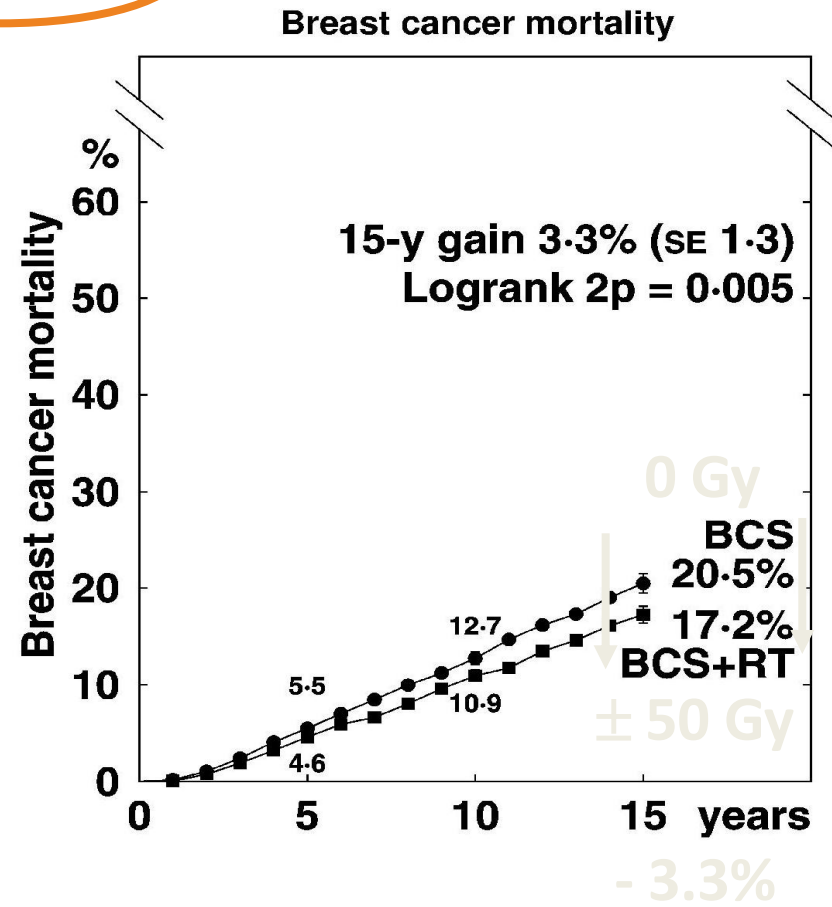
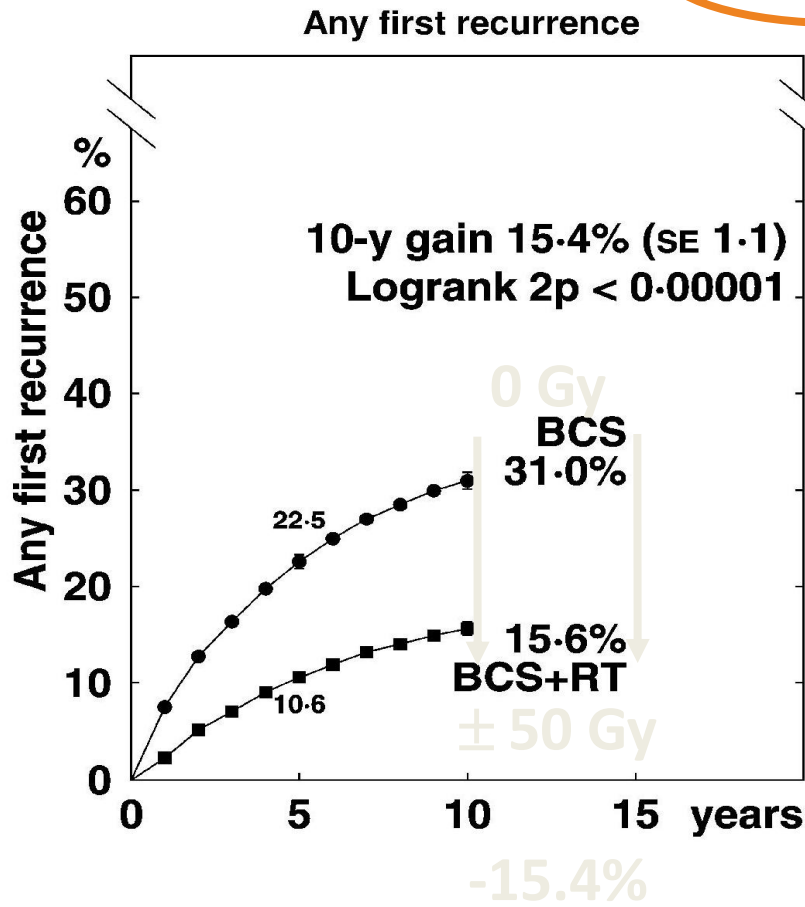
*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**

***Lancet* 2011; 378: 1707-16**

RT in early stage breast cancer: RT & BCT

Effect of RT after BCS on recurrence and breast cancer mortality in pN0 women.

7287 pN0 women



RT in early stage breast cancer:

BCT = standard for the majority of the pts

*BCT = surgery + RT: **which radiotherapy?***

RT in early stage breast cancer: *Introduction*

Side effects

Radiation therapy:

- Inconvenience
- Skin
- Breast tissue
- Pulmonary
- Heart
- Secondary tumours
- Contralateral breast:
more

21st C, only local RT:

- 7→5→3→1 weeks
- Lowered
- No boost in selected pts.
- Unlikely
- Unlikely
- Seldom
- Less for older pts/proper
techniques

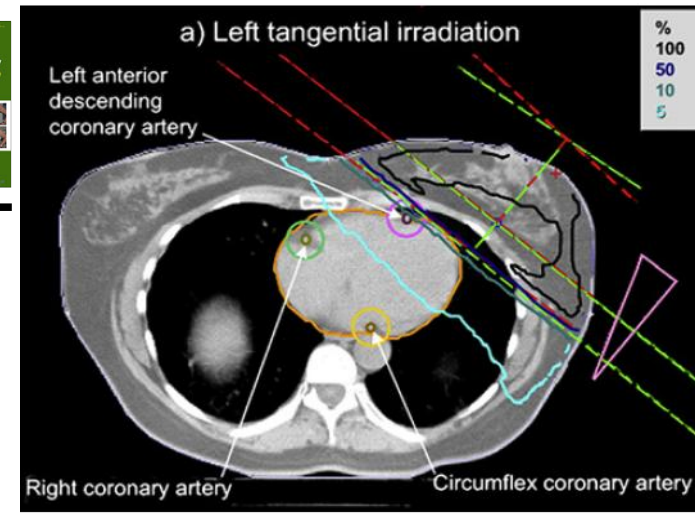
RT in early stage breast cancer: PBI

Radiotherapy and Oncology 94 (2010) 264–273

Contents lists available at ScienceDirect

Radiotherapy and Oncology

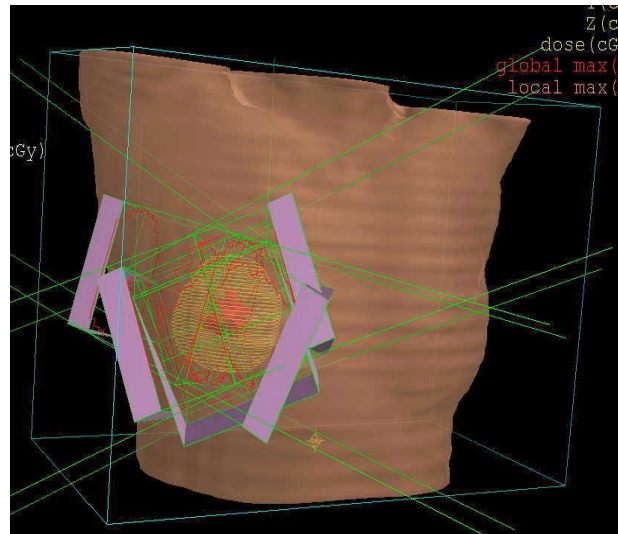
journal homepage: www.thegreenjournal.com



GEC-ESTRO Recommendations

Patient selection for accelerated partial-breast irradiation (APBI) after breast-conserving surgery: Recommendations of the Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) breast cancer working group based on clinical evidence (2009)

Csaba Polgár^{a,*}, Erik Van Limbergen^b, Richard Pötter^c, György Kovács^d, Alfredo Polo^e, Jaroslaw Lyczek^f, Guido Hildebrandt^g, Peter Niehoff^h, Jose Luis Guinotⁱ, Ferran Guedea^j, Bengt Johansson^k, Oliver J. Ott^l, Tibor Major^a, Vratislav Strnad^l, On behalf of the GEC-ESTRO breast cancer working group



Int. J. Radiation Oncology Biol. Phys., Vol. 74, No. 4, pp. 987–1001, 2009
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Printed in the USA.
0360-3016/09/\$—see front matter

doi:10.1016/j.ijrobp.2009.02.031

CONSENSUS STATEMENT

ACCELERATED PARTIAL BREAST IRRADIATION CONSENSUS STATEMENT FROM THE AMERICAN SOCIETY FOR RADIATION ONCOLOGY (ASTRO)

BENJAMIN D. SMITH, M.D.,^{*†} DOUGLAS W. ARTHUR, M.D.,[‡] THOMAS A. BUCHHOLZ, M.D.,[†]
BRUCE G. HAFFTY, M.D.,[§] CAROL A. HAHN, M.D.,^{||} PATRICIA H. HARDENBERGH, M.D.,[¶]
THOMAS B. JULIAN, M.D.,[#] LAWRENCE B. MARKS, M.D.,^{**} DORIN A. TODOR, PH.D.,[‡]
FRANK A. VICINI, M.D.,^{††} TIMOTHY J. WHELAN, M.D.,^{‡‡} JULIA WHITE, M.D.,^{§§} JENNIFER Y. WO, M.D.,^{|||}
AND JAY R. HARRIS, M.D.^{¶¶}

External beam accelerated partial breast irradiation versus whole breast irradiation after breast conserving surgery in women with ductal carcinoma in situ and node-negative breast cancer (RAPID): a randomised controlled trial

*Timothy J Whelan, Jim A Julian, Tanya S Berrang, Do-Hoon Kim, Isabelle Germain, Alan M Nichol, Mohamed Akra, Sophie Lavertu, Francois Germain, Anthony Fyles, Theresa Trotter, Francisco E Perera, Susan Balkwill, Susan Chafe, Thomas McGowan, Thierry Muanza, Wayne A Beckham, Boon H Chua, Chu Shu Gu, Mark N Levine, Ivo A Olivotto, for the RAPID Trial Investigators**

Lancet 2019; 394: 2165-72

DCIS or IDC < 2,5 cm, N0-N1mic

Post menopausal

Conservative surgery

1070 pts APBI

1065 pts WBI

	APBI	WBI
All patients		
n	1070	1065
Age at entry, years; median (IQR)	61 (54-68)	61 (54-68)
Histology		
Invasive disease	879 (82%)	875 (82%)
DCIS only	191 (18%)	190 (18%)
Tumour size		
<1.5 cm	758 (71%)	734 (69%)
≥1.5 cm	312 (29%)	331 (31%)
Patients with invasive disease		
n	879	875
Age at entry, years; median (IQR)	62 (55-68)	62 (54-68)
Tumour size		
<1.5 cm	613 (70%)	587 (67%)
≥1.5 cm	266 (30%)	288 (33%)
Oestrogen receptor		
Positive	803 (91%)	779 (89%)
Negative	76 (9%)	96 (11%)
Her2neu status		
Positive	56 (6%)	44 (5%)
Negative	794 (90%)	802 (92%)
Unknown	29 (3%)	29 (3%)

	APBI	WBI
Nodal status		
pN0	874 (99%)	865 (99%)
pN0(i+), pN1mi	5 (<1%)	10 (1%)
Nodal assessment		
Sentinel node biopsy	643 (73%)	651 (74%)
Axillary node dissection	229 (26%)	224 (26%)
Unknown	7 (1%)	0
Overall grade		
1	387 (44%)	362 (41%)
2	353 (40%)	361 (41%)
3	133 (15%)	143 (16%)
Unknown	6 (1%)	9 (1%)
Lymphovascular invasion		
Present	60 (7%)	51 (6%)
Not present	819 (93%)	824 (94%)
Adjuvant therapy		
Endocrine therapy	540 (61%)*	510 (58%)*
Chemotherapy	109 (12%)*	115 (13%)*
No adjuvant therapy	300 (34%)	319 (36%)

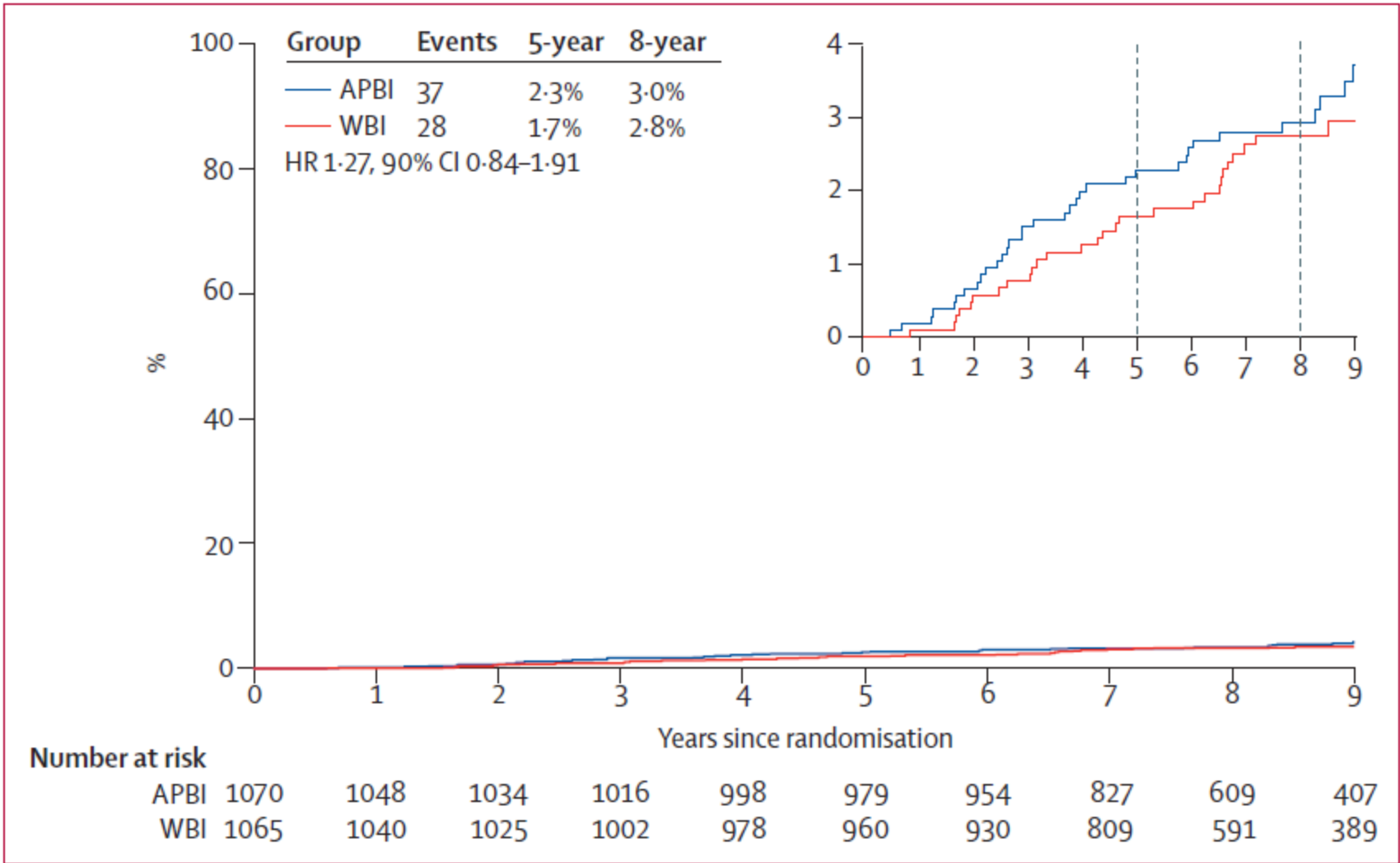


Figure 2: Rates of IBTR over time

Long-term primary results of accelerated partial breast irradiation after breast-conserving surgery for early-stage breast cancer: a randomised, phase 3, equivalence trial

Frank A Vicini, Reena S Cecchini, Julia R White, Douglas W Arthur, Thomas B Julian, Rachel A Rabinovitch, Robert R Kuske, Patricia A Ganz, David S Parda, Michael F Scheier, Kathryn A Winter, Soonmyung Paik, Henry M Kuerner, Laura A Vallow, Lori J Pierce, Eleftherios P Mamounas, Beryl McCormick, Joseph P Costantino, Harry D Bear, Isabelle Germain, Gregory Gustafson, Linda Grossheim, Ivy A Petersen, Richard S Hudes, Walter J Curran Jr, John L Bryant*, Norman Wolmark

Lancet 2019; 394: 2155-64

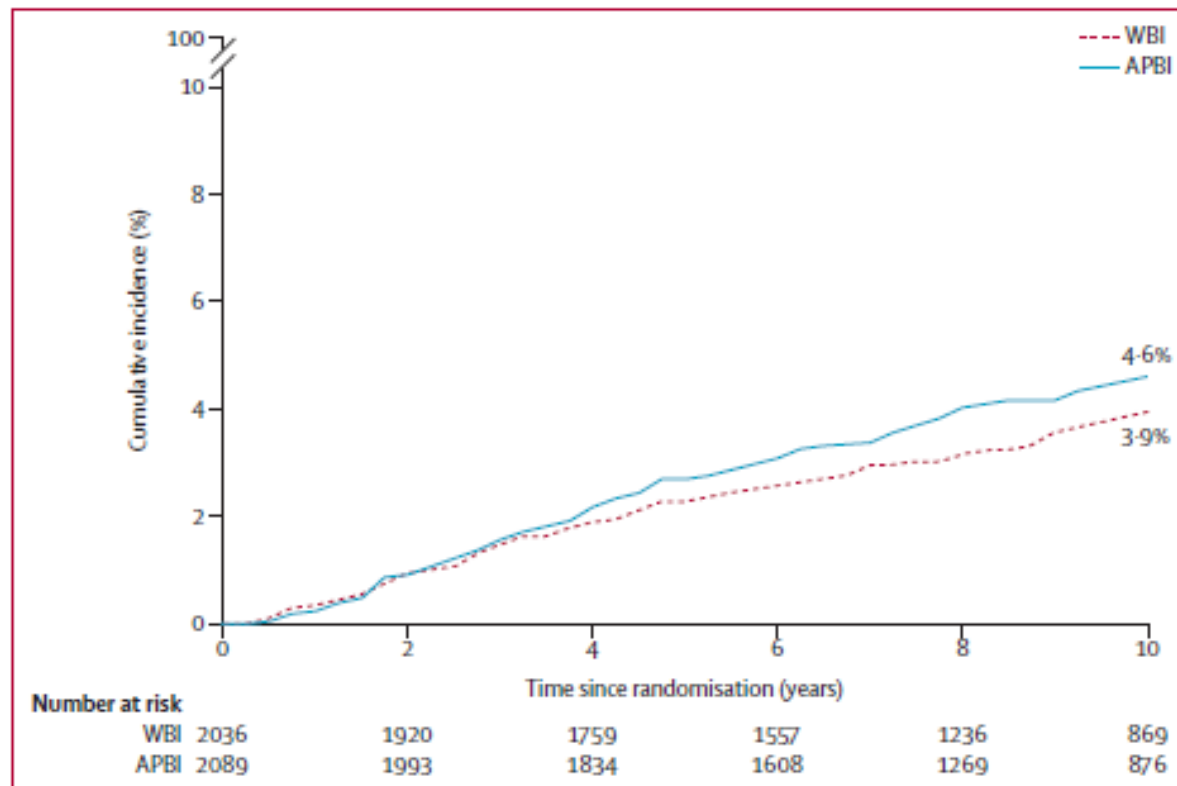
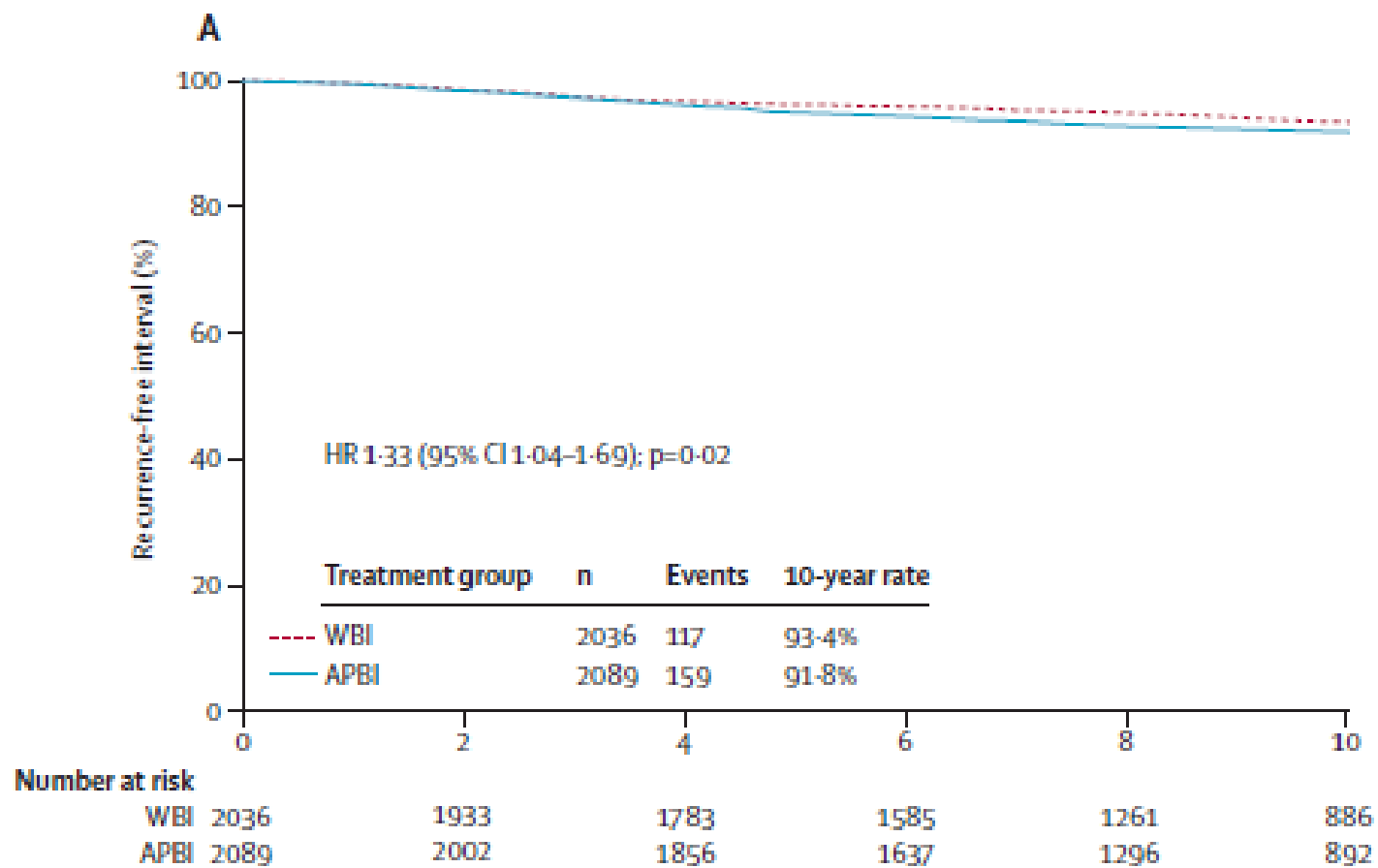
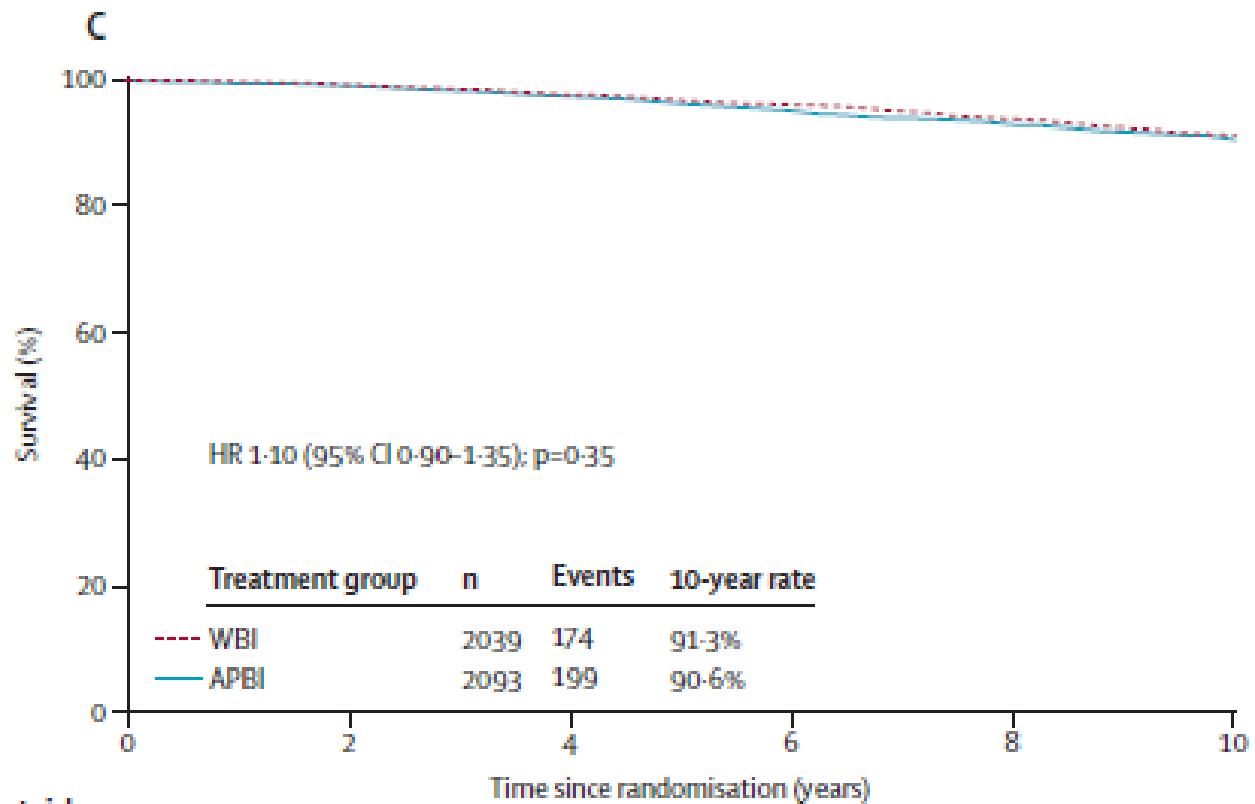


Figure 2: Cumulative incidence of in-breast tumour recurrence
APBI=accelerated partial breast irradiation. WBI=whole-breast irradiation.

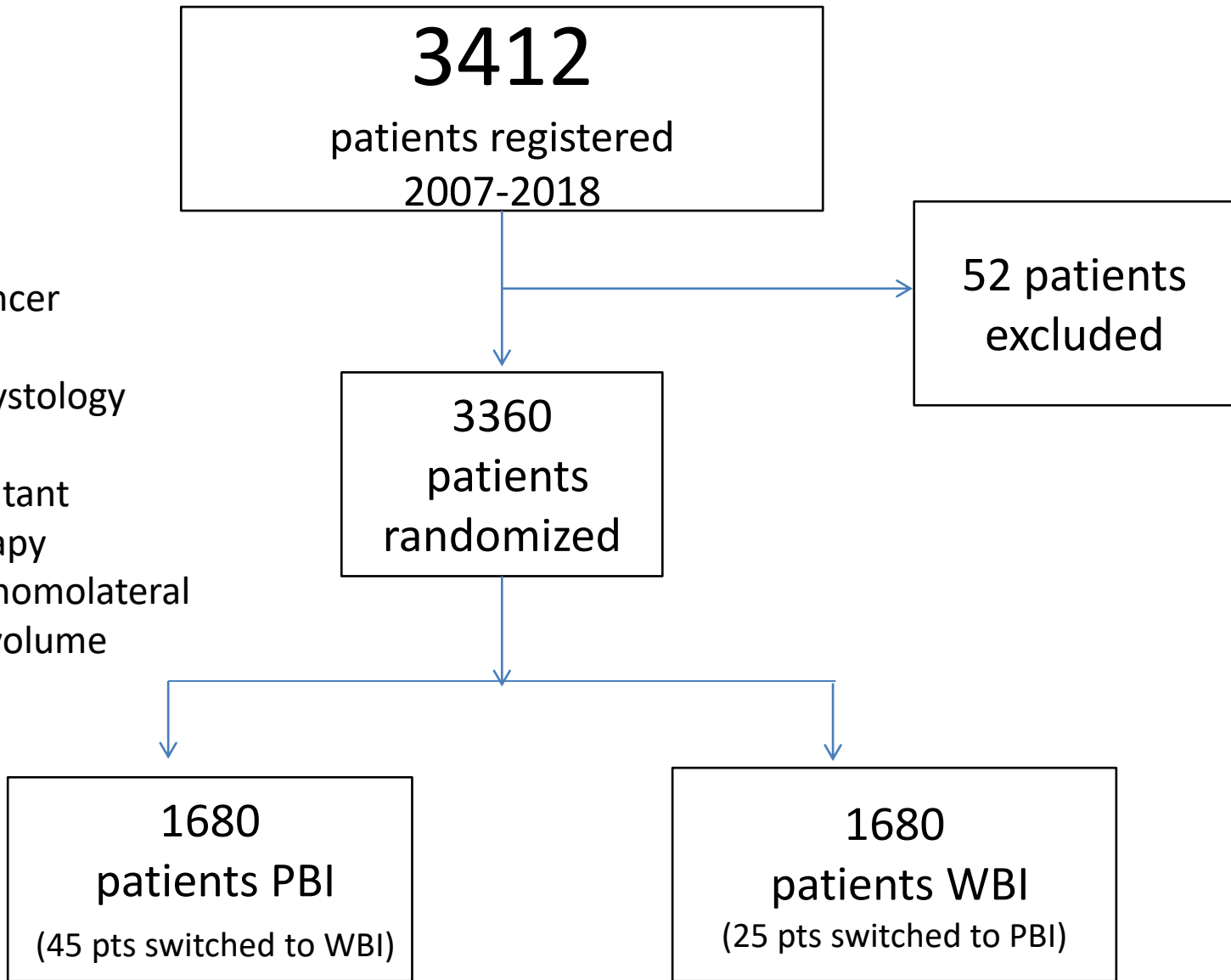




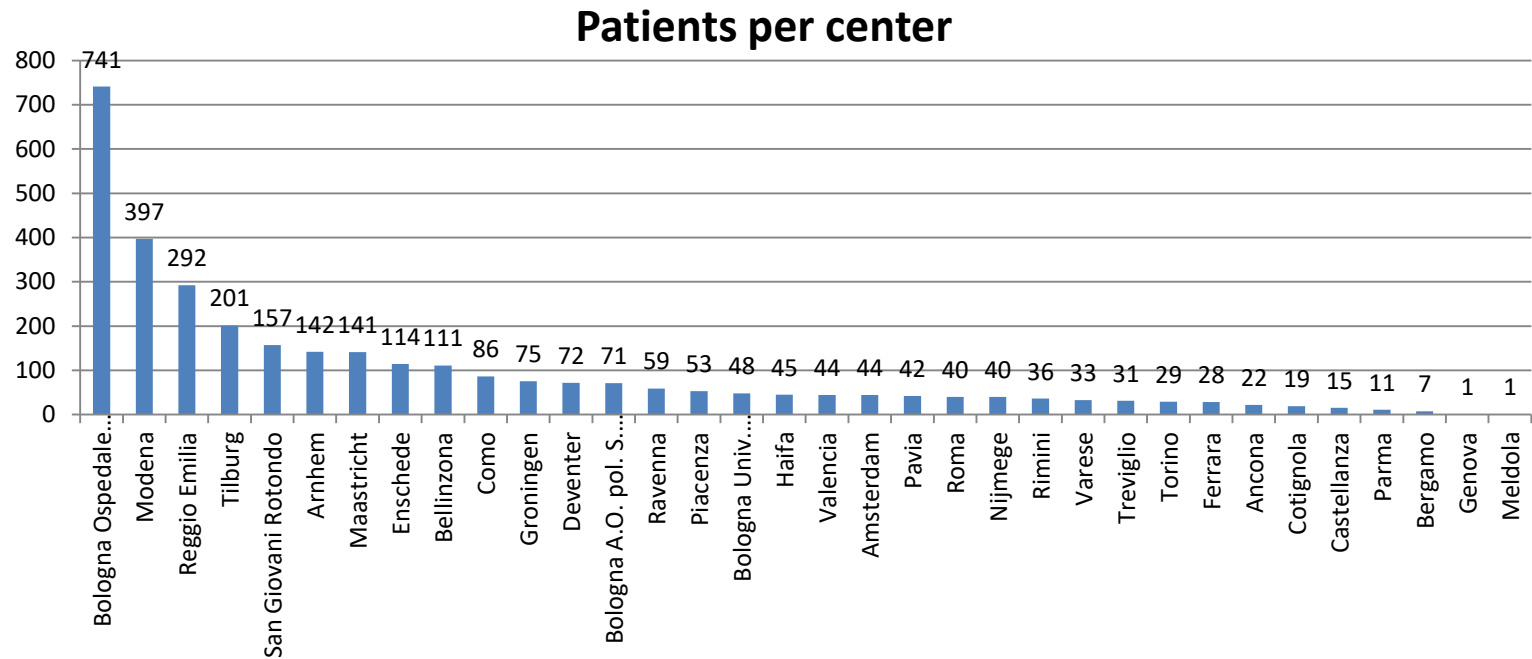
Number at risk		Time since randomisation (years)				
	0	2	4	6	8	10
WBI	2039	1977	1861	1682	1368	1010
APBI	2093	2040	1945	1762	1438	1027

IRMA TRIAL

Age > 49 ys
T = < 3 cms
Unifocal cancer
N0, N1
Epithelial hystology
No EDCIS
No concomitant
chemotherapy
CTV < 30% homolateral
mammary volume



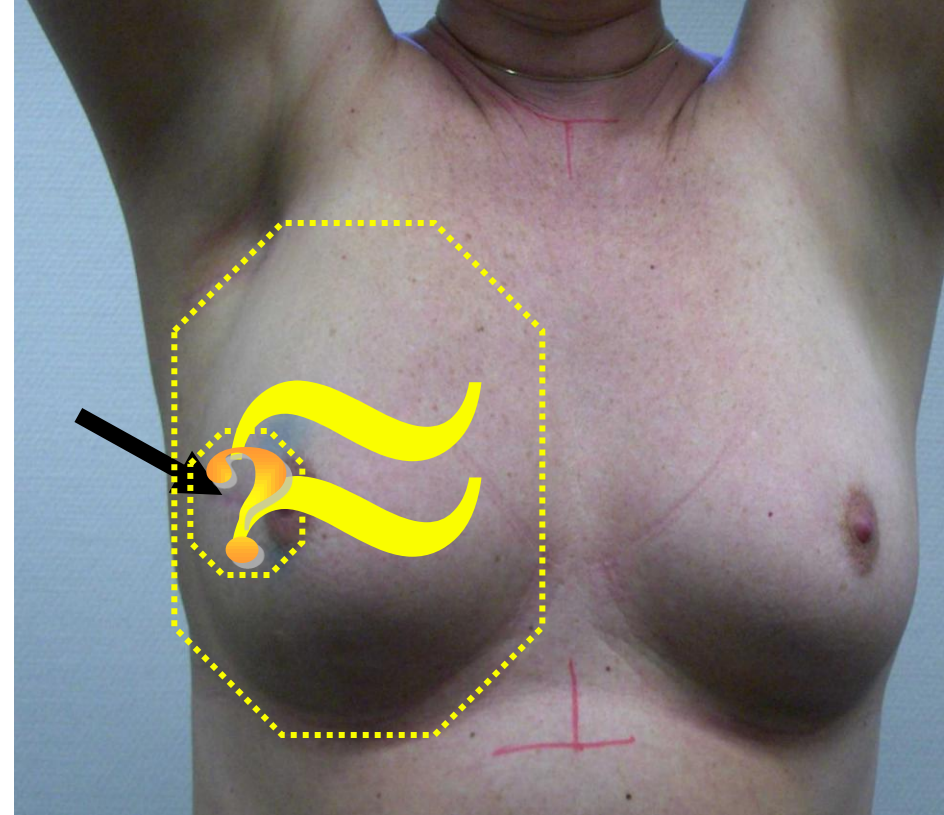
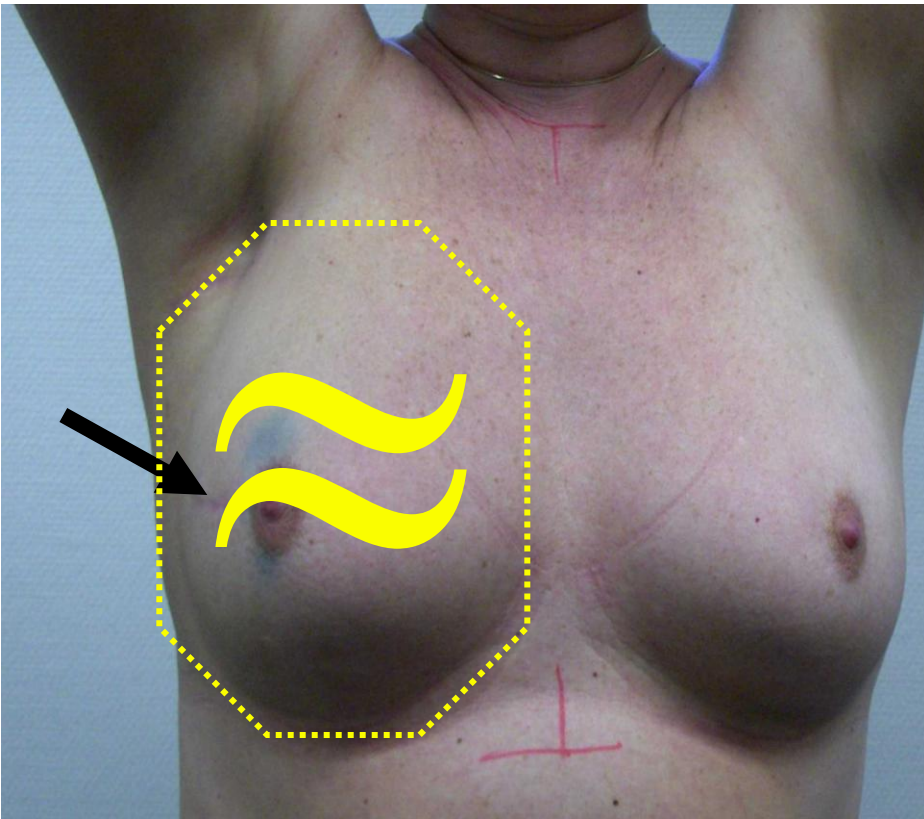
Enrollment- number of patients per center



RESULTS PENDING (late 2021)

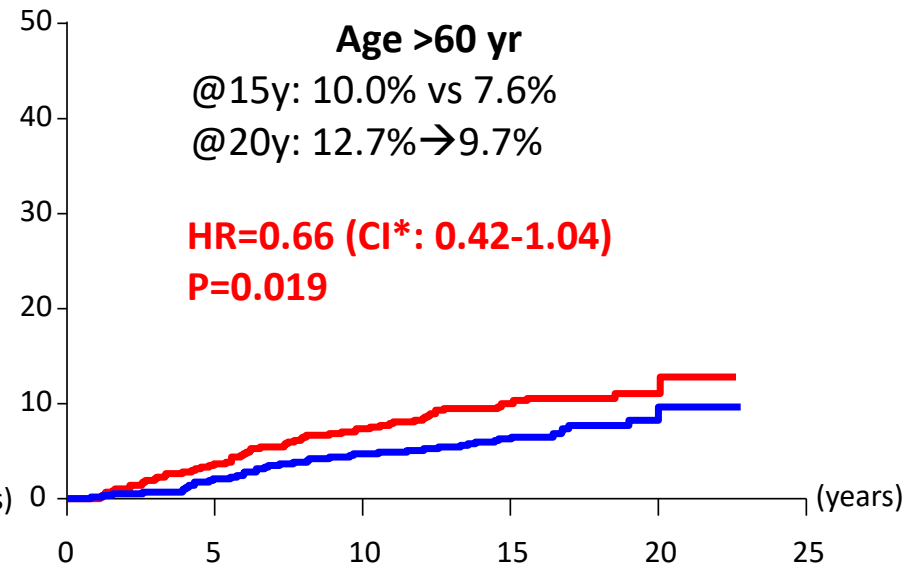
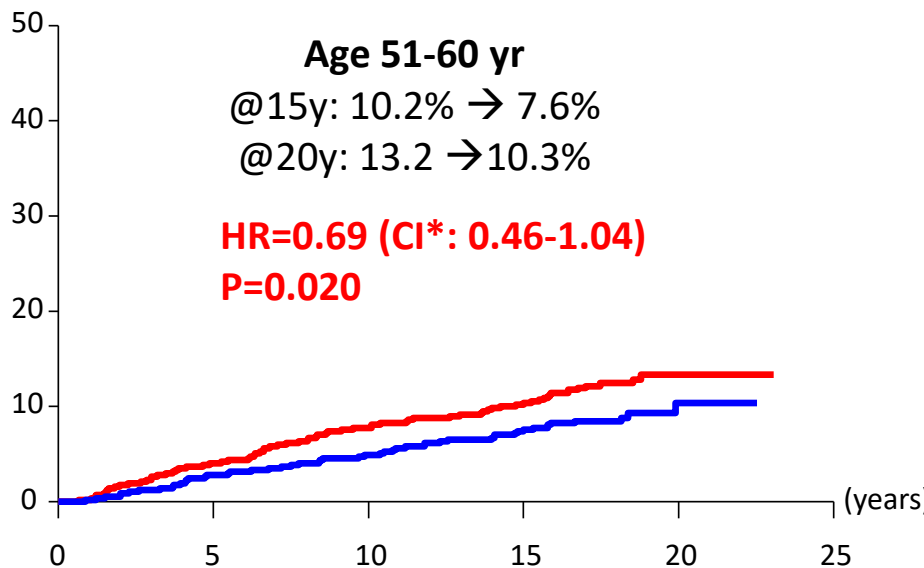
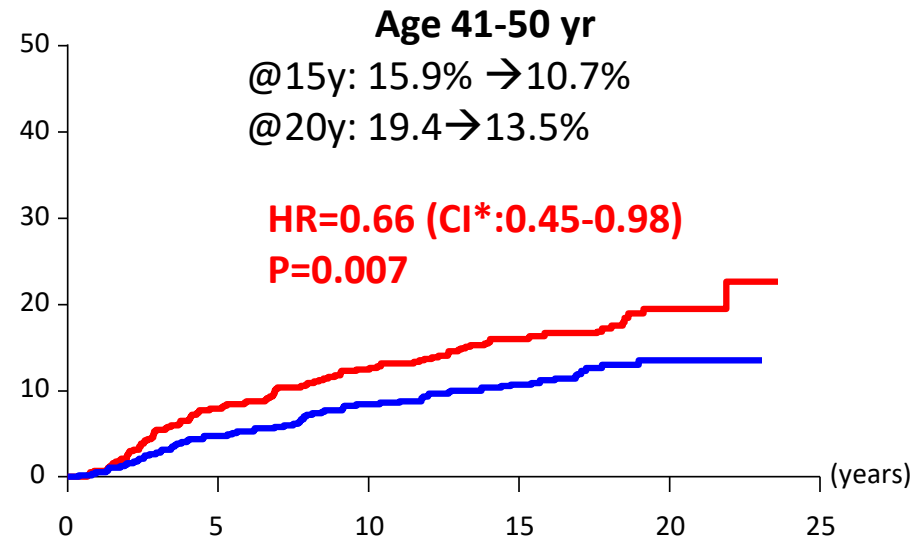
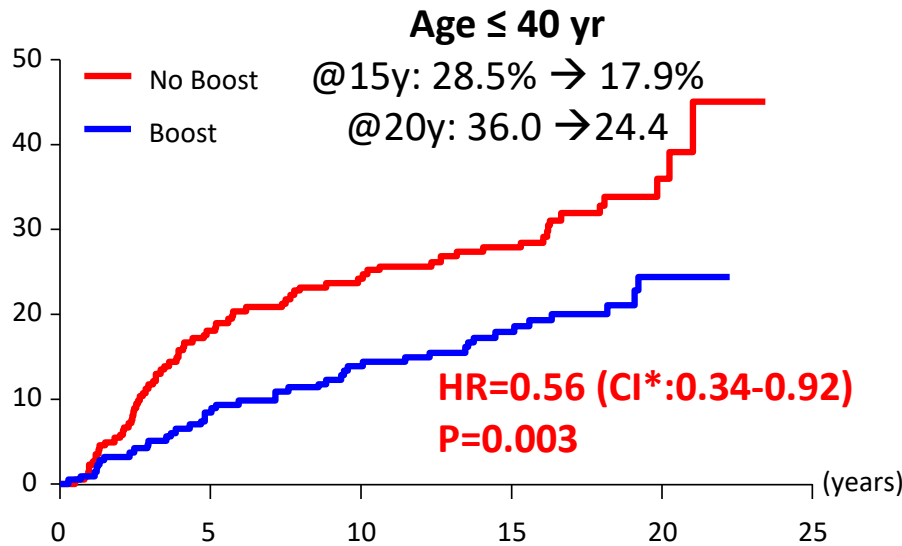
Breast conserving therapy: *boost*

EORTC 22881/10882 “boost no-boost trial”



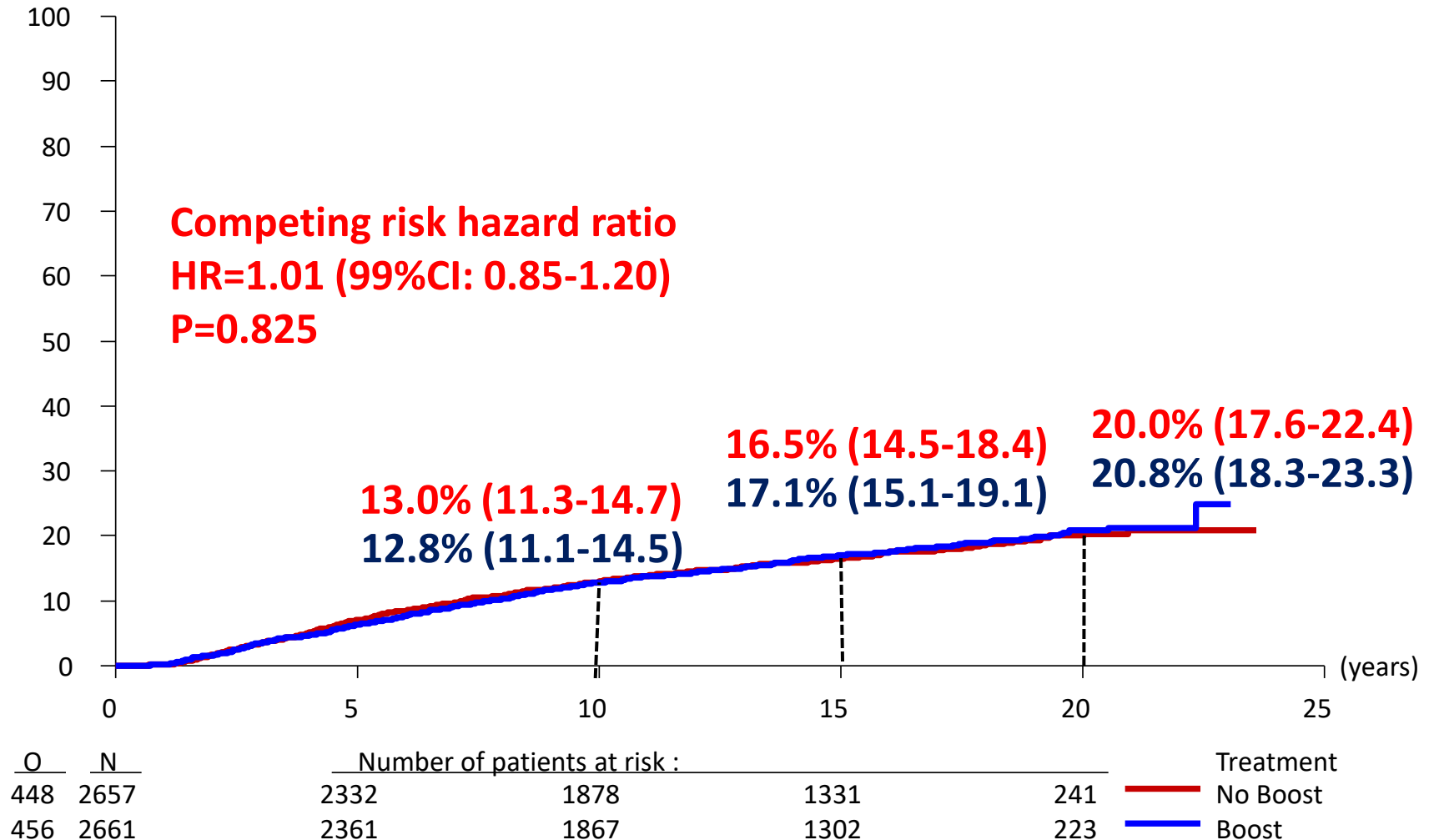
Endpoints: local control & cosmesis

Breast conserving therapy: *boost after 17.2 years*



Breast conserving therapy: *boost after 17.2 years*

Deaths due to breast cancer



Breast conserving therapy: *boost*

The trial → the boost:

- ✓ Reduces local recurrence rate by 35%
- ✓ This is seen in all age groups
- ✓ The absolute gain decreases with increasing age
- ✓ The salvage mastectomy rate reduces by 35%
- ✓ Cosmetic outcome is worse after a boost
- ✓ Severe fibrosis increased from 1.8% to 5.2%
- ✓ No other differences

RT in early stage breast cancer: *Surgery or RT?*

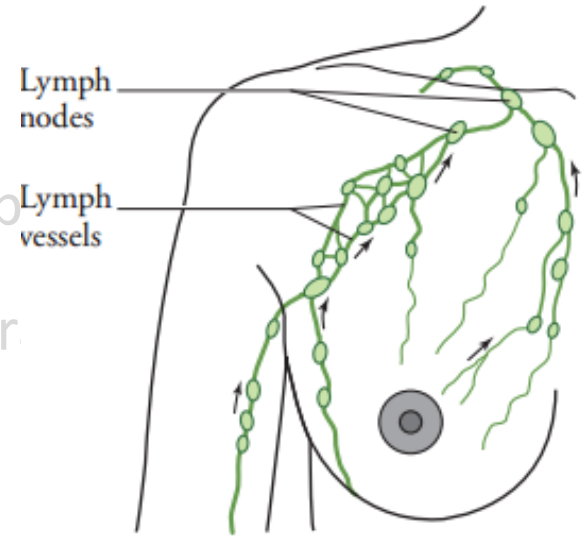
1. Introduction

- therapy in BCT
- The role of PMRT

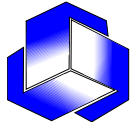
2. Interaction with other treatments

- Surgery or radiation therapy?
- Competition with systemic therapy
- The case of primary systemic therapy

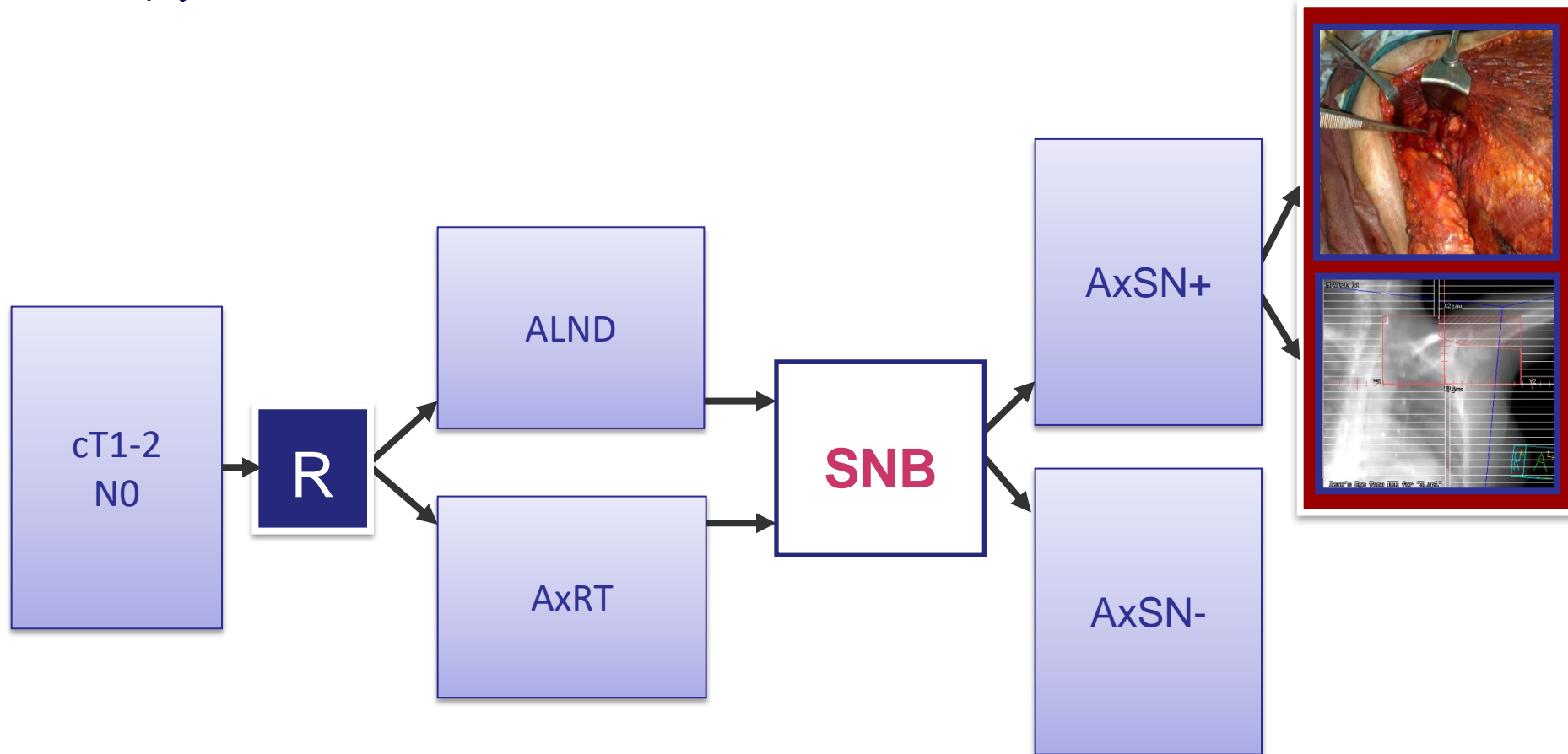
3. Discussion & Conclusions



RT in early stage breast cancer: *Surgery or RT?*



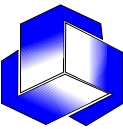
EORTC 10981-22023 "AMAROS"



Stratification: institution

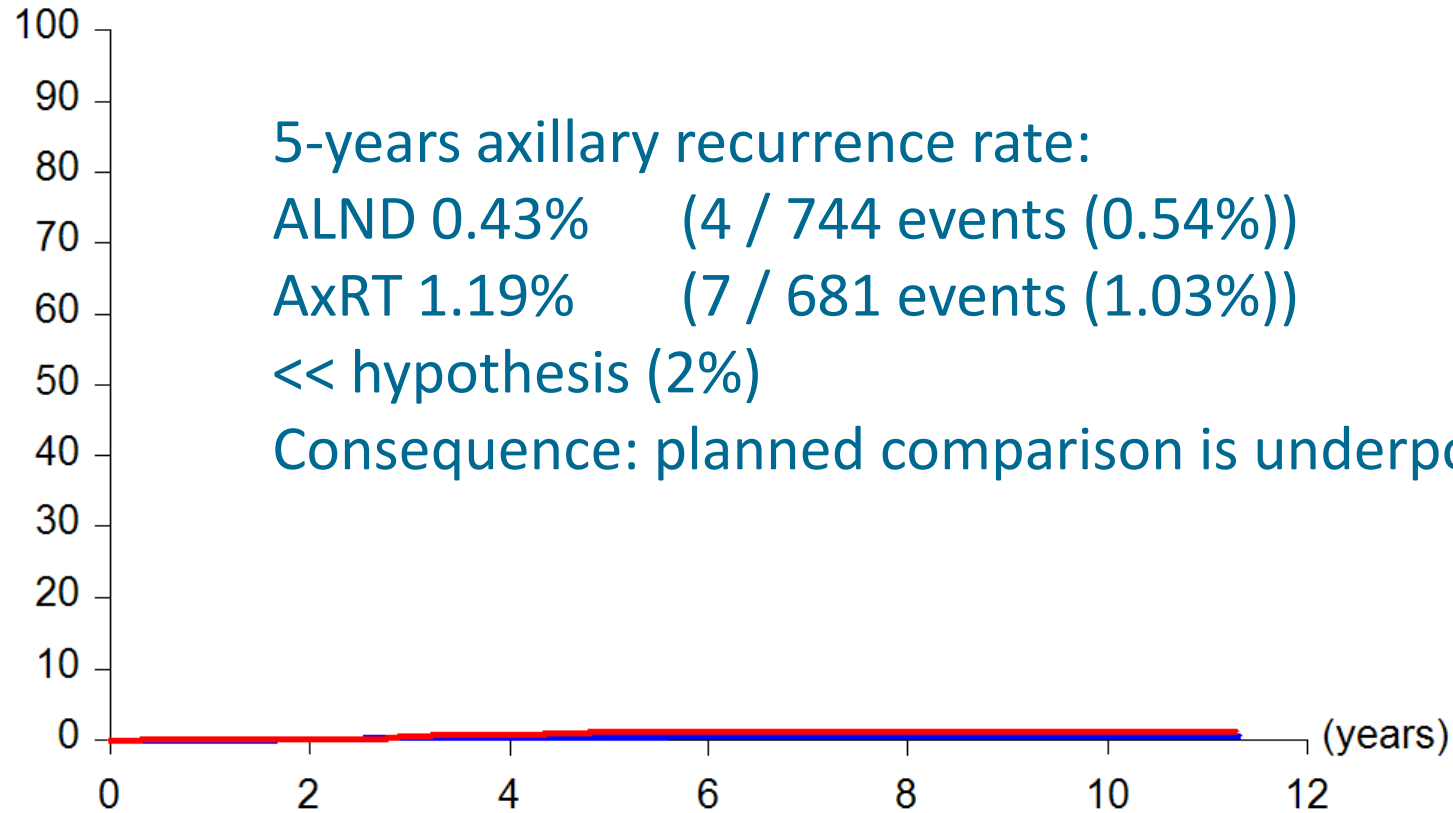
Adjuvant systemic therapy by choice

Regional treatment: *AMAROS: ALND vs. AxRT?*



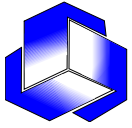
Cumulative Incidence of axillary recurrence

AxSN+ ITT

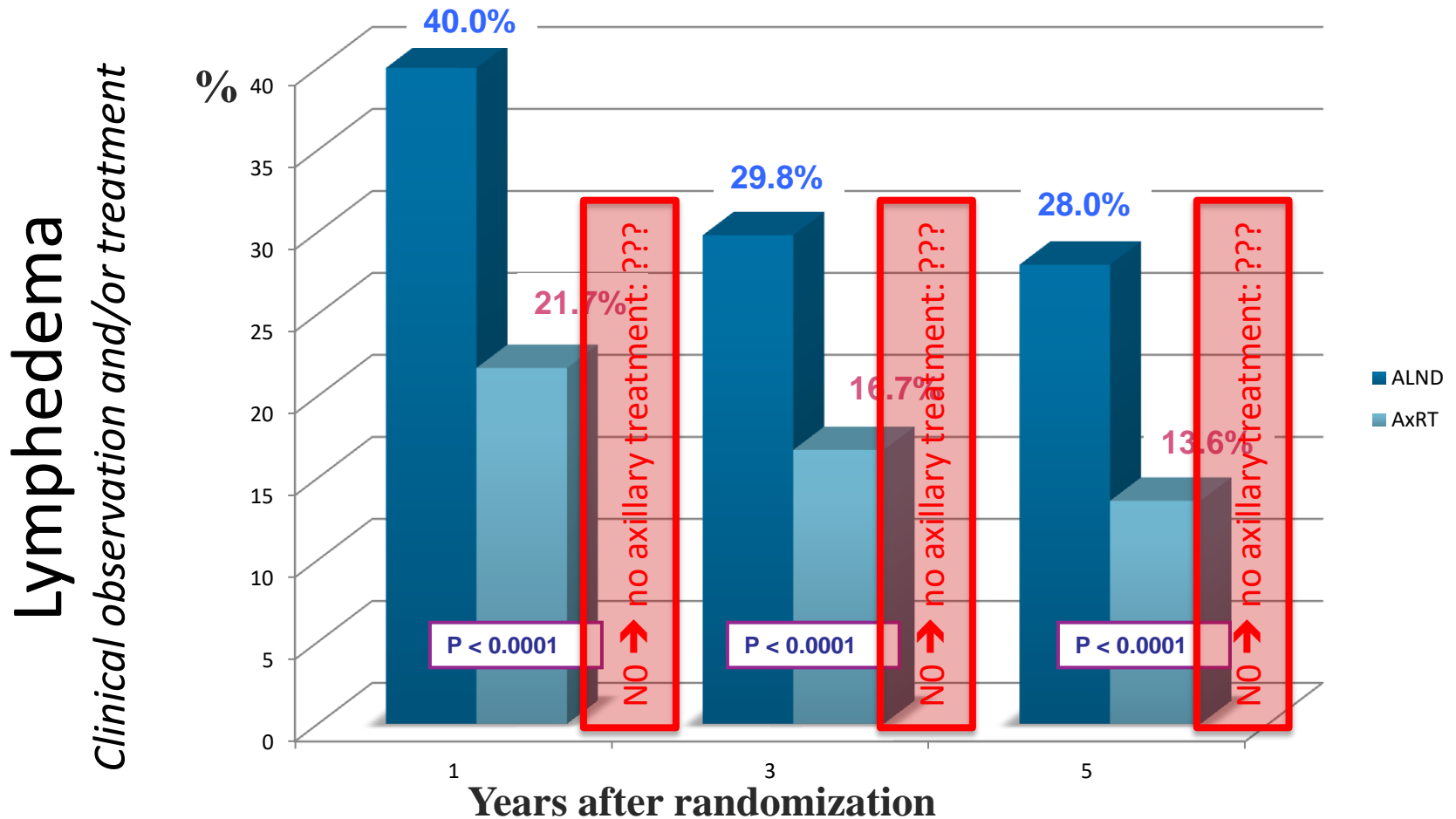


O	N	Number of patients at risk :					
4	744	707	550	349	156	38	— ALND
7	681	659	503	314	151	29	— AxRT

RT in early stage breast cancer: *Surgery or RT?*

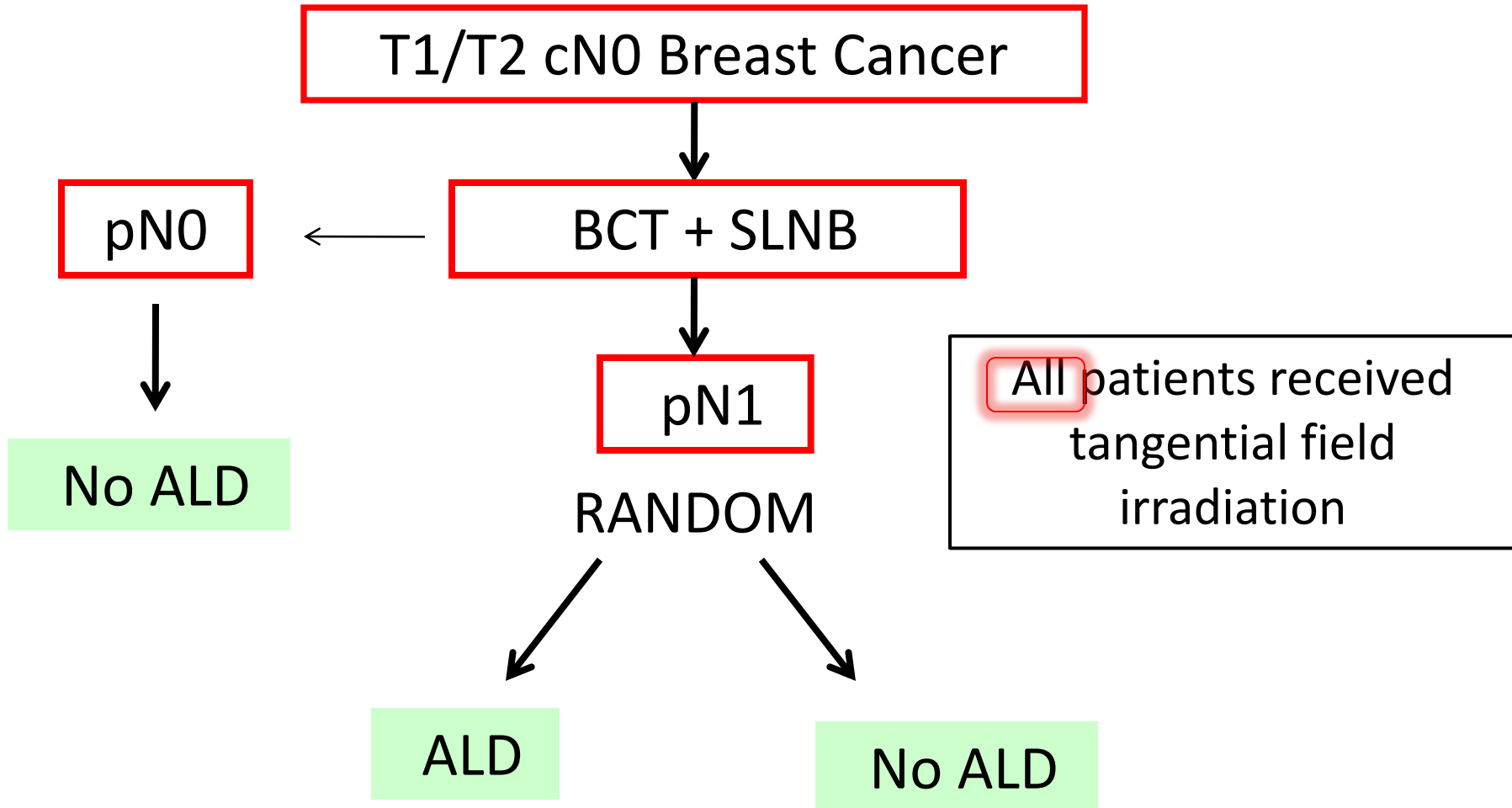


EORTC 10981-22023 "AMAROS"



RT in early stage breast cancer: *Surgery or RT?*

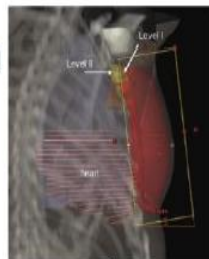
ACOSOG Z0011



Axillary Dissection vs No Axillary Dissection in Women With Invasive Breast Cancer and Sentinel Node Metastasis

A Randomized Clinical Trial

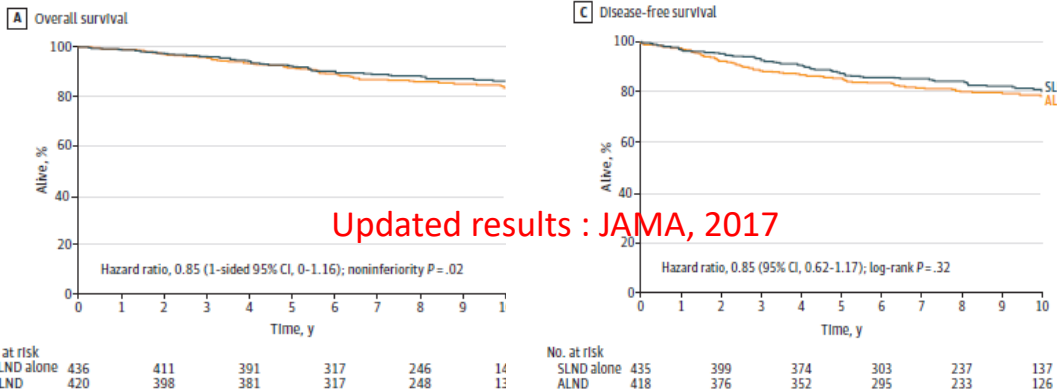
Giuliano, JAMA, 2011



Baseline Patient and Tumor Characteristics by Study Group

Characteristic	No. (%)	
	ALND (n = 420)	SLND Alone (n = 436)
Age, median (range), y	56 (24-92)	54 (25-90)
Missing	7	10
Clinical T stage		
T1	284 (67.9)	303 (70.6)
T2	134 (32.1)	126 (29.4)
Missing	2	7
Tumor size, median (range), cm	1.7 (0.4-7.0)	1.6 (0.0-5.0)
Missing	6	14
Receptor status		
ER+/PR+	256 (66.8)	270 (68.9)
ER+/PR-	61 (15.9)	54 (13.8)
ER-/PR+	3 (0.8)	4 (1.0)
ER-/PR-	63 (16.5)	64 (16.3)
Missing	37	44
LV		
Yes	129 (40.6)	113 (35.2)
No	189 (59.4)	208 (64.8)
Missing	102	115
Modified Bloom-Richardson score		
1	71 (22.0)	81 (25.6)
2	158 (48.9)	148 (46.8)
3	94 (29.1)	87 (27.5)
Missing	97	120

Figure 2. Survival of the ALND Group Compared With SLND-Along Group



Updated results : JAMA, 2017

ALND indicates axillary lymph node dissection; SLND, sentinel lymph node dissection.



biologia
sfavorevole

Conclusion Among patients with limited SLN metastatic breast cancer treated with breast conservation and systemic therapy, the use of SLND alone compared with ALND did not result in inferior survival.

RT in early stage breast cancer: *Omitting RT*

The Breast 31 (2017) 295–302



Contents lists available at [ScienceDirect](#)

The Breast

journal homepage: www.elsevier.com/brst



Original article

Over-irradiation

Philip M.P. Poortmans ^{a,*}, Meritxell Arenas ^b, Lorenzo Livi ^c



RT in early stage breast cancer: *RT & ST*

**Breast-Conservative Surgery With and Without Radiotherapy
in Patients Aged 55–75 Years With Early-Stage Breast Cancer:
A Prospective, Randomized, Multicenter Trial Analysis After 108
Months of Median Follow-up**

N = 749

C. Tinterri, MD¹, W. Gatzemeier, MD¹, A. Costa, MD², M. A. Gentilini, PhD³, V. Zanini, MD⁴, L. Regolo, MD⁴,
C. Pedrazzoli, MD⁵, E. Rondini, MD⁵, C. Amanti, MD⁶, G. Gentile, MD⁷, M. Taffurelli, MD⁸, P. Fenaroli, MD⁹,
C. Tondini, MD⁹, G. Sacchetto, MD¹⁰, P. Sismondi, MD¹¹, R. Murgo, MD¹², M. Orlandi, MD¹³, E. Cianchetti, MD¹⁴,
and C. Andreoli, MD¹

Unifocal; infiltrating; ≤ 25 mm; N0-1a; no EIC; no (L)VI

96.5% adjuvant systemic treatment:

- 81.3% HT
- 9.5% ChT
- 5.7% both

RT in early stage breast cancer: *RT & ST*

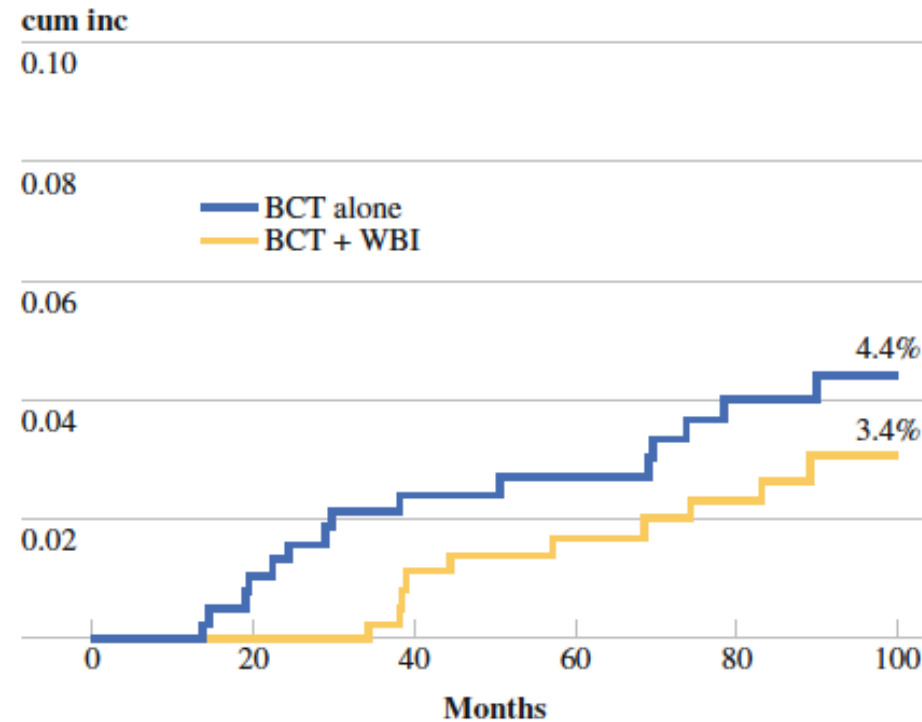


FIG. 1 Nine-year cumulative incidence of in-breast recurrence

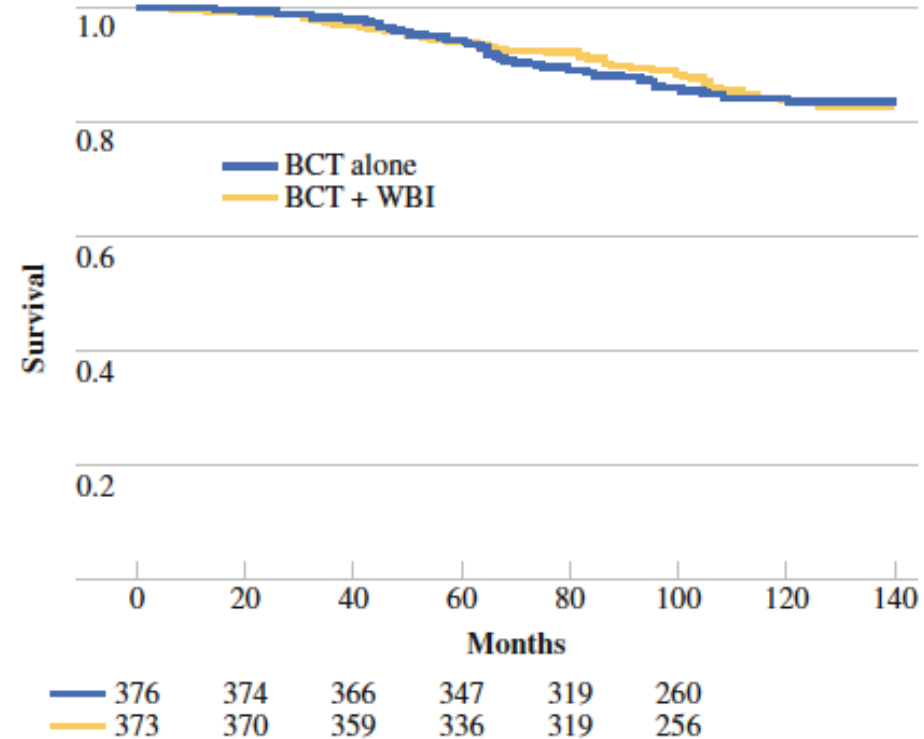


FIG. 2 Overall Survival (108 months)

RT in early stage breast cancer: *RT & ST*

Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial

Ian H Kunkler, Linda J Williams, Wilma J L Jack, David A Cameron, J Michael Dixon, on behalf of the PRIME II investigators

N = 1326; age \geq 65 y

Invasive BC; < 30 mm; N0; ER+; low risk

All had adjuvant endocrine therapy

RT in early stage breast cancer: *RT & ST*

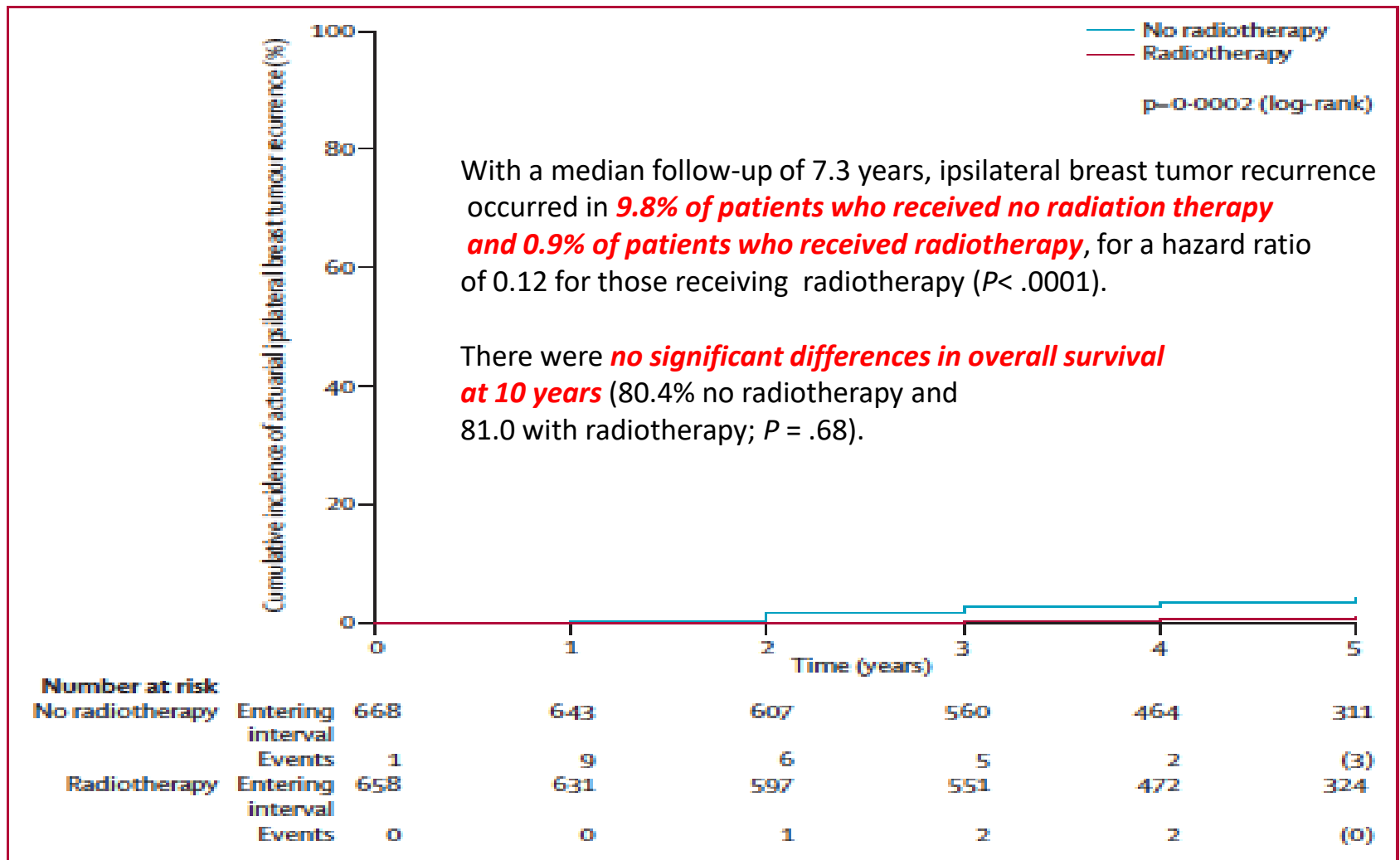


Figure 2: Time to actuarial ipsilateral breast tumour recurrence

RT in early stage breast cancer: *RT & ST*

RT after tumorectomy: not always required?

- 0.5% (1% still acceptable?) per year = limit for LRR
- Mind late relapses!
- Role of systemic treatment?

RT in early stage breast cancer: *Omitting HT*

Stage (all 65y;N0;ER+;Her-)	Benefit HT DFS (%)	Benefit HT OS (%)
T1a-bG1-3	4.9-9.5	0.3-1.4
T1cG1	5.7-8.2	0.9
T1cG2	7.8-11.1	2.0
T1cG3	9.6-13.9	3.3
T2<3cmG1	8.1-11.6	2.4
T2<3cmG2	10.8-15.7	4.3
T2<3cmG3	12.7-18.7	5.9

RT in early stage breast cancer: *RT & ST*

Side effects

Hormonal therapy (TAM/AI):

- Hot flushes
- Mood disturbances
- Insomnia
- Joint pain
- Osteoporosis
- Coagulopathy
- Endometrial cancer
- Contralateral breast: less
- Treatments
- Switch to AI
- Switch to TAM
- Big issue
- Prevention/treatment
- Prefer AI if risk
- Switch to AI
- No problem

RT in early stage breast cancer: *RT & ST*

Side effects

Persistence in patients with breast cancer treated with tamoxifen or aromatase inhibitors: a retrospective database analysis

P. Hadji · V. Ziller · J. Kyvernitakis ·
M. Bauer · G. Haas · N. Schmidt · K. Kostev

- ≤ 3 years FU \rightarrow discontinuation = 52.2% for tamoxifen, 47% for anastrozole, 55.1% for exemestane, and 44.3% for letrozole.
- Switch to: 33% tamoxifen, 20% anastrozole, 22.9% exemestane, and 23% letrozole.

RT in early stage breast cancer: *RT & ST*

Omitting hormonal therapy in very low risk patients (T1, > 65ys; N0; ER+; Her2 -), in which the overall survival benefit is < 3%, could significantly improve the quality of life ?

RT in early stage breast cancer: *current trials*

Single arm prospective cohort studies investigating omission of RT

Name	TOP-1	Precision	Primetime	IDEA	LUMINA
Age (yr)	≥70	50-75	≥60	50-69	≥55
Tumour	pT1N0	pT1N0	pT1N0	pT1N0	pT1N0 Non-lobular
Characteristics	pT1a/b: grade 1+2 pT1c: grade 1	PAM-50 Luminal A Grade 1-2	IHC4+ (ER/PR/HER2/Ki67)	Oncotype DX RS≤18	Luminal A (IHC)
Receptors	ER>50% HER2 neg	ER/PR+ HER2 neg	ER/PR+ HER2 neg	ER/PR+ HER2 neg	ER≥1%, PR>20% HER2 neg
Margins	neg	neg	≥1mm	≥2mm	≥1mm
Therapy	No ET	ET only	ET only	ET only	ET only
Primary endpoint	5-yr LRR <10% accepted	5-yr LRR 1% expected <5% accepted	5-yr LR <5% expected	5-yr LRR	5-yr LR <5% expected
Number of patients	800	690	1500	200	500
Country, PI	NL Liefers	USA Harris	UK Coles	USA Jagsi	Canada Whelan
Status 2020	Accrual open	Accrual open	Accrual open	Accrual closed	Accrual closed

RT in early stage breast cancer: *trials*

Randomised trials investigating omission of RT

Name	EXPERT	DBCG RT NATURAL	EUROPA
Age (yr)	≥55	≥60	≥70
Tumour	pT1N0	pT1N0	pT1N0
Characteristics	PAM-50 Luminal A ROR ≤60 Grade 1-2 Non-lobular	Luminal A (IHC) Grade 1-2 Non-lobular	Luminal A (IHC) Ki67 <20%
Receptors	ER/PR≥10% HER2 neg	ER≥10% HER2 neg	ER>50%, PR>20% HER2 neg
Margins	neg	≥2mm	neg
Therapy	ET+RT vs ET	(ET) + PBI vs (ET)	APBI vs ET
Primary endpoint	5-yr LRR 1% expected 4% accepted	5-yr LRR 1% expected 4% accepted	2-yr HRQoL
Number of patients	926	926	600
Country, PI	Australia Chua	Denmark Offersen	EORTC Meattini
Status 2020	Accrual open	Accrual open	No funding

RT in early stage breast cancer:

Discussion and conclusions

- We know what we know – and that comes from the past → we have to cope with that
- Regional treatment improves outcome
- Evidence tells us to reserve surgery for macroscopic resectable disease and radiation therapy for all others
- Current & future trials are superfluous; results will be outdated before they are known
- Use treatment protocols, register data and continue finetuning
- Precision medicine: Biological + technological optimisation → personalised/individualised/stratified approaches