





Cirugía conservadora - tratamientos en bajo riesgo:

Ensayo EUROPA: Radioterapia vs hormonoterapia





Philip Poortmans, MD, PhD
Iridium Netwerk & Antwerp University, Antwerpen (B)









Conflict of interest

Affidea – medical advisor

MSD - consultant

And I worry about the future...



RT-omission in HR+/HER2- breast cancer

- Introduction
- Less radiation therapy
- EBCTCG 2011: impact of RT & ET
- Endocrine therapy: the ugly truth
- EUROPA trial RT versus ET
- Discussion
- Conclusions

A success story:

Evolution of sites of recurrence after EBC over the last 20 years

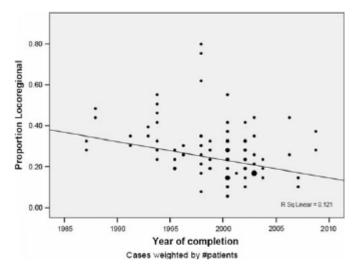


Fig. 1 Proportion of locoregional recurrences over time

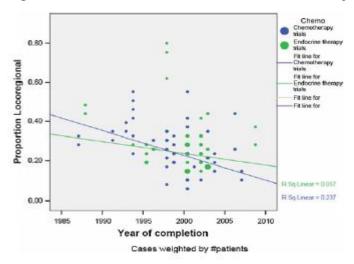
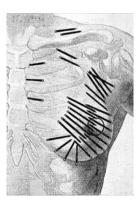


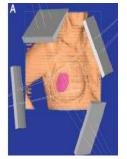
Fig. 2 Proportion of locoregional recurrences for endocrine and chemotherapy over time

Advances in treatment have differentially reduced the proportion of LRR compared with DR → down to 10-15% of all recurrences → influence design new clinical trials.



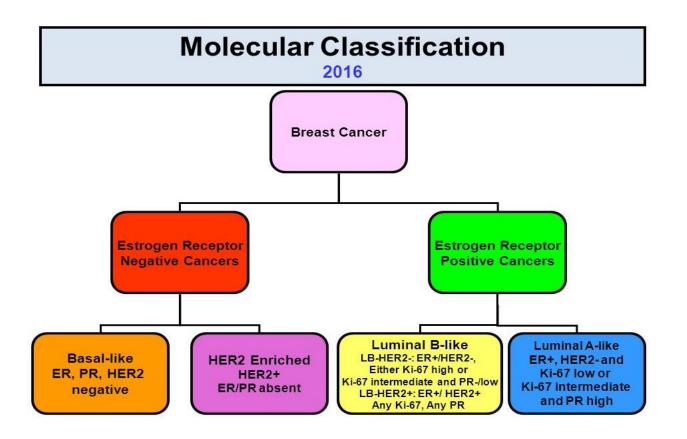






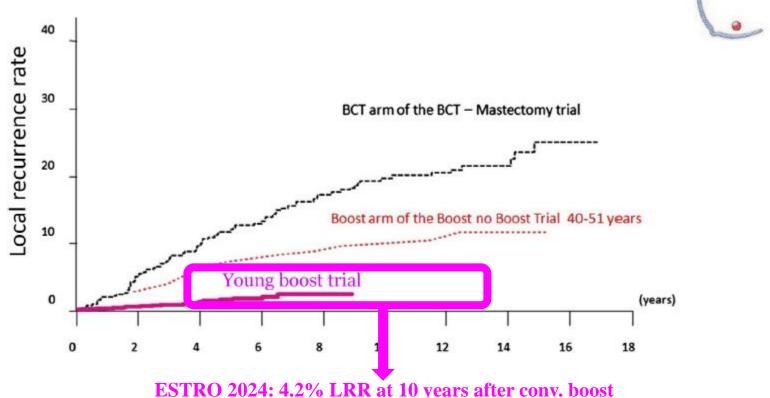








Recurrence rates after BCT decreased a lot!



Poortmans P, et al. Breast. 2017;31:295-302.

Bosma SCJ, et al. Radiother Oncol 2021;156:127-135.

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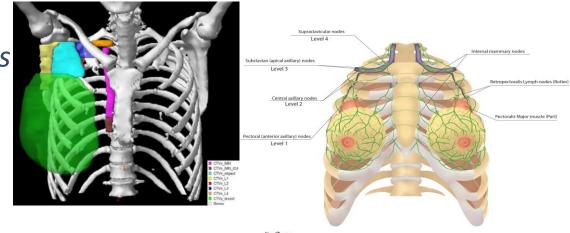
Transition $20^{th} \rightarrow 21^{st}$ century

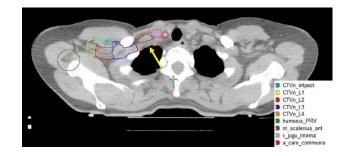
Number of target volumes

Size of target volumes

Dose

Number of fractions





European Society for Radiotherapy and Oncology Advisory Committee in Radiation Oncology Practice consensus recommendations on patient selection and dose and fractionation for external beam radiotherapy in early breast cancer

Icro Meattini, Carlotta Becherini, Liesbeth Boersma, Orit Kaidar-Person, Gustavo Nader Marta, Angel Montero, Birgitte Vrou Offersen, Marianne C Aznar, Claus Belka, Adrian Murray Brunt, Samantha Dicuonzo, Pierfrancesco Franco, Mechthild Krause, Mairead MacKenzie, Tanja Marinko, Livia Marrazzo, Ivica Ratosa, Astrid Scholten, Elżbieta Senkus, Hilary Stobart, Philip Poortmans*, Charlotte E Coles*

Panel: Final consensus statements

1. Whole breast irradiation

- a Moderate hypofractionated whole breast irradiation should be offered regardless of age at breast cancer diagnosis, pathological tumour stage, breast cancer biology, surgical margins status, tumour bed boost, breast size, invasive or pre-invasive ductal carcinoma in situ (DCIS) disease, oncoplastic breast conserving surgery, and use of systemic therapy.
- b Ultrahypofractionated (26 Gy in five fractions) whole breast irradiation can be offered as (1) standard of care or
 (2) within a randomised controlled trial or prospective registration cohort

2. Chest wall irradiation

- a Moderate hypofractionation can be offered for chest wall irradiation without breast reconstruction
- Moderate hypofractionation can be offered for chest wall irradiation regardless of time and type of breast reconstruction
- c Ultrahypofractionation (26 Gy in five fractions) for chest wall irradiation without breast reconstruction can be offered as (1) standard of care or (2) within a randomised controlled trial or prospective registration cohort
- d Ultrahypofractionation (26 Gy in five fractions) for chest wall irradiation after breast reconstruction can be offered within a randomised controlled trial or prospective registration cohort

3. Nodal irradiation

- a Moderate hypofractionation should be offered for nodal irradiation
- b Ultrahypofractionation (26 Gy in five fractions) should not be offered for nodal irradiation until ongoing trials results are reported

4. Partial breast irradiation-patient selection for external beam radiotherapy

Low risk-features suitable for partial breast irradiation are: luminal-like subtypes small tumour (\leq 3 cm), absence of lymph vascular space invasion, non-lobular invasive carcinoma, tumour grade 1–2, low-to-intermediate grade DCIS (sized \leq 2·5 cm with clear surgical margins \geq 3 mm), age at diagnosis 50 years or more, unicentric or unifocal lesion, clear surgical margins (>2 mm), node negative (including isolated tumour cells), and no use of primary systemic therapy and neoadjuvant chemotherapy

5. Partial breast irradiation-dose and fractionation

- Moderate hypofractionation (40 Gv in 15 fractions) and ultrahypofractionation (26–30 Gy in five fractions) represent acceptable schedules for external beam partial breast irradiation
- Twice a day external beam partial breast irradiation dose and fractionations similar to those used in the RAPID trial should not be offered

DCIS=ductal carcinoma in situ.

Panel: Final consensus statements

4. Partial breast irradiation-patient selection for external beam radiotherapy

Low risk-features suitable for partial breast irradiation are: luminal-like subtypes small tumour (≤3 cm), absence of lymph vascular space invasion, non-lobular invasive carcinoma, tumour grade 1–2, low-to-intermediate grade DCIS (sized ≤2.5 cm with clear surgical margins ≥3 mm), age at diagnosis 50 years or more, unicentric or unifocal lesion, clear surgical margins (>2 mm), node negative (including isolated tumour cells), and no use of primary systemic therapy and neoadjuvant chemotherapy

Meattini I, et al. Lancet Oncol 2022;23:e21-31.

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RT-omission in HR+/HER2- BC: EBCTCG 2011

Articles

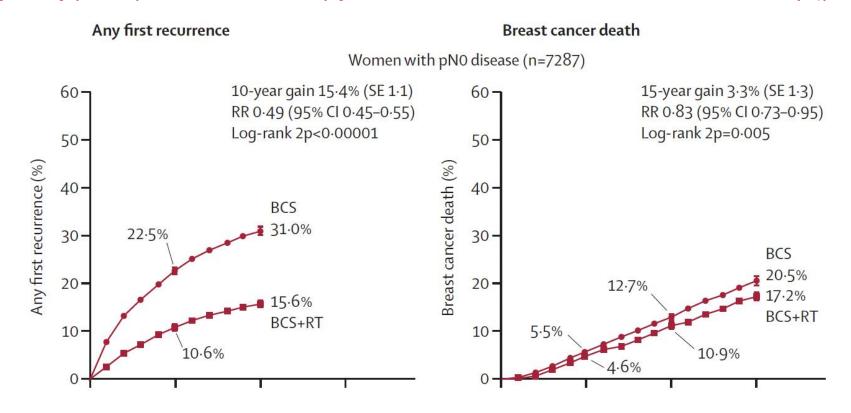


Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomised trials

Early Breast Cancer Trialists' Collaborative Group (EBCTCG)*

RT-omission in HR+/HER2- BC: EBCTCG 2011

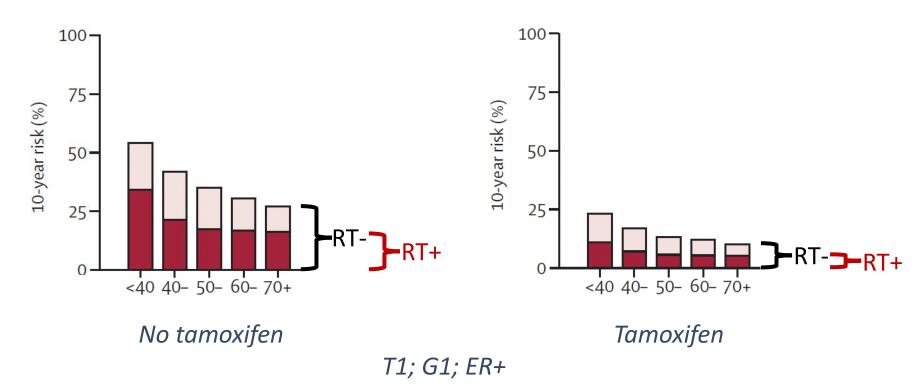
Effect of postoperative RT on any first recurrence and breast cancer mortality (pN0)



EBCTCG. Lancet 2011;378:1707-16.

RT-omission in HR+/HER2- BC: EBCTCG 2011

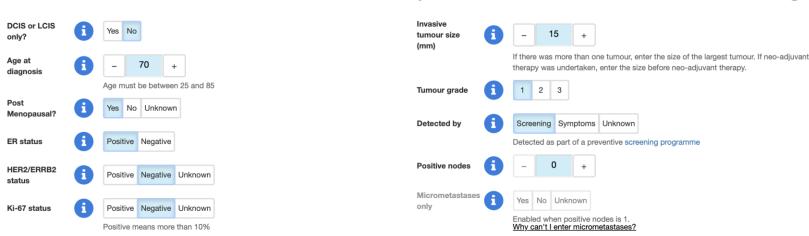
10-years risks of any first recurrence per age category (pN0; n=7287)



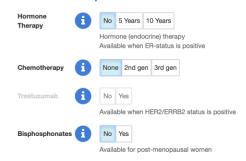
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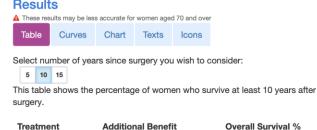






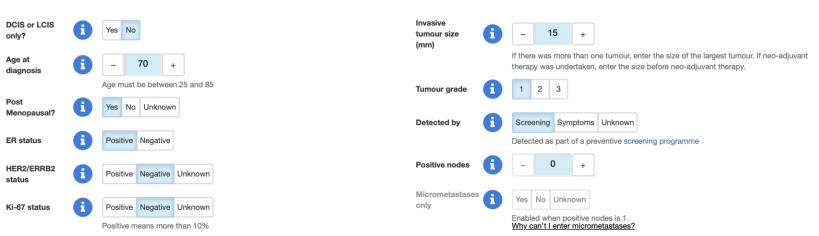
Results

Surgery only

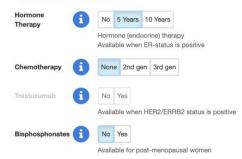


If death from breast cancer were excluded, 80% would survive at least 10 years, and 20% would die of other causes.

78%



Treatment Options



Results

+ Hormone therapy

These results may be less accurate for women aged 70 and over

Table Curves Chart Texts Icons

Select number of years since surgery you wish to consider:

5 10 15

This table shows the percentage of women who survive at least 10 years after surgery.

Treatment Additional Benefit Overall Survival %

Surgery only - 78%

If death from breast cancer were excluded, 80% would survive at least 10 years, and 20% would die of other causes.

0.8% (0.5% - 1.0%)

78%

https://breast.predict.nhs.uk/tool.



Annals of Oncology 30: 1784–1795, 2019 doi:10.1093/annonc/mdz298 Published online 8 October 2019

ORIGINAL ARTICLE

Differential impact of endocrine therapy and chemotherapy on quality of life of breast cancer survivors: a prospective patient-reported outcomes analysis

A. R. Ferreira^{1,2}, A. Di Meglio¹, B. Pistilli³, A. S. Gbenou¹, M. El-Mouhebb¹, S. Dauchy⁴, C. Charles⁴, F. Joly⁵, S. Everhard⁶, M. Lambertini^{7,8}, C. Coutant⁹, P. Cottu¹⁰, F. Lerebours¹¹, T. Petit¹², F. Dalenc¹³, P. Rouanet¹⁴, A. Arnaud¹⁵, A. Martin⁶, J. Berille¹⁶, P. A. Ganz¹⁷, A. H. Partridge¹⁸, S. Delaloge³, S. Michiels^{19,20}, F. Andre^{1,3} & I. Vaz-Luis^{1,3*}

Ferreira AR, et al. Annals of Oncology 30: 1784–1795, 2019.

QoL deterioration persisted at 2 years after diagnosis with different trajectories by treatment received. ET, but not CT, had a major detrimental impact on C30-SumSc, especially in postmenopausal women. These findings highlight the need to properly select patients for adjuvant ET escalation.

Ferreira AR, et al. Annals of Oncology 30: 1784–1795, 2019.

Adverse events profile phase 3 trials (in bold adverse events ≥20%).

Reference trial	Trial design	Number of patients	Median follow-up time, years	Experimental arm	Reported Adverse Event (experimental arm only)	Occurrence rate, %		
Endocrine therapy trials								
NSABP-B14	Placebo or tamoxifen	1,172	6.75	Tamoxifen	Hot flushes	64.0		
[10, 11]					Weight gain	38.0		
					Fluid retention	32.0		
					Vaginal discharge	30.0		
					Irregular menses	25.0		
					Nausea	24.0		
					Weight loss	22.0		
					Skin changes	19.0		
					Diarrhoea	11.0		
					Thromboembolic (venous)	1.7		
					Second primary cancer (all) °	10.8		
					Contralateral breast cancer °	2.9		
					Endometrial cancer °	2.1		
ATLAS [12]	Tamoxifen 5 years or 10 years	12,894 °°	Not specified	Tamoxifen 10 years (n=6,454)	Stroke	2.0		
					Pulmonary embolus	0.6		
					Ischaemic heart disease	2.0		
					Vascular death (Stroke, pulmonary embolus, heart disease)	2.2		
					Neoplastic death	1.5		
					Second primary cancer (all)	13.4		
					Contralateral breast cancer	6.9		
					Endometrial cancer	1.8		

Adverse events profile phase 3 trials (in bold adverse events ≥20%).

Reference trial	Trial design	Number of patients	Median follow-up time, years	Experimental arm	Reported Adverse Event (experimental arm only)	Occurrence rate, %				
	Endocrine therapy trials									
BIG 1-98 [13-15]	Tamoxifen or Letrozole or sequence	8,100	12.6	Letrozole (n=2 463)	Hypercholesterolemia Hot flushes Arthralgia Night sweating Nausea Bone fractures Myalgia Vaginal bleeding Vomiting Cerebrovascular accident/transient ischemic attack Thromboembolic event	50.6 32.8 20.0 14.2 9.9 8.6 7.1 3.8 3.0				
ATTA CITIC		(24)	10		Cardiac event Ischemic heart disease Cardiac failure Second nonbreast primary (all) Contralateral breast cancer Endometrial cancer	5.5 2.2 1.0 2.6 0.6 0.2				
ATAC [16, 17]	Tamoxifen or Anastrozole	6,241	10	Anastrozole (n=3,125)	Hot flushes Arthralgia Mood disturbances Fatigue/tiredness Nausea and vomiting Vaginal bleeding Vaginal discharge Endometrial cancer Fractures Ischaemic cardiovascular disease Ischaemic cerebrovascular events Venous thrombo-embolic events Deep venous thromboembolic events Cataracts	35.7 35.6 19.3 18.6 12.7 5.4 3.5 0.8 11 4.1 2.0 2.8 1.6 5.9				
					Second primary (all) Contralateral breast cancer °°° Endometrial cancer	13.7 3.2 0.2				

Meattini I, et al. Radiother Oncol 2024;190:110045.

Adverse events profile phase 3 trials (in bold adverse events ≥20%).

Reference trial	Trial design	Number of patients	Median follow-up time, vears	Experimental arm	Reported Adverse Event (experimental arm only)	Occurrence rate, %			
	Radiation therapy trials								
START B [18, 19]	50Gy/25 or 40Gy/15 WBI	2,215	9.9	40Gy/15fx WBI (n=1,110)	Breast shrinkage * Breast induration (index) * Telangiectasia * Breast oedema * Shoulder stiffness * Arm oedema * Ischaemic heart disease Symptomatic rib fracture Symptomatic lung fibrosis Second nonbreast primary Contralateral breast cancer	11.4 9.6 1.8 4.7 3.1 2.8 0.6 0.2 0.3 2.3 1.5			
FAST: Forward [6]	40Gy/15 or 26Gy/5 WBI	3,024	6	26Gy/5fx WBI (n=1,026)	Any moderate/marked adverse event in breast/chest wall Breast distortion Breast shrinkage Breast induration (index) Breast induration (outside index) Telangiectasia Breast/chest wall oedema Breast/chest wall discomfort Symptomatic rib fracture Symptomatic lung fibrosis Ischemic heart disease Second nonbreast primary Contralateral breast cancer	12 5 7 4 2 1 1 3 1.5 0.9 0.9			

Meattini I, et al. Radiother Oncol 2024;190:110045.

Adverse events profile phase 3 trials (in bold adverse events ≥20%).

Reference trial	Trial design	Number of patients	Median follow-up time, years	Experimental arm	Reported Adverse Event (experimental arm only)	Occurrence rate, %
				Radiation therapy trials		
IMPORT-	40Gy/15 WBI or 40Gy/15 PBI	2,018	6	40Gy/15fx PBI (n=669)	Worst normal-tissue effects *	10
Low [7]					Breast shrinkage *	7
					Breast induration (index) *	5
					Breast induration (outside index) *	<1
					Telangiectasia *	1
					Breast oedema *	0
					Cardiac death	<1
					Cerebrovascular accident death	<1
					Pulmonary embolism death	0
					Second nonbreast primary	4
					Contralateral breast cancer	2
RAPID [20]	WBI or Accelerated PBI	2,135	8.6	38.5Gy/10fx BID PBI	Acute period **	
		, , , ,		(n=1,070)	Radiation dermatitis	< 0.5
				(== -,,	Fatigue	0.8
					Breast swelling	< 0.5
					Breast pain	< 0.5
					Pneumonitis	0
					Any acute toxicity	1.8
					Late period **	
					Induration or fibrosis	2.9
					Telangiectasia	1.2
					Breast pain	< 0.5
					Chest wall pain	<0.5
					Fatty necrosis	0.5
					Any late toxicity	4.5
					Cardiac death	<1
					Second nonbreast primary	7.9
					Contralateral breast cancer	2.7

Meattini I, et al. Radiother Oncol 2024;190:110045.

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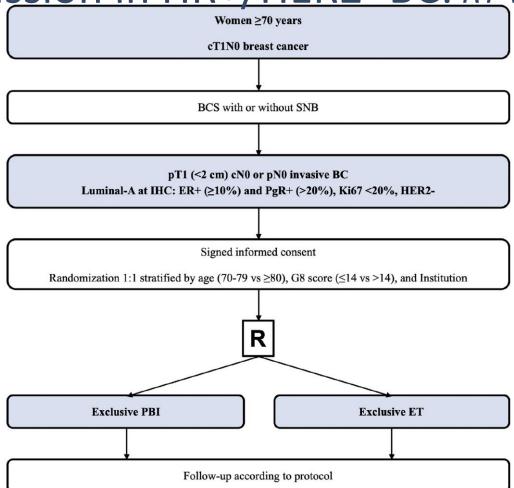
Contents lists available at ScienceDirect

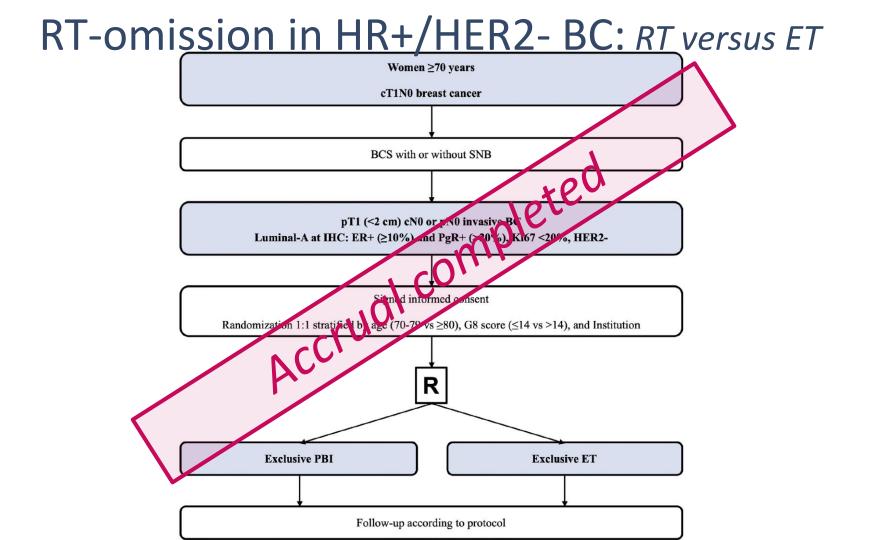
Journal of Geriatric Oncology



Exclusive endocrine therapy or partial breast irradiation for women aged ≥70 years with luminal A-like early stage breast cancer (NCT04134598 – EUROPA): Proof of concept of a randomized controlled trial comparing health related quality of life by patient reported outcome measures

Icro Meattini ^{a,b,*}, Philip M.P. Poortmans ^{c,d}, Livia Marrazzo ^b, Isacco Desideri ^{a,b}, Etienne Brain ^e, Marije Hamaker ^f, Matteo Lambertini ^{g,h}, Guido Miccinesi ⁱ, Nicola Russell ^j, Calogero Saieva ⁱ, Vratislav Strnad ^k, Luca Visani ^{a,b}, Orit Kaidar-Person ¹, Lorenzo Livi ^{a,b}





DECEMBER 10-13, 2024

HENRY B. GONZALEZ CONVENTION CENTER • SAN ANTONIO, TX

Exclusive endocrine therapy or radiation therapy in women aged 70+ years with luminal-like early breast cancer (EUROPA): preplanned interim analysis of a randomized phase 3 trial

Icro Meattini, MD

University of Florence, Florence, Italy

Icro Meattini, Maria Carmen De Santis, Luca Visani, Marta Scorsetti, Alessandra Fozza, Bruno Meduri, Fiorenza De Rose, Elisabetta Bonzano, Agnese Prisco, Valeria Masiello, Eliana La Rocca, Ruggero Spoto, Carlotta Becherini, Gladys Blandino, Luca Moscetti, Riccardo Ray Colciago, Francesca Martella, Lorenzo Vinante, Sara Ramella, Marco Gatti, Sara Pedretti, Patrizia Vici, Nadia G. Di Muzio, Alice Pastorino, Maria Cristina Leonardi, Ivica Ratosa, Jure Verbancic, Riccardo A. Audisio, Etienne Brain, Saverio Caini, Marije Hamaker, Orit Kaidar Person, Matteo Lambertini, Livia Marrazzo, Calogero Saieva, Tanja Spanic, Vratislav Strnad, Sally Wheelwright, Philip M. P. Poortmans, Lorenzo Livi, on behalf of the EUROPA trial Investigators







Exclusive endocrine therapy or radiation therapy in women aged 70+ years with luminal-like early breast cancer (EUROPA): a randomized phase 3 trial Conclusions



Summary – interim analysis

RT offers better HRQOL GHS preservation than ET at 24 months

Lower incidence of treatment-related AEs in the RT arm

No warning signals regarding stopping rules

Future Directions

Ongoing patient recruitment and follow-up Final analysis will include IBTR rates and long-term outcomes

Take-Home Message

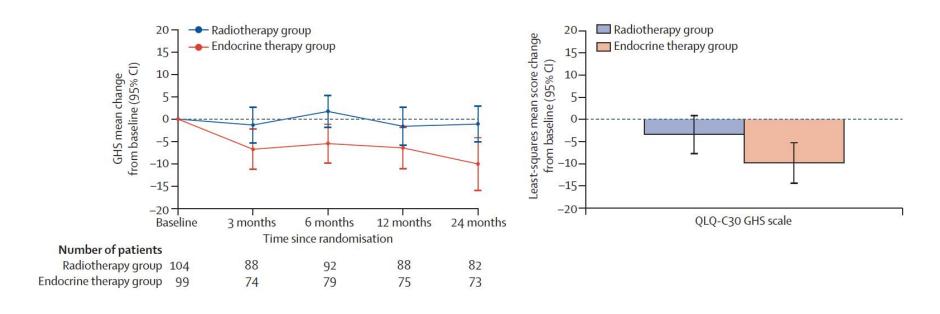
RT or ET may be a viable **single-modality** treatment option, emphasizing the need for a **patient-centred personalized care**

Single-modality endocrine therapy versus radiotherapy after breast-conserving surgery in women aged 70 years and older with luminal A-like early breast cancer (EUROPA): a preplanned interim analysis of a phase 3, non-inferiority, randomised trial

Icro Meattini, Maria Carmen De Santis, Luca Visani, Marta Scorsetti, Alessandra Fozza, Bruno Meduri, Fiorenza De Rose, Elisabetta Bonzano, Agnese Prisco, Valeria Masiello, Eliana La Rocca, Ruggero Spoto, Carlotta Becherini, Gladys Blandino, Luca Moscetti, Riccardo Ray Colciago, Riccardo A Audisio, Etienne Brain, Saverio Caini, Marije Hamaker, Orit Kaidar-Person, Matteo Lambertini, Livia Marrazzo, Calogero Saieva, Tanja Spanic, Vratislav Strnad, Sally Wheelwright, Philip M P Poortmans*, Lorenzo Livi*, on behalf of the EUROPA Trial Investigators†

<u>Summary – interim analysis:</u>

- ✓ RT offers better HRQOL GHS preservation than ET at 24 months
- ✓ Lower incidence of treatment-related AEs in the RT arm
- ✓ No warning signals regarding stopping rules



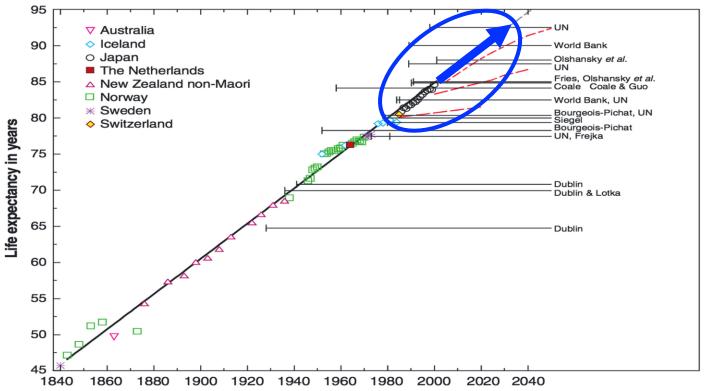
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Record female life expectancy from 1840 to the present - Oeppen and Vaupel (2002)

Shown is the record female life expectancy and the country with the highest female life expectancy at each point in time.

- The linear-regression trend is depicted by a bold black line (slope = 0.243) and the extrapolated trend by a dashed gray line.
- The horizontal black lines show asserted ceilings on life expectancy, with a shorter vertical line indicating the year of publication.
- The dashed red lines denote projections of female life expectancy in Japan published by the United Nations in 1986, 1999, and 2001.



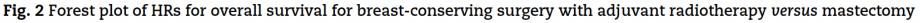
RT-omission in HR+/HER2- BC: Discussion The breast: MRM vs BCT

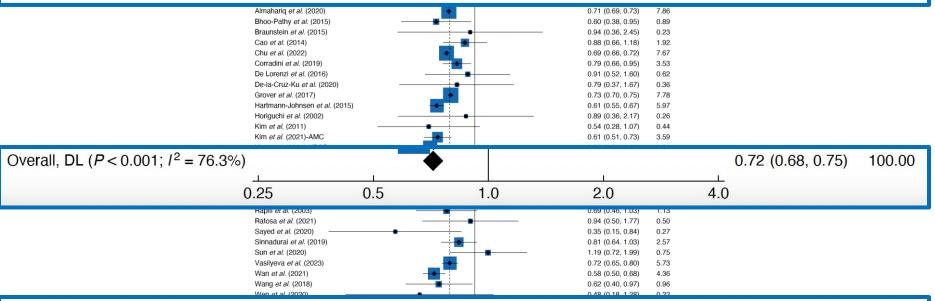
Overall survival after mastectomy versus breast-conserving surgery with adjuvant radiotherapy for early-stage breast cancer: meta-analysis

- Systematic review
- 2000 2023
- 35 observational studies
- 909,077 patients (362,390 MRM & and 546,687 BCT incl RT)

The breast: MRM vs BCT

Weight Weight



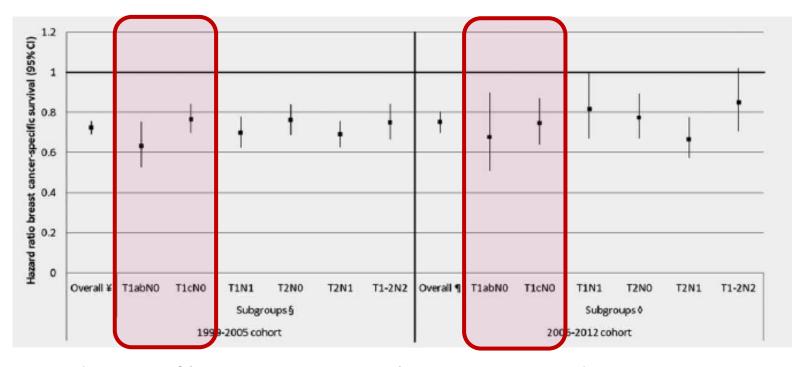


Conclusion: This meta-analysis provides evidence suggesting a survival advantage for women undergoing breast-conserving surgery with adjuvant radiotherapy for early-stage breast cancer compared with mastectomy. Although these results should be interpreted with caution, they should be shared with patients to support informed surgical decision-making.

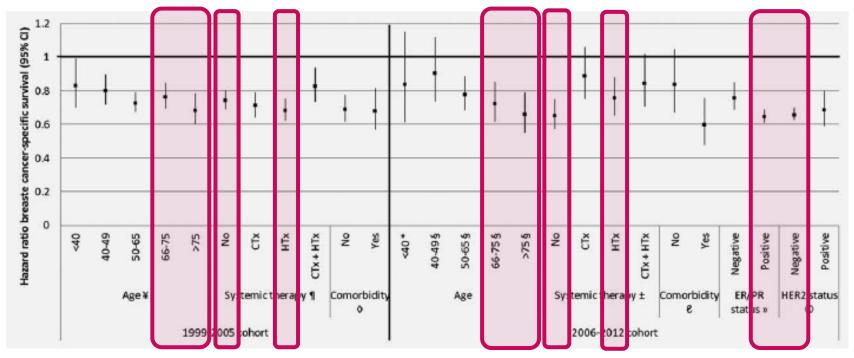
Rajan KK, et al. BJS Open, 2024, zrae040.

Nationwide population-based study of trends and regional variation in breast-conserving treatment for breast cancer

M. C. van Maaren^{1,2}, L. J. A. Strobbe³, L. B. Koppert⁴, P. M. P. Poortmans⁵ and S. Siesling^{1,2}



Hazard ratios of breast-conserving therapy compared to mastectomy on BCSS for both cohorts, overall and specified for T and N stage.



Hazard ratios of breast-conserving therapy compared to mastectomy on BCSS in T1–2N0–1 stage breast cancer, specified for predefined prognostic factors.

RT-omission in HR+/HER2- BC: Discussion The breast: MRM vs BCT

Hypothesis: favourable effect of RT

- > Treatment of residual subclinical disease?
- ➤ More volume (rBGT; lymphatics) effectively treated?
- Immunological phenomenon?

RT after tumourectomy: not always required?

Table 2Summary of recent randomized controlled trials evaluating omission of radiotherapy in early breast cancer.

Randomized controlled trials	Number of patients	Age, years	Tumor size (cm)	Histology	Grade	Hormone Receptors	Axillary nodal status	Surgery	Margins	Median follow-up (years)	Incidence of IBTR (%)
Hughes et al, 2013 [16]	636	≥70	≤2	Invasive carcinomas	All	Positive	N0	BCS	Negative	12.6	8.5 (TAM only) 1.9 (TAM + RT)
Veronesi et al, 2001 [17]	579	≤70	≤2.5	Invasive carcinomas	All	Any	N0-N3a	BCS + ALND	Negative	9	23.5 (no RT) 5.8 (RT)
Fyles et al, 2004 [18]	769	≥50 (median 68)	≤5	Invasive carcinomas and DCIS	All	Any	N0	BCS	Negative	5.6	7.7 (TAM only) 0.6 (TAM + RT)
Fisher et al, 2002 [19]	1009	All	≤1	Invasive carcinomas	All	Positive	N0	BCS + ALND	Negative	8	16.5 (TAM) 9.3 (RT+ placebo 2.8 (TAM + RT)
Blamey et al, 2013 [20]	1135	≤70 (median 57)	≤2	All invasive carcinomas and DCIS	G1 for invasive carcinomas	Positive	N0	BCS	Negative	12	10.2 (no RT) 3.9 (RT)
Kunkler et al, 2015 [14]	1326	≥65 (median 70)	≤3	Invasive carcinomas	All (not both G3 and LVI permitted)	Positive	N0	BCS	≥1 mm	5	4.1 (ET only) 1.3 (RT + ET)
Holli et al, 2001 [21]	152	≥40 (median 55)	≤2	Invasive unifocal carcinomas	G1-G2	Positive	N0	BCS	≥1 cm	6.7	18.1 (no RT) 7.5 (RT)
Tinterri et al, 2014 [22]	749	55-75	≤2.5	Invasive unifocal carcinomas	All	Any	N0-N1	BCS	Negative	9	4.4 (no RT) 3.4 (RT)
Winzer et al, 2010 [23]	347	45–75	≤2	Invasive carcinomas	G1-G2	Positive	N0	BCS	≥2 mm	9.9	34 (BCS) 9.6 (BCS + RT) 7.5 (BCS + TAM) 5.3 (BCS + RT +

Meattini I, et al. J Geriatr Oncol. 2021;12:182-189.

BASO - II

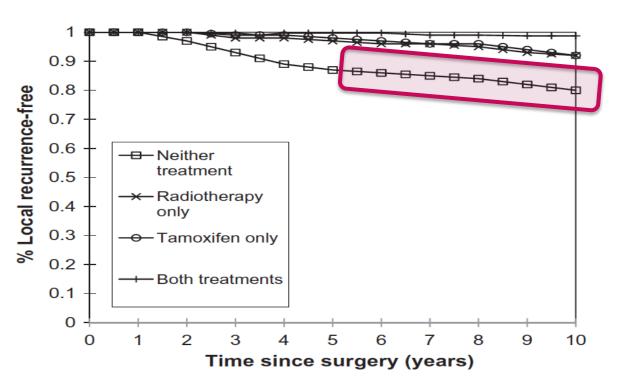
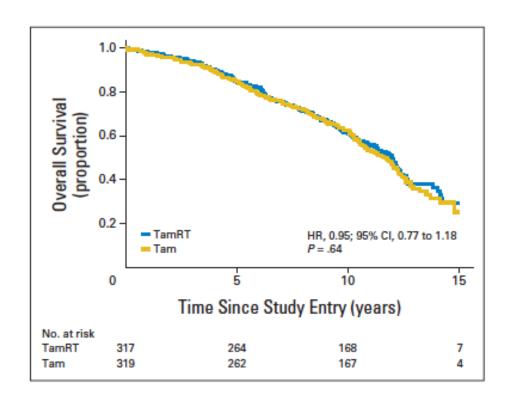


Fig. 2. Survival to first local recurrence by treatment actually received.

Blamey RW, et al. Eur J Cancer. 2013;49:2294-302.

CALGB 9343



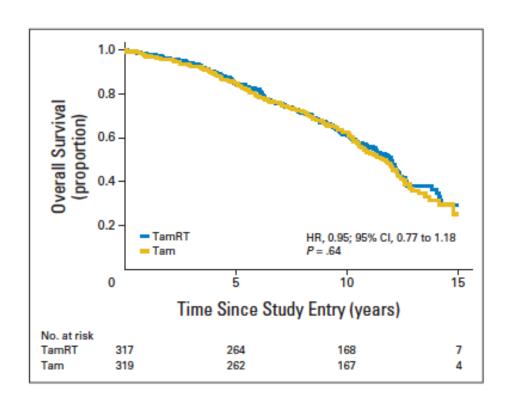
- 8% LRR benefit at 10y
- 3% died < breast ca
- 49% died unrelated

Pt selection: EORTC 22922

= 82.3% 10y OS

= 73.1% 15y OS

CALGB 9343



- 8% LRR benefit at 10y
- 3% died < breast ca
- 49% died unrelated

Pt selection: EORTC 22922

= 82.3% 10y OS

= 73.1% 15y OS

Sneak preview: >60% @ 20 years

RT-omission in BC: Less when possible

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

FEBRUARY 16, 2023

VOL. 388 NO. 7

Breast-Conserving Surgery with or without Irradiation in Early Breast Cancer

Ian H. Kunkler, M.B., B.Chir., Linda J. Williams, Ph.D., Wilma J.L. Jack, M.B., Ch.B., David A. Cameron, M.D., and J. Michael Dixon, M.D.

RT-omission in BC: Less when possible PRIME - 2

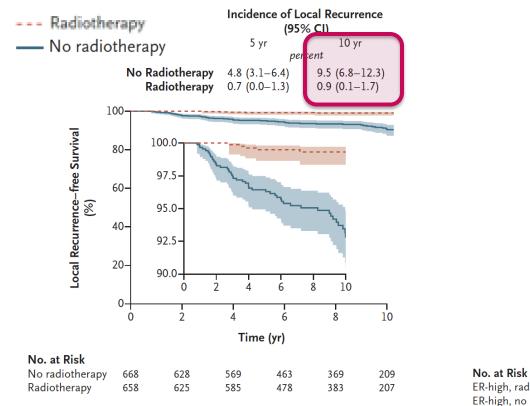
Phase 3 randomized trial:

- Age ≥ 65 years
- ➤ Tumour ≤ 3cm; ER+; NO
- Breast-conserving surgery with clear excision margins
- Adjuvant endocrine therapy

- → Yes/No whole-breast irradiation (40 to 50 Gy)
- Primary endpoint = local breast cancer recurrence.
- Secondary endpoints: RR; DR; BCS; OS

RT-omission in BC: Less when possible

PRIME - 2



--- ER-low, radiotherapy --- ER-low, no radiotherapy Incidence of Local Recurrence (95% CI) 5 yr 10 yr ER-high, Radiotherapy 0.7(0.0-1.5)1.0(0.1-1.9)ER-high, No Radiotherapy 3.9(2.3-5.6)8.6 (5.7-11.4)ER-low, Radiotherapy 0.0 19.1 (8.2-29.9) 12.7 (4.3-21.2) ER-low, No Radiotherapy Local Recurrence-free Survival (%) 100 80-60-40-20-10 Year ER-high, radiotherapy 574 537 439 356 193 603 560 507 329 189 ER-high, no radiotherapy 593 414 ER-low, radiotherapy 53 50 47 38 27 14 ER-low, no radiotherapy 65 59 53 42 38 19

ER-high, radiotherapy

- ER-high, no radiotherapy

Kunkler I, et al. NEJM 2023;388:585-594.

RT-omission in BC: Less when possible

EDITORIAL

Overcoming Resistance — Omission of Radiotherapy for Low-Risk Breast Cancer



Alice Y. Ho, M.D., and Jennifer R. Bellon, M.D.

- Any doubt that radiotherapy cannot be omitted in women 65 years of age or older with ERpositive, early-stage breast cancer can be put to rest.
- ➤ The 10-year follow-up in the trials are extremely reassuring, given the long natural history of ER-positive breast cancer.
- These results do not undermine the value of radiotherapy in enhancing local control, which is a compelling end point in and of itself, particularly now that radiotherapy can be delivered in less burdensome ways.
- Individualizing the treatment so that it is concordant with the patient's goals and values is critical.
- Taken together, these data will help patients navigate these complex choices so that they can make well-informed and prudent decisions for the management of their breast cancer.

Ho AY & Bellon JR. NEJM 2023;388:552-553.

ORIGINAL ARTICLE

Omitting Radiotherapy after Breast-Conserving Surgery in Luminal A Breast Cancer

- Prospective cohort study; women ≥ 55 years; BCS; T1N0G1-2; lum-A
- Arr Ki-67 ≤ 13,25%; ER ≥ 1%; PR > 20%
- ➤ Adjuvant endocrine therapy
- >740 registered → 500 eligible patients
- ➤ After 5 years: recurrence in 2.3% (1.2-4.1%)
- ➤ Contralateral BC in 1.9%
- ➤ Any recurrence in 2.7%

Whelan TJ, et al. N Engl J Med 2023;389:612-9.

Omission of Radiotherapy After Breast-Conserving Surgery for Women With Breast Cancer With Low Clinical and Genomic Risk: 5-Year Outcomes of IDEA

Reshma Jagsi, MD, DPhil^{1,2} (b); Kent A. Griffith, MS² (b); Eleanor E. Harris, MD³ (b); Jean L. Wright, MD⁴ (b); Abram Recht, MD⁵ (b); Alphonse G. Taghian, MD, PhD⁶ (D); Lucille Lee, MD⁷; Meena S. Moran, MD⁸ (D); William Small Jr, MD⁹ (D); Candice Johnstone, MD¹⁰; Asal Rahimi, MD¹¹; Gary Freedman, MD¹²; Mahvish Muzaffar, MD¹³ (D); Bruce Haffty, MD¹⁴ (D); Kathleen Horst, MD¹⁵; Simon N. Powell, MD, PhD¹⁶ (D); Jody Sharp, BS²; Michael Sabel, MD²; Anne Schott, MD² (5); and Mahmoud El-Tamer, MD¹⁶ (6)

DOI https://doi.org/10.1200/JC0.23.02270

ABSTRACT

PURPOSE Multiple studies have shown a low risk of ipsilateral breast events (IBEs) or other recurrences for selected patients age 65-70 years or older with stage I breast cancers treated with breast-conserving surgery (BCS) and endocrine therapy (ET) without adjuvant radiotherapy. We sought to evaluate whether younger postmenopausal patients could also be successfully treated without radiation therapy, adding a genomic assay to classic selection factors.

Postmenopausal patients age 50-69 years with pT1No unifocal invasive breast cancer with margins ≥2 mm after BCS whose tumors were estrogen receptor positive, progesterone receptor-positive, and human epidermal growth factor

ACCOMPANYING CONTENT



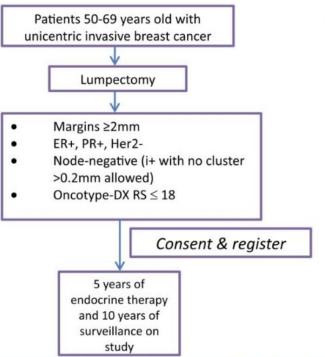


Accepted November 3, 2023 Published December 7, 2023

J Clin Oncol 00:1-9 © 2023 by American Society of Clinical Oncology

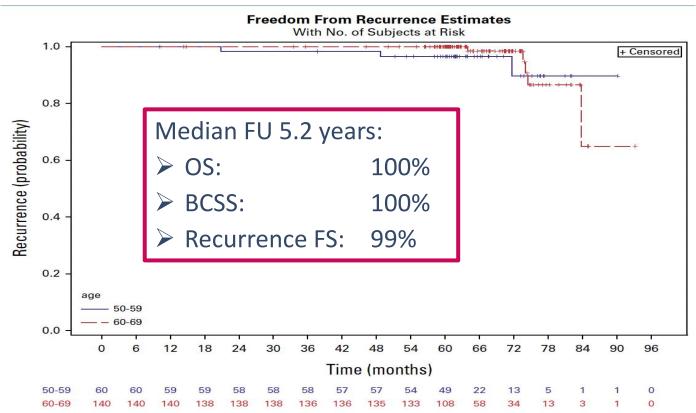
Jagsi R, et al. J Clin Oncol. 2024;42:390-398.

IDEA – Individualised decisions for endocrine therapy alone



- Prospective multicenter cohort trial, first to use genomic assay and consider younger post-menopausal patients (NCT02400190)
- 200 patients enrolled over 3.3 years (June 2015-October 2018) at 13 collaborating sites:
 - University of Michigan, MSKCC, Hopkins, Harvard (MGH/BIDMC), Penn, Stanford, Yale, Loyola, MCW, ECU, UTSW, CINJ/Rutgers, Northwell
- Primary analysis to be conducted 5 years after last patient enrolled completed surgery

IDEA



Jagsi R, et al. J Clin Oncol. 2024;42:390-398.

	•							
	Study	Design	Number of patients	Inclusion criteria	Arm 1	Arm 2	Arm 3	Primary end point
Studies on	CARTE NCT 05058196	Prospective cohort	250	Female, age ≥ 65 Unifocal pT1 pN0 Non-lobular histology HR+: HER2-	WBI	IORT	No RT	Patient's choice when de- escalation is proposed
	DBCG RT Natural Trial NCT 03646955	Randomized, Phase III	926	Female, age ≥ 60 Unicentric pT1 pN0 Non-lobular histology	РВІ	No RT	NA	5-year invasive LR
optimisation	DEBRA NCT 04852887	Randomized,Phase III	1,670	G1-2; ER \geq 10 %; HER2–FSM \geq 2 mm Female, age 50–70 Unicentric pT1 pN0 ER \geq 1 % or PgR \geq 1 %; HER2–Oncotype DX RS \leq 18	RT (WBI or PBI) and ET	Exclusive ET	NA	5-year IBTR
for low-risk	EXPERT NCT 02889874	Randomized,Phase III	1,167	FSM no tumour on ink Female, age \geq 50 Unifocal pT1 pN0G1-2; ER \geq 10 % and PgR \geq 10 %; HER2 $-$ Prosigna PAM50 RoR \leq 60	RT (WBI) and ET	Exclusive ET	NA	5-year LR
RC natients				FSM no tumour on ink				
BC patients	EUROPA NCT 04134598	Randomized, Phase III	926	Female, age \geq 70Unifocal pT1 pN0Any G (pT \leq 10 mm); G1-2 (pT 11–19 mm) ER \geq 10 % and PgR \geq 10 %; HER2–; Ki67 \leq 20 %	Exclusive RT (WBI or PBI)	Exclusive ET	NA	2-year HRQoL 5-year IBTR
after breast				FSM no tumour on ink				
	IDEA NCT 02400190	Prospective single- armcohort	202	Female, age 50–69 Unifocal pT1 pN0ER + and PgR+; HER2– Oncotype DX RS \leq 18 FSM \geq 2 mm	Exclusive ET	NA	NA	5-year LRR
conserving	PRECISION NCT 02653755	Prospective single- armcohort	672	Female, age 50–75 Unicentric pT1 pN0G1-2; ER ≥ 10 % or PgR+; HER2– Prosigna PAM50 RoR low-risk FSM no tumour on ink	Exclusive ET	NA	NA	5-year LRR
surgery	PRIMETIME ISRCTN 41579286	Prospective single- arm cohort	2,400°	Female, age ≥ 60 or postmenopausal Unifocal pT1 pN0G1-2; HR+; HER2– Very low risk based on IHC4 + C FSM ≥ 1 mm	Exclusive ET °°	NA	NA	5-year IBTR
	REaCT-70 NCT 04921137	Randomized, Phase IV	100	Female, age ≥ 70 pT1-2 pN0G1 (pT ≤ 50 mm); G2 (pT ≤ 30 mm); G3 (pT ≤ 10 mm) ER + and/or PR+; HER2-	ET	No ET	NA	Accrual of 100 participants across 8 centres within 2 years
	TOP-1 NTR 6147	Prospective single- arm cohort	1,200	Female, age ≥ 70 Unilateral pT1 pNoG1-2 (pT < 10 mm); G1 (pT 10–20 mm)ER > 50 %; HER2– FSM no tumour on ink	No RT	NA	NA	5-year LRR

No indication for adjuvant ET

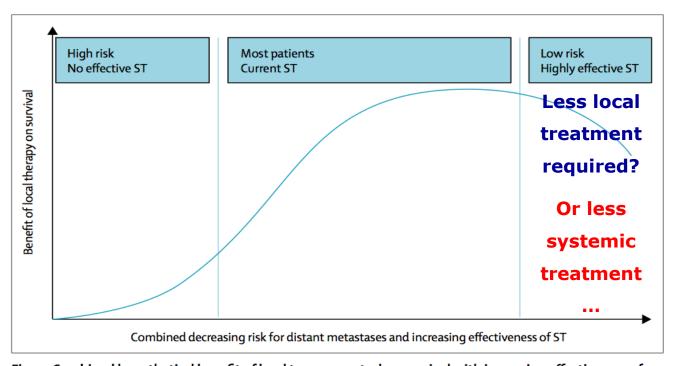


Figure: Combined hypothetical benefit of local tumour control on survival with increasing effectiveness of systemic therapy (ST) and decreasing risk of distant metastases of the primary tumour

Interaction between

systemic and

locoregional

treatments

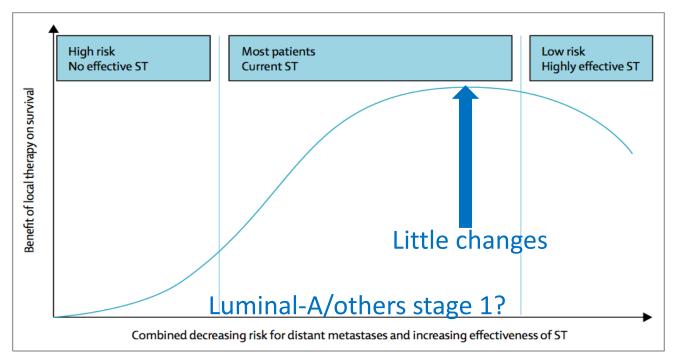


Figure: Combined hypothetical benefit of local tumour control on survival with increasing effectiveness of systemic therapy (ST) and decreasing risk of distant metastases of the primary tumour

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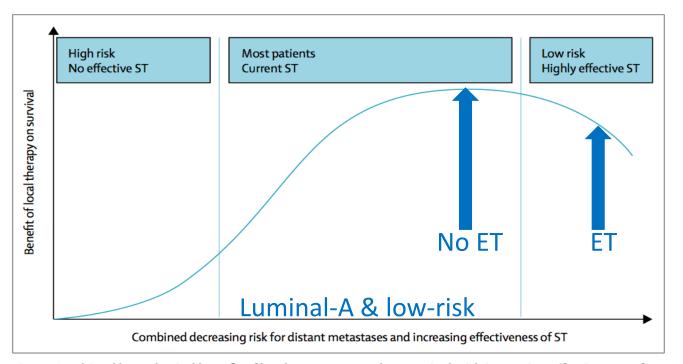


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Interaction between

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https://www.evidencio.com/models/show/1383

IBTR! 2.0: 10-year Ipsilateral Breast Tumor Recurrence (with RT)

- > Designed for physicians to guide medical decision-making after BCT & axillary staging
- > Evidence-based estimate with vs. without WBI

- ➤ Not for post-mastectomy setting
- Not for patients with multicentric disease or in-situ only disease
- ➤ pN+ patients (excl. pNmi) → systemic therapy
- > Benefit of hormonal therapy based on tamoxifen + extrapolated to AI

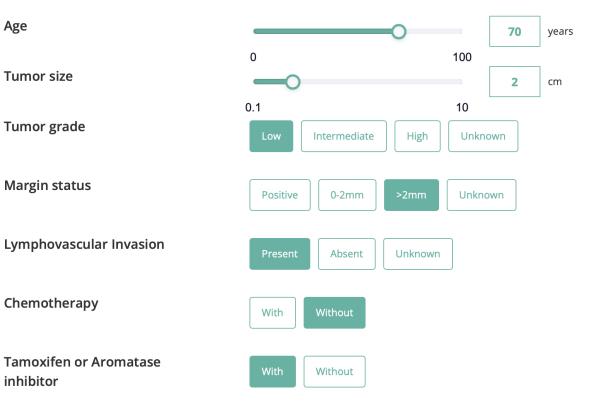
https://www.evidencio.com/models/show/1383

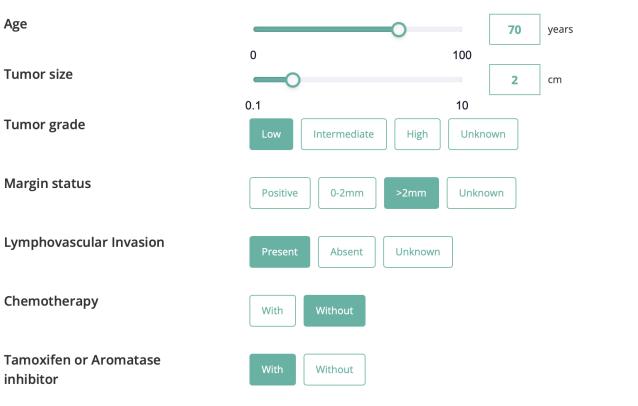
IBTR! 2.0: 10-year Ipsilateral Breast Tumor Recurrence (with RT)

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- Evidence-based estimate with vs. without WBI

Predicted RR without RT → relative risk reduction of 0.7

- ➤ Not for post-mastectomy setting
- Not for patients with multicentric disease or in-situ only disease
- ➤ pN+ patients (excl. pNmi) → systemic therapy
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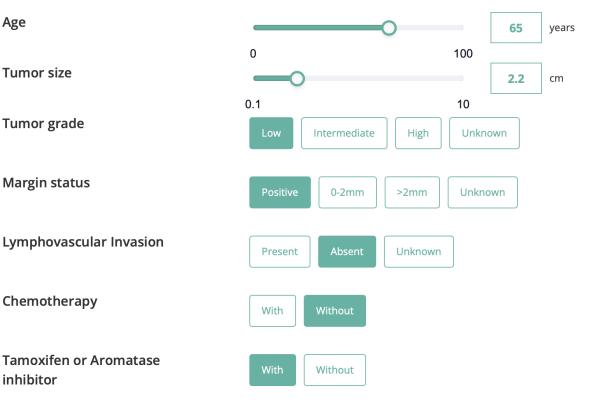




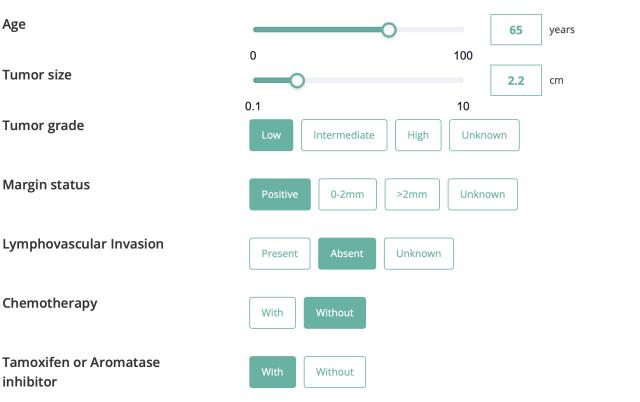
10-Year risk of ipsilateral breast tumor recurrence with radiation therapy is:

1.8 %

So without RT ~ 6.0%



Mona Sanghani, Pauline T. Truong, Rita Abi Raad, Andrzej Niemierko, Mary Lesperance, Ivo A. Olivotto, David E. Wazer, Alphonse G. Taghian. V1.6



10-Year risk of ipsilateral breast tumor recurrence with radiation therapy is: **3.7** %

So without RT ~ 12.3%

RT-omission in HR+/HER2- BC: Discussion Pre-operative RT – ESTRO project

WG1, recommendations:

- Low-risk patients = criteria for partial breast irradiation
- Primary aim of preoperative PBI → reduce treatment burden:
 - Better identification CTV
 - No confounding by surgical (oncoplastic) effects
 - Excision of part of high dose volume → less fibrosis and cosmetic impact
 - Tumour down-staging → omitting surgery in selected patients

RT-omission in HR+/HER2- BC: Discussion Pre-operative RT – ESTRO project

WG1, recommendations:

- Likely best 8 weeks minimum interval RT surgery; explore up to 6 months (with evaluation by imaging @ 2-3 months)
- Fractionation to be further investigated
- Consensus required for timing SLNB
- Longer follow-up required: ≥ 3 years for fibrosis and cosmesis; ≥ 10 years for oncological outcomes

Table 7. Summary of ongoing clinical trials on pre-operative partial breast irradiation in early-stage breast cancer.

Trial ID, status	Title	Treatment	Primary endpoints	Secondary endpoints	Estimated primary completion date
NCT05350722, recruiting	Single-dose Preoperative Partial Breast Irradiation in Low-risk Breast Cancer Patients (ABLATIVE-2)	Pre-operative single-dose radiation therapy (20Gy) and BCS after 12 months	Pathologic complete response	Radiologic complete response, treatment-related adverse events, quality of life, cosmetic outcome, oncologic outcomes, immune response and biomarkers	March 2025
NCT03917498, active/not recruiting	Single Pre-Operative Radiation Therapy - With Delayed Surgery for Low-Risk Breast Cancer (SPORT-DS)	Pre-operative single-dose radiation therapy and BCS after 3 months ^a	Pathologic complete response	Radiation toxicity	February 28, 2020 (actual)
NCT02212860, active/not recruiting	Stereotactic Image-Guided Neoadjuvant Ablative Radiation Then Lumpectomy (SIGNAL 2)	Pre-operative PBI (21 Gy or 3x 10 Gy) and BCS after 14-20 days.	Immune priming, angiogenesis, proliferation/hypoxia/apoptos is/invasion markers, toxicity	Cosmetic outcome, survival	April 2021 (actual)
NCT04679454, recruiting	Single Fraction Preoperative Radiation therapy for Early-Stage Breast Cancer (CRYSTAL)	Pre-operative single dose radiation therapy (18 Gy, 21 Gy, 24 Gy) and BCS after 4-8 weeks	Dose escalation, pathologic complete response	Chronic toxicity, cosmetic outcome, postoperative complications, oncologic outcomes	March 2026
NCT03909282, recruiting	Phase 2 Surgical Excision vs Neoadjuvant Radiation therapy + Delayed Surgical Excision of Ductal Carcinoma (NORDIS)	Pre-operative PBI (5x 6 Gy) and BCS after 3 months vs. upfront surgery	Rate of DCIS pathologic complete response	Wound complication, correlation of imaging characteristics and pathologic findings, rate of invasive carcinoma	September 2024
NCT04040569, recruiting	A Phase I Dose Escalation Study of Single Fraction Pre-operative Stereotactic Partial Breast Irradiation (S-PBI) for Early Stage Breast Cancer	Pre-operative single dose radiation therapy (30 Gy, 34 Gy, 38 Gy) and BCS ^b	Dose escalation, cosmetic outcome	-	September 2024
NCT02482376, active/not recruiting	Preoperative Single-Fraction Radiation therapy in Early-Stage Breast Cancer	Pre-operative single-dose radiation therapy (21 Gy) and BCS ^b	Physician reported cosmetic outcome	Ki-67, patient reported cosmetic outcome, gene expression, local control, circulating cell free DNA	March 2025

BCS Breast conserving surgery PBI Partial breast irradiation ^aDose not reported ^bTiming of surgery not specified Zamagni A, et al. ESTRO project, paper under review.

RT-omission in HR+/HER2- breast cancer

- Introduction
- Less radiation therapy
- EBCTCG 2011: impact of RT & ET
- Endocrine therapy: the ugly truth
- EUROPA trial RT versus ET
- Discussion
- Conclusions

RT-omission in HR+/HER2- BC: Conclusions Currently...

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



Poortmans P, et al. Breast. 2017;31:295-302.

RT-omission in HR+/HER2- BC: Conclusions Uncertainties

Patient selection:

- Patient's characteristics: age; co-morbidity; life expectancy; ...
- Tumour's parameters: size vs type vs prognostic and predictive factors

Local treatment:

- Surgery: margins; re-excision; ...
- Other local approaches: cryotherapy; RFA; SBRT; ...

Regional treatment:

ALND → SLNB → nothing

Systemic treatment:

Endocrine therapy – compliance & duration

RT-omission in HR+/HER2- BC: Conclusions Uncertainties

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ALND → SLNB → nothing

Systemic treatment:

Endocrine therapy – compliance & duration

Early stage, low risk – Dutch guidelines

Graad	Tumordiameter	N0/N0(i+)	N1mi/N1-3
Graad 1	≤ 1 cm	Groen (Oranje
	1,1-2 cm	Groen	Oranje
	2,1-5 cm	Oranje	Oranje
	> 5 cm	Oranje	Oranje
Graad 2	≤ 1 cm	Groen	Oranje
	1,1-2 cm	Oranje	Oranje
	2,1-5 cm	Oranje	Oranje
	> 5 cm	Oranje	Oranje
Graad 3	≤ 1 cm	Groen	Oranje
	1,1-2 cm	Oranje	Oranje
	2,1-5 cm	Oranje	Oranje
	> 5 cm	Oranje	Oranje

Wel endocriene therapie;

geen endocriene therapie

Early stage, low risk

RT
Low rates of side effects
Benefit LR ++; Benefit OS ±

5 days
120 hours
7,200 minutes
432,000 seconds
duration of treatment

ET High rates of side effects Benefit LR +; benefit OS ± 5 years 60 months 1,826 days 43,828 hours 2,629,743 minutes 157,784,629 seconds duration of treatment



Radiotherapy and Oncology 190 (2024) 110045



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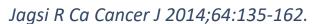
Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com



Omission of radiation therapy after breast-conserving surgery for biologically favourable tumours in younger patients: The wrong answer to the right question









Cost Effectiveness Analysis of Breast Cancer Radiation Therapy

Technische Universität München School of Medicine and Health Klinik für RadioOnkologie und Strahlentherapie Institut für Strahlenmedizin (IRM)

05.11.2025







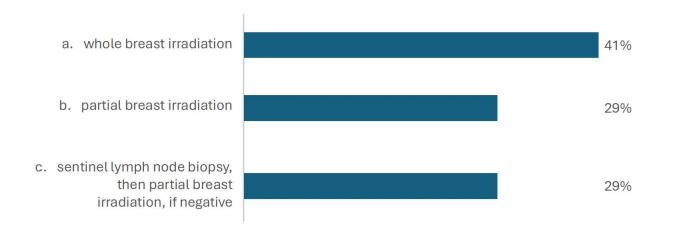
SPECIAL ARTICLE

Tailoring treatment to cancer risk and patient preference: the 2025 St Gallen International Breast Cancer Consensus Statement on individualizing therapy for patients with early breast cancer

H. J. Burstein^{1*†}, G. Curigliano^{2,3†}, M. Gnant^{4,5}, S. Loibl⁶, M. M. Regan¹, S. Loi⁷, C. Denkert⁸, P. Poortmans^{9,10}, D. Cameron¹¹, B. Thurlimann¹² & W. P. Weber¹³, Panelists of the St. Gallen International Breast Cancer Consensus 2025



For a postmenopausal woman in her 60s who has a T1c cancer with low risk features, and a negative axillary ultrasound. You would recommend which of the following?



Total Votes: 68

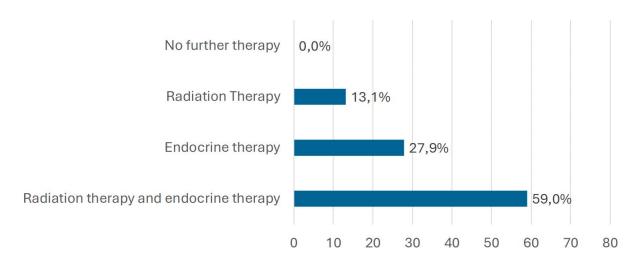


19TH ST.GALLEN INTERNATIONAL BREAST CANCER CONFERENCE 2025

12 - 15 March 2025, Vienna / Austria

submitted by a delegate

A 70 year old woman has undergone breast conserving surgery for a 1.3 cm, grade 1-2 of 3, and strongly ER positive, PR positive breast cancer, and HER2 0 by IHC. You would recommend:



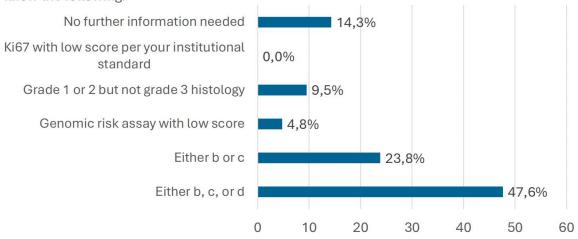
Total votes: 61



19TH ST.GALLEN INTERNATIONAL BREAST CANCER CONFERENCE 2025

12 - 15 March 2025, Vienna / Austria

You are consulting on a vigorous 74 year old woman who has had breast surgery for an ER positive, HER2 negative tumor, stage T1cN0. Her estimated life expectancy is at least 12 years. You and she would like to proceed without radiation therapy. Before omitting radiation therapy, you would like to know the following:



Total votes: 63

Early stage, low risk

Long life expectancy: - Surgery + RT

Short life expectancy: - Surgery alone

- Endocrine alone

- RT alone?

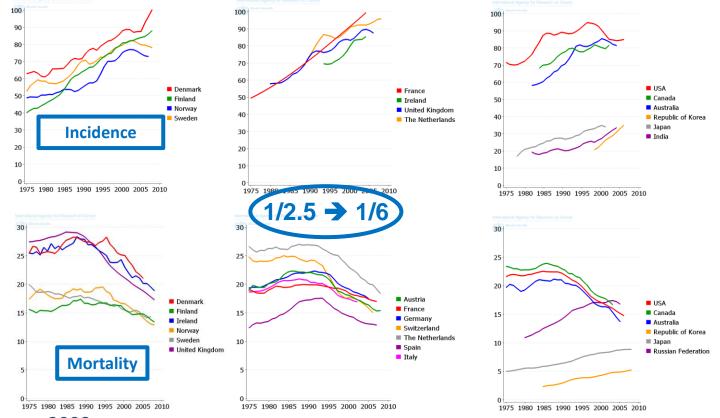
- Nothing?

Early stage, low risk

Long life expectancy: - Surgery + RT

- ✓ Partial breast if feasible
- ✓ ≤ 5 fractions

Evolution of incidence and mortality over the last 40 years



Source: Globocan, 2008. Rates shown are age-standardised rate per 100,000 using the standard world population.



Salvador Dalí: Don Quijote de la Mancha









Toma de Decisiones Compartida





Philip Poortmans, MD, PhD Iridium Netwerk & Antwerp University, Antwerpen (B)









RT-omission in HR+/HER2- BC: Acknowledgements

Too many to list...

... risking forgetting people...

Orit Kaidar-Person · Icro Meattini · Philip Poortmans Editors Breast Cancer Radiation Therapy A Practical Guide for Technical Applications

The book provides, in a comprehensive yet concise way, essential information to improve the knowledge and skills of all healthcare providers involved in the treatment of patients with breast cancer. The content does not focus on general information that is widely available via different sources, but on technical aspects – "hands-on" daily practices and principles of radiation oncology that are not included in other books. Druming on information taught in coursest at eg. the ESTRO School, as well as the authors' broad clinical experience, the respective contributions reflect and share the expertise of leading experts in breast cancer radiation therapy, supported by sound data and evidence. Each chapter includes a short introduction summarizing the evidence in the literature and "pearls" (as hort bullet-point summary), and is enriched by tables, figures and illustrations to provide a concise, easy-to-follow and appealing overview.

The book, containing also useful electronic supplementary material, will be of interest to a wide range of readers, including radiation oncologists, radiation technicians, medical physicists, and others involved in breast cancer care.

aidar–Person • Meattini • Poortmans *Ed:*

Breast Cancer Radiation Therapy



Breast Cancer Radiation Therapy

A Practical Guide for Technical Applications

Orit Kaidar-Person Icro Meattini Philip Poortmans Editors



▶ springer.com

