EVIDENCE AND PRACTICE CHANGHING TREATMENTS IN BREAST TUMORS

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DICHIARAZIONE:
Relatore: Isabella Palumbo

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazione ad Advisory Board **(NIENTE DA DICHIARARE)**
- Titolarietà di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Altro

BREAST CANCER RADIOTHERAPY

DE-ESCALATION

INTENSIFICATION

HIGHLIGHTS in RAD

HYPOFRACTIONATION - ULTRA-HYPOFRACTIONATION

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*

OCOG[2]	50/25/5 vs 42·5/16/3
START B[1]	50/25/5 vs 40/15/3
DBCG HYPO[5]	50/25/5 vs 40/15/3
Beijing trial[30]	50/25/5 vs 43·5/15/3
FAST trial[4]	50/25/5 vs 30/5/5 vs 28·5/5/5
FAST-Forward trial[3]	40/15/3 vs 27/5/1 vs 26/5/1

APBI-IMRT-Florence[44]	PBI: IMRT 30 Gy in 5 fractions vs WBI: IMRT 50 Gy in 25 fractions plus TBB 10 Gy in 5 fractions
NSABP B-39/ RTOG 0413[26]	PBI: HDR brachytherapy 34 Gy or 3DCRT 38·5 Gy in 10 fractions, twice a day vs WBI: EBRT 50 Gy in 25 fractions
RAPID trial[14]	PBI: 3DCRT or IMRT 38·5 Gy in 10 fractions, twice a day vs WBI: EBRT 42·5 Gy in 16 fractions or 50 Gy in 25 fractions with or without TBB 10 Gy in 5 fractions
UK IMPORT LOW trial[45]	PBI: IMRT 40 Gy in 15 fractions vs WBI: IMRT 40 Gy in 15 fractions
GEC-ESTRO[57]	PBI: HDR brachytherapy 32 Gy in 8 fractions or 30·1 Gy in 7 fractions, twice a day vs PBI: PDR brachytherapy 50 Gy, pulses of 0·6–0·8 Gy per h, 24 h per day vs WBI: (4–10 MV) EBRT 50–50·4 Gy in 25–28 fractions with or without TBB 10 Gy in 5 fractions

***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

b 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 (≤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

5. Partial breast irradiation–dose and fractionation

a Moderate hypofractionation (40 Gy in 15 fractions) and ultrahypofractionation (26–30 Gy in five fractions) represent acceptable schedules for external beam partial breast irradiation

b 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.

Modificato da *Lancet Oncol* 2022; 23: e21–31

HYPOFRACTIONATION - ULTRA-HYPOFRACTIONATION

The Italian Association for Radiotherapy and Clinical Oncology (AIRO) position statements for postoperative breast cancer radiation therapy volume, dose, and fractionation

Icro Meattini[1,2] · Isabella Palumbo[3] · Carlotta Becherini[2] · Simona Borghesi[4] · Francesca Cucciarelli[5] · Samantha Dicuonzo[6] · Alba Fiorentino[7] · Ruggero Spoto[8] · Philip Poortmans[9,10] · Cynthia Aristei[3] · Lorenzo Livi[1,2]

Volume, dose, fractionation AIRO breast cancer group recommendations

	50 Gy in 25 fractions	40–42.5 Gy in 15–16 fractions	26 Gy in 5 fractions
Whole breast irradiation	Not recommended	Recommended°	Recommended°
Partial breast irradiation	Not recommended	Recommended°	Recommended°*
Chest wall irradiation without reconstruction	Not recommended ^	Recommended°	Recommended
Chest wall irradiation with reconstruction	Not recommended ^	Recommended°	Not recommended
Regional nodal irradiation	Not recommended ^	Recommended°	Not recommended

^ Except for highly selected cases, such as concomitant chemoradiation and hyperthermia to enhance the radio-sensitisation effects of the combined systemic or local agents

° Gold standard schedule

* Gold standard for partial breast irradiation (26-30 Gy in 5, once-daily, consecutive fractions)

Associazione Italiana
Radioterapia e Oncologia clinica

LA MAIL DEL LUNEDÌ

16 Gennaio 2023

SURVEY AIRO

"Radioterapia post-operatoria nel tumore mammario: quale modifica nella pratica clinica riguardo a volumi dosi e frazionamenti in seguito alla pubblicazione del consensus ESTRO-ACROP e del position statement AIRO?" - deadline 28-02-2023

Si invita alla compilazione della Survey del Gruppo di Studio AIRO Mammella dal titolo "Radioterapia post-operatoria nel tumore mammario: quale modifica nella pratica clinica riguardo a volumi dosi e frazionamenti in seguito alla pubblicazione del consensus ESTRO-ACROP e del position statement AIRO?"

LETTERA DI INVITO ALLA COMPILAZIONE | LINK PER LA COMPILAZIONE

Modificato da La radiologia medica https://doi.org/10.1007/s11547-022-01563-9

ULTRA-HYPOFRACTIONATED RT *vs* ET

Cost-Effectiveness Analysis of Ultra-Hypofractionated Whole Breast Radiation Therapy Alone vs. Endocrine Therapy Alone or Combined Treatment for Low-Risk ER-positive Early-Stage Breast Cancer in Women Age 65 and Older

Matthew C. Ward, MD[1,2], Abram Recht, MD[3], Frank Vicini, MD[4], Zahraa Al-Hilli, MD[5], Wafa Asha, MD[6], Manjeet Chadha, MD[7], Abel Abraham[6], Nikhil Thaker, MD[8], Atif J Khan, MD[9], Martin Keisch, MD[10], Chirag Shah, MD[6]

Purpose: The optimal management of early-stage, low-risk, hormone-positive breast cancer in older women remains controversial. Recent trials have shown that 5-fraction ultra-hypofractionated whole-breast irradiation (U-WBI) has similar outcomes to longer courses, reducing the cost and inconvenience of treatment. We performed a cost-utility analysis to compare U-WBI to endocrine therapy (ET) alone or their combination.

Methods: We simulated three different treatment approaches for women age 65 years or older with pT1-2N0 ER-positive invasive ductal carcinoma treated with lumpectomy with negative margins using a Markov microsimulation model. The strategies were U-WBI performed with a three-dimensional conformal technique over 5 fractions without a boost ("RT Alone"), adjuvant ET (anastrozole for 5 years) without RT ("AI Alone"), or the combination of the two. The combination strategy was calibrated to match trial results, and the relative effectiveness of the RT Alone and AI Alone strategies were inferred from previous randomized trials. The primary endpoint was the cost-effectiveness of the 3 strategies over a lifetime horizon as measured by th incremental cost-effectiveness ratio (ICER), with a value of $100,000/QALY deemed "cost-effective".

Results: The model results compared to the pre-specified target outcomes. On average, RT Alone was the least expensive strategy ($14,775), with AI Alone slightly more ($14,998), and combination therapy the costliest ($19,802). RT Alone dominated AI Alone (ICER -$5,089). Combination therapy, when compared to RT alone, was slightly more expensive than our definition of cost-effective (ICER $113,468) but was cost-effective when compared to AI Alone (ICER $54,451). Probabilistic sensitivity analysis demonstrated RT Alone to be cost-effective in 50% of trials, with combination therapy in 36% and AI Alone in 14%.

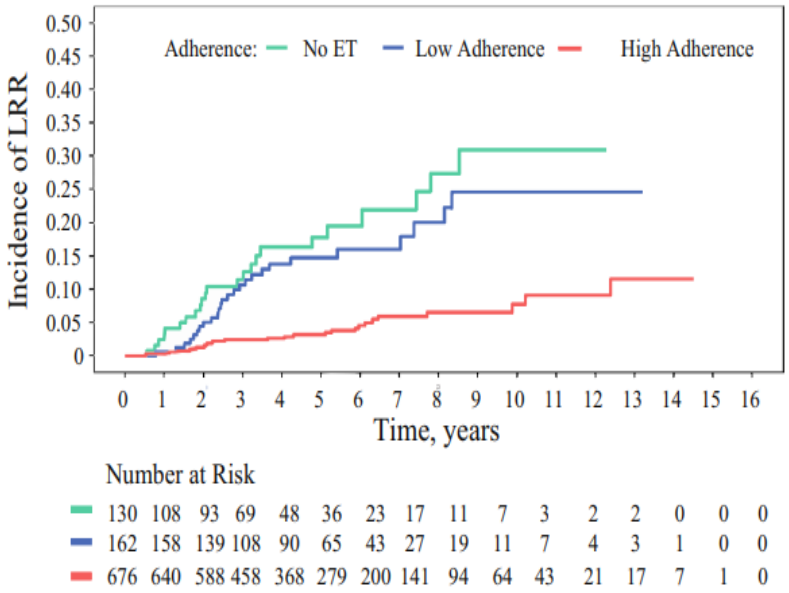
Conclusions: U-WBI alone appears the more cost-effective de-escalation strategy for these patients, compared to AI alone. Combining U-WBI and AI appears more costly but may be preferred by some patients.

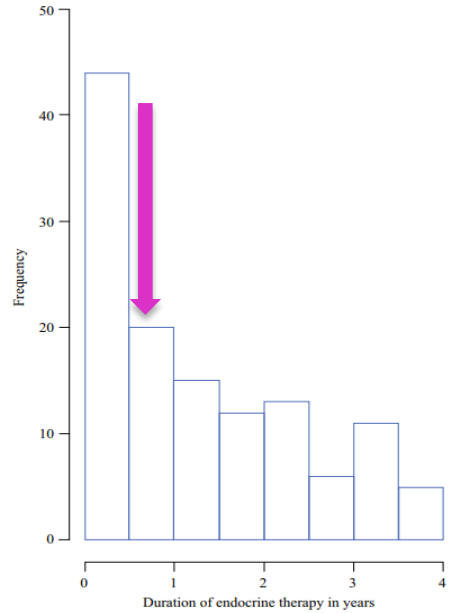
Modificato da International Journal of Radiation Oncology, Biology, Physics (2022)

ET *vs* RT

Impact of Endocrine Therapy Adherence on Outcomes in Elderly Women with Early-Stage Breast Cancer Undergoing Lumpectomy Without Radiotherapy

Regina Matar, MD[1], Varadan Sevilimedu, MBBS, DrPH[2], Mary L. Gemignani, MD[1], and Monica Morrow, MD[1]





Histogram of duration of ET use in women with low adherence to endocrine therapy (ET)

Background. National Comprehensive Center Network guidelines recommend radiotherapy (RT) omission in women age ≥ 70 years with estrogen receptor-positive (ER+), cN0, T1 tumors post-lumpectomy if they receive endocrine therapy (ET). However, little is known about the impact of poor adherence on locoregional recurrence (LRR) in elderly women forgoing RT.

Methods. Women age ≥ 70 years with pT1–2 ER+ breast cancer undergoing lumpectomy without RT from 2004 to 2019 were identified from a prospectively maintained database. ET adherence, calculated as treatment duration over follow-up time up to 5 years, was determined by chart review. We compared clinicopathologic characteristics and rates of LRR between women with high adherence (≥ 80%), low adherence (< 80%), and no ET.

Results. Of 968 women (27 bilateral cancers), adherence was high in 676 (70%) and low in 162 (17%); 130 (13%) took no ET. Younger age and use of aromatase inhibitor were associated with high adherence. On multivariable analysis, tumor size (hazard ratio [HR] 1.67, 95% confidence interval [CI] 1.03–2.68, $p = 0.04$) and high adherence (HR 0.13, 95% CI 0.07–0.26, $p < 0.001$) were significantly associated with LRR. At 53 months median follow-up, the 5-year rate of LRR was 3.1% (95% CI 2.4–3.9%) with high adherence, 14.7% (95% CI 11.7–17.7%) with low adherence, and 17.9% (95% CI 13.9–21.8%) with no ET ($p < 0.01$).

Conclusions. Although adherence to ET was high overall, in the 30% of women with low adherence or no ET, LRR rates were significantly increased. Counseling regarding the distinct toxicities of ET and RT can help patients choose the therapy to which they will likely adhere to.

Modificato da Ann Surg Oncol (2022) 29:4753–4760

Partial Breast Irradiation Versus Whole Breast Irradiation for Early Breast Cancer Patients in a Randomized Phase III Trial: The Danish Breast Cancer Group Partial Breast Irradiation Trial

PBI *vs* WBI

Birgitte V. Offersen, MD, PhD[1,2]; Jan Alsner, MSc, PhD[1]; Hanne M. Nielsen, MD, PhD[2]; Erik H. Jakobsen, MD[3]; Mette H. Nielsen, MD, PhD[4]; Lars Stenbygaard, MD[5]; Anders N. Pedersen, MD, PhD[6]; Mette S. Thomsen, MSc, PhD[7]; Esben Yates, MSc[7]; Martin Berg, MSc[8]; Ebbe L. Lorenzen, MSc, PhD[4]; Ingelise Jensen, MSc[9]; Mirjana Josipovic, MSc, PhD[6]; Maj-Britt Jensen, MSc[10]; and Jens Overgaard, MD, DMSc[1]; on behalf of the Danish Breast Cancer Group Radiotherapy Committee

PURPOSE On the basis of low risk of local recurrence in elderly patients with breast cancer after conservative surgery followed by whole breast irradiation (WBI), the Danish Breast Cancer Group initiated the noninferiority external-beam partial breast irradiation (PBI) trial (ClinicalTrials.gov identifier: NCT00892814). We hypothesized that PBI was noninferior to WBI regarding breast induration.

METHODS Patients operated with breast conservation for relatively low-risk breast cancer were randomly assigned to WBI versus PBI, and all had 40 Gy/15 fractions. The primary end point was 3-year grade 2-3 breast induration.

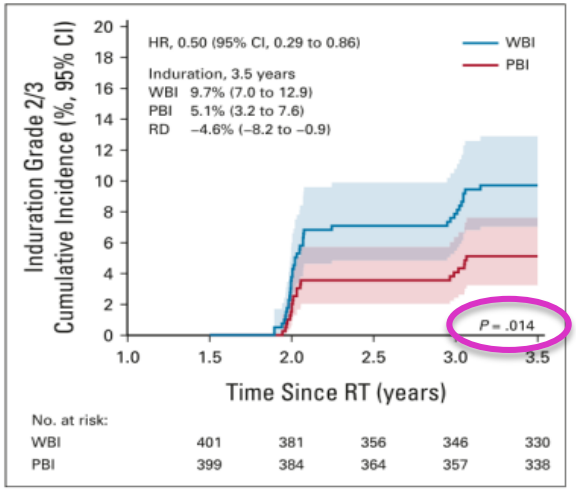
RESULTS In total, 865 evaluable patients (434 WBI and 431 PBI) were enrolled between 2009 and 2016. Median follow-up was 5.0 years (morbidity) and 7.6 years (locoregional recurrence). The 3-year rate of induration was 9.7% for WBI and 5.1% for PBI ($P = .014$). Large breast size was significantly associated with induration with a 3-year incidence of 13% (WBI) and 6% (PBI) for large-breasted patients versus 6% (WBI) and 5% (PBI) for small-breasted patients. PBI showed no increased risk of dyspigmentation, telangiectasia, edema, or pain, and patient satisfaction was high. Letrozole and smoking did not increase the risk of radiation-associated morbidity. Sixteen patients had a locoregional recurrence (six WBI and 10 PBI; $P = .28$), 20 patients had a contralateral breast cancer, and eight patients had distant failure (five WBI and three PBI). A nonbreast second cancer was detected in 73 patients (8.4%), and there was no difference between groups.

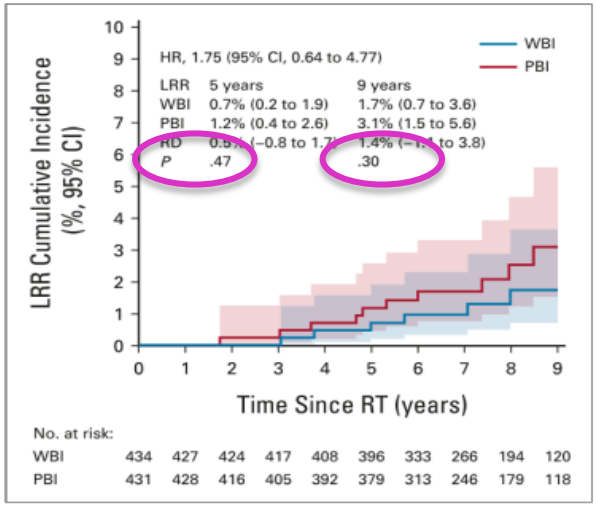
CONCLUSION External-beam PBI for patients with low-risk breast cancer was noninferior to WBI in terms of breast induration. Large breast size was a risk factor for radiation-associated induration. Few recurrences were detected and unrelated to PBI.

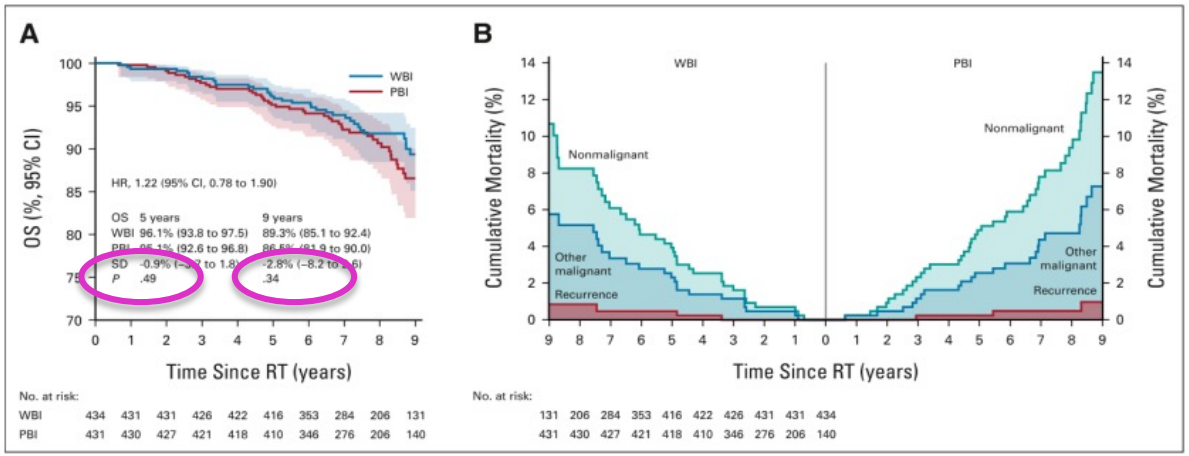
Primary endpoint:
3 years grade 2-3 breast induration

865 pts
WBI: 434 pts
PBI: 431 pts

Modificato da J Clin Oncol 40:4189-4197.







In conclusion, the DBCG PBI trial provides long-term robust evidence in favor of moderately hypofractionated external-beam PBI; so, on the basis of the trial results, the DBCG recommends this treatment for selected patients: age ≥ 50 years, breast conservation for pT1N0, unifocal, nonlobular breast cancer, ER+, HER2−, grade 1-2, and margin ≥ 2 mm. The breast morbidity was low for all patients, and cosmetic outcome was favorable and mostly even slightly better after PBI. Low grades of morbidity were also documented for patients treated with letrozole; however, large breast size was a risk factor for developing breast induration. The risk of recurrence was low and not influenced by treated volume.

Modificato da Radiotherapy and Oncology 177 (2022) 231–235

DCIS: Risk Assessment in the Molecular Era

Christin A. Knowlton,* Rachel B. Jimenez,† and Meena S. Moran*

DUCTAL CARCINOMA IN SITU

Comparison of oncotype DCIS score and DCISionRT assays

Assay	Oncotype DCIS score	DCISionRT
Technique	Genomic molecular assay to quantify expression of a 12-gene panel to determine ODX-DCIS score[25]	Immunohistochemical assay of 7 biomarkers plus 4 CPF (age, tumor size, margin status, palpability) to calculate DCISionRT score[28]
Risk groups	Low: <39 Intermediate: 39-54 High: >55-100	Low: 0-3 Elevated: >3-10
Information provided to clinician	ODX-DCIS score 10-year estimated risk of IBR and i-IBR without RT	DCISionRT score 10-year estimated risk of IBR and i-IBR without RT and predicted absolute risk reduction with RT
Use of CPF	Patient age, tumor size and year of diagnosis (>2000) used to determine 10-year IBR and i-IBR estimates	Patient age, tumor size, margin status and palpability used in the calculation of the DCISionRT score
Cost	>$4600[64]	$1010*,[67]

Abbreviations: DCIS, ductal carcinoma in situ; ODX, Oncotype DX; CPF, clinic-pathologic features; IBE, in-breast recurrence; iIBR, invasive in-breast recurrence; RT, radiation therapy.
* Base price from manufacturer.

Modificato da Semin Radiat Oncol 32:189–197 © 2022

A Novel Biosignature Identifies Patients With DCIS With High Risk of Local Recurrence After Breast Conserving Surgery and Radiation Therapy

Frank A. Vicini, MD,* G. Bruce Mann, MBBS, PhD,† Chirag Shah, MD,‡ Sheila Weinmann, PhD, MPH,§ Michael C. Leo, PhD,‖ Pat Whitworth, MD,‖ Rachel Rabinovitch, MD,¶ Mylin A. Torres, MD,# Julie A. Margenthaler, MD,** David Dabbs, MD,†† Jess Savala, MD,†† Steven C. Shivers, PhD,†† Karuna Mittal, PhD,†† Fredrik Wärnberg, MD, PhD,‡‡ and Troy Bremer, PhD††

DCIS Pts treated with BCS with or without RT at centers in the US, Australia, and Sweden (n = 926) were evaluated.

Purpose: There is an unmet need to identify women diagnosed with ductal carcinoma in situ (DCIS) with a low risk of in-breast recurrence (IBR) after breast conserving surgery (BCS), which could omit radiation therapy (RT), and also to identify those with elevated IBR risk remaining after BCS plus RT. We evaluated a novel biosignature for a residual risk subtype (RRt) to help identify patients with elevated IBR risk after BCS plus RT.

Methods and Materials: Women with DCIS treated with BCS with or without RT at centers in the US, Australia, and Sweden (n = 926) were evaluated. Patients were classified into 3 biosignature risk groups using the decision score (DS) and the RRt category: (1) Low Risk (DS ≤2.8 without RRt), (2) Elevated Risk (DS >2.8 without RRt), and (3) Residual Risk (DS >2.8 with RRt). Total and invasive IBR rates were assessed by risk group and treatment.

Results: In patients at low risk, there was no significant difference in IBR rates with or without RT (total, $P = .8$; invasive IBR, $P = .7$), and there were low overall 10-year rates (total, 5.1%; invasive, 2.7%). In patients with elevated risk, IBR rates were decreased with RT (total: hazard ratio [HR], 0.25; $P < .001$; invasive: HR, 0.28; $P = .005$); 10-year rates were 20.6% versus 4.9% (total) and 10.9% versus 3.1% (invasive). In patients with residual risk, although IBR rates decreased with RT after BCS (total: HR, 0.21; $P < .001$; invasive: HR, 0.29; $P = .028$), IBR rates remained significantly higher after RT compared with patients with elevated risk (HR, 2.5; 95% CI, 1.2-5.4; $P = .010$), with 10-year rates of 42.1% versus 14.7% (total) and 18.3% versus 6.5% (invasive).

Conclusions: The novel biosignature identified patients with 3 distinct risk profiles: Low Risk patients with a low recurrence risk with or without adjuvant RT, Elevated Risk patients with excellent outcomes after BCS plus RT, and Residual Risk patients with an elevated recurrence risk remaining after BCS plus RT, warranting potential intensified or alternative treatment approaches.

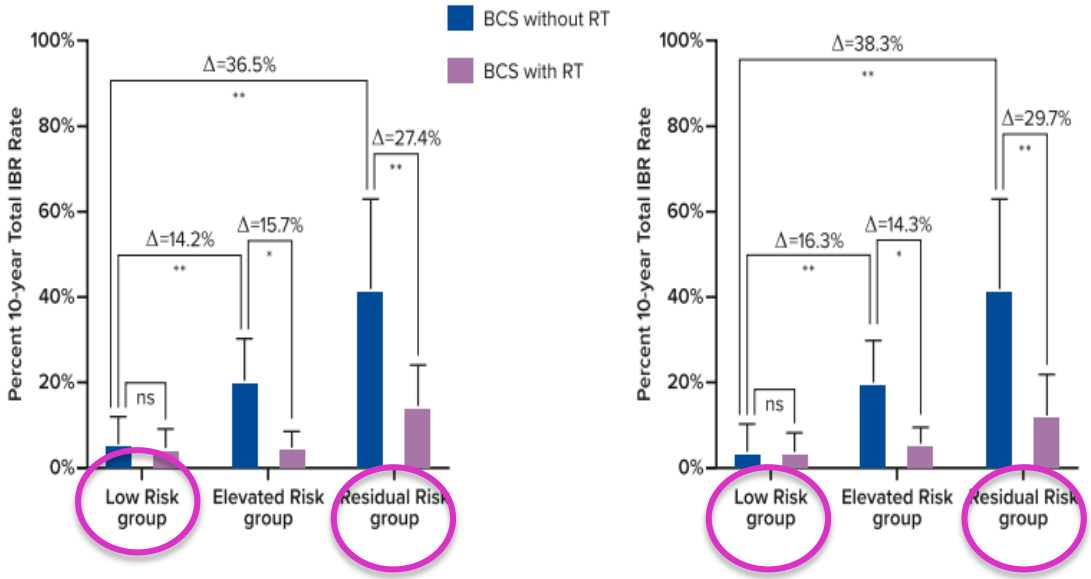
926 pts

RRt: Residual Risk subtype

An algorithm was prespecified to combine biomarkers (used by the DS biosignature) in a novel manner (distinct from the original DS biosignature) based on the biologic hypothesis that an activated EGFR/HER2/KRAS pathway would drive a proliferative, aggressive disease profile and thus could identify a subgroup of patients with higher residual risk after adjuvant RT. It was hypothesized that a test that integrates the DS biosignature with this novel biosignature would identify a subgroup of patients with a high risk of recurrence after BCS and a worse-than-expected outcome after treatment with BCS adjuvant RT—ie, a residual risk subtype (RRt) group.

Modificato da Int J Radiation Oncol Biol Phys, Vol. 115, No. 1, pp. 93–102, 2023

The DS biosignature result alone was cross-validated in cohorts from Uppsala University Hospital and Västmanland County Hospital, Sweden (UUH), (patients recruited between 1986 and 2004), University of Massachusetts, Worcester (UMASS),11 (patients recruited between 1999 and 2008), and independently validated in patients recruited between 1990 to 2007 at Kaiser Permanente Northwest (KPNW)12 and between 2006 and 2011 at The Royal Melbourne Hospital and Royal Women's Hospital, Parkville, Victoria, Australia (RMH).



Ten-year in-breast recurrence (IBR) rates after breast conserving surgery (BCS) by radiation therapy (RT) treatment and by biosignature risk group. Rates of IBR 10 years after treatment with BCS plus RT or BCS without RT by biosignature risk groups. Biosignature risk groups (defined by decision score [DS] and residual risk subtype [RRt]): Low- Risk group (DS < 2.8, without RRt), Elevated- Risk group (DS >2 .8 without RRt), and Residual Risk group (DS > 2.8 with RRt). (A) All evaluable patients (n = 926). (B) RMH/KPNW study cohorts (n = 593). *P < .05; **P < .001; ns = not significant.

Relative rate reduction in IBR from radiation therapy treatment by biosignature risk groups*

	Total IBR relative RT risk reduction in all evaluable patients†			Total IBR relative RT risk reduction in RMH/KPNW study cohorts‡		
Risk group	n (%) (926 patients, 77 events)	HR (95% CI)§	*P* value	n (%) (593 patients, 45 events)	HR (95% CI)§	*P* value
Low Risk	338 (37)	0.82 (0.29-2.3)	.71	230 (39)	0.81 (0.19-3.4)	.78
Elevated Risk	399 (43)	0.23 (0.11-0.47)	<.001	242 (41)	0.28 (0.11-0.69)	.006
Residual Risk	189 (20)	0.20 (0.10-0.42)	<.001	121 (20)	0.16 (0.06-0.42)	<.001

Abbreviations: HR = hazard ratio; IBR = in-breast recurrence; RT = radiation therapy.
* Relative IBR rate reduction for RT treatment by biosignature risk group over an interval of 0-10 years.
† Total IBR relative risk reduction for RT among all evaluable patients.
‡ Total IBR relative risk reduction for RT among the RMH/KPNW study cohorts.
§ Cox proportional hazards analysis for patients treated with breast-conserving surgery (BCS) plus RT compared with BCS without RT within biosignature risk groups. *P* values are from the Wald test. Biosignature risk categories: LowRisk group (decision score [DS] <2.8, without residual risk subtype [RRt]), Elevated Risk group (DS >2.8 without RRt), and Residual Risk group (DS >2.8 with RRt).

Boost?
ET?

Modificato da Int J Radiation Oncol Biol Phys, Vol. 115, No. 1, pp. 93–102, 2023

Radiation doses and fractionation schedules in non-low-risk ductal carcinoma in situ in the breast (BIG 3–07/TROG 07.01): a randomised, factorial, multicentre, open-label, phase 3 study

Boon H Chua, Emma K Link, Ian H Kunkler, Timothy J Whelan, A Helen Westenberg, Guenther Gruber, Guy Bryant, Verity Ahern, Kash Purohit, Peter H Graham, Mohamed Akra, Orla McArdle, Peter O'Brien, Jennifer A Harvey, Carine Kirkove, John H Maduro, Ian D Campbell, Geoff P Delaney, Joseph D Martin, T Trinh T Vu, Thierry M Muanza, Anthony Neal, Ivo A Olivotto, on behalf of the BIG 3-07/TROG 07.01 trial investigators*

Methods The study was an international, randomised, unmasked, phase 3 trial involving 136 participating centres of six clinical trials organisations in 11 countries (Australia, New Zealand, Singapore, Canada, the Netherlands, Belgium, France, Switzerland, Italy, Ireland, and the UK). Eligible patients were women aged 18 years or older with unilateral, histologically proven, non-low-risk DCIS treated by breast-conserving surgery with at least 1 mm of clear radial resection margins. They were assigned to one of four groups (1:1:1:1) of no tumour bed boost versus boost after conventional versus hypofractionated WBI, or randomly assigned to one of two groups (1:1) of no boost versus boost after each centre prespecified conventional or hypofractionated WBI. The conventional WBI used was 50 Gy in 25 fractions, and hypofractionated WBI was 42·5 Gy in 16 fractions. A boost dose of 16 Gy in eight fractions, if allocated, was delivered after WBI. Patients and clinicians were not masked to treatment allocation. The primary endpoint was time to local recurrence. This trial is registered with ClinicalTrials.gov (NCT00470236).

Findings Between June 25, 2007, and June 30, 2014, 1608 patients were randomly assigned to have no boost (805 patients) or boost (803 patients). Conventional WBI was given to 831 patients, and hypofractionated WBI was given to 777 patients. Median follow-up was 6·6 years. The 5-year free-from-local-recurrence rates were 92·7% (95% CI 90·6–94·4%) in the no-boost group and 97·1% (95·6–98·1%) in the boost group (hazard ratio 0·47; 0·31–0·72; p<0·001). The boost group had higher rates of grade 2 or higher breast pain (10% [8–12%] *vs* 14% [12–17%], p=0·003) and induration (6% [5–8%] *vs* 14% [11–16%], p<0·001).

1608 pts

BOOST: 803 pts

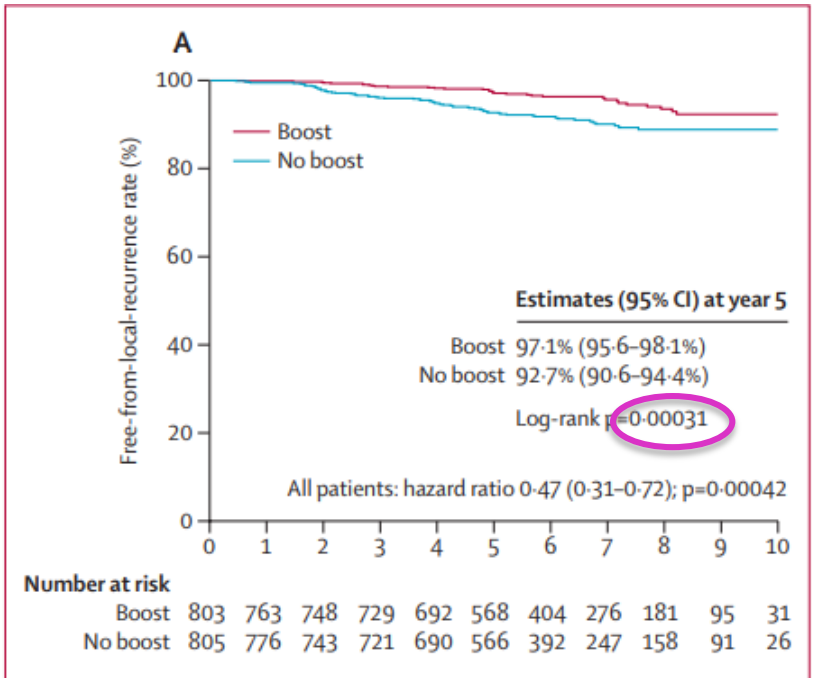
NO BOOST: 805 pts

NON-LOW-RISK CDIS: **age (<50 years) symptomatic presentation, palpable tumour, tumour size measuring 15 mm or more, multifocal disease, intermediate or high nuclear grade, central necrosis, comedo-histology, or a radial surgical margin of less than 10 mm**

Primary endpoint: time to local recurrence

The study was designed to detect a clinically relevant 3% difference in 5-year free-from-local-recurrence rates between the no-boost and boost groups (93% vs 96%; hazard ratio, 0·56) with 90% power, a 5% two-sided α level, and 1:1 allocation between the groups

Modificato da Lancet 2022; 400: 431–40



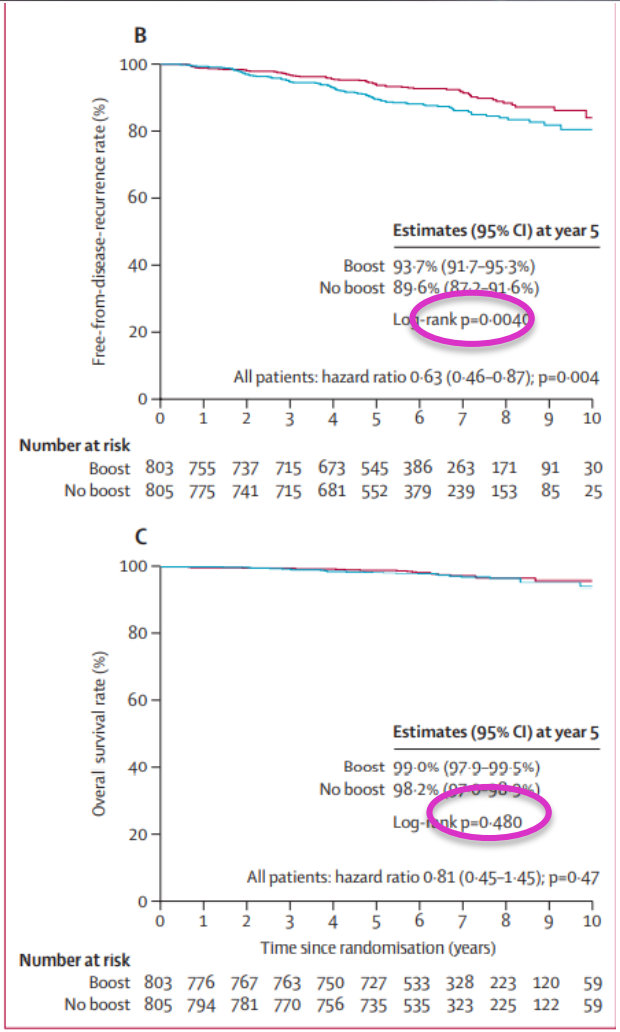
Category A was a random assignment of patients to one of four groups: boost to the tumour bed versus no boost and conventional versus hypofractionated WBI (allocation ratio, 1:1:1:1). Category B was a two-group random assignment of boost versus no boost after conventional WBI, and category C was a two-group random assignment between boost versus no boost after hypofractionated WBI (allocation ratio for both, 1:1).

Between June 25, 2007, and June 30, 2014, 1608 patients were randomly assigned (category A, 503 patients; category B, 581 patients; category C, 524 patients) to the no-boost group (805 patients) or the boost group (803 patients). WBI was conventional in 831 patients, and hypofractionated in 777 patients.

No statistically significant differences in 5-year free-from-disease-recurrence rates between conventional versus hypofractionated WBI groups

The boost group had higher rates of grade 2 or greater breast pain (p=0·003) and induration (p<0.001) than no boost group, with no suggestion of interaction with WBI dose fractionation

Modificato da Lancet 2022; 400: 431–40



Implications of all the available evidence

Our results provide the first randomised trial data to support the use of boost radiation after postoperative WBI, and moderately hypofractionated WBI in patients with non-low-risk DCIS to improve the balance of local control, toxicity, and socioeconomic burdens of treatment. The international scale of our study supports the generalisability of the findings. Because the moderately hypofractionated WBI schedule used in our study might not be the clinical limit of hypofractionation in DCIS, future research on shorter WBI dose fractionation in DCIS might further improve patient convenience and streamline the use of radiotherapy resources to improve access to care for these patients.

Modificato da Lancet 2022; 400: 431–40

HIGHLIGHTS in RADIOTERAPIA

Update degli Studi Practice Changing 2022

Postmastectomy radiotherapy in high-risk breast cancer patients given adjuvant systemic therapy. A 30-year long-term report from the Danish breast cancer cooperative group DBCG 82bc trial ☆

POST MASTECTOMY RT

Marie Overgaard [a], Hanne Melgaard Nielsen [b], Trine Tramm [c], Inger Højris [b], Trine Lønbo Grantzau [a], Jan Alsner [a], Birgitte Vrou Offersen [a,b], Jens Overgaard [a,*], on behalf of the DBCG Radiotherapy Group [1]

Background: Between 1982 and 1990 the Danish Breast Cancer Cooperative Group (DBCG) conducted a randomized trial in high-risk pre- and postmenopausal (<70 years) breast cancer patients comparing mastectomy plus adjuvant systemic therapy alone versus the same treatment plus postoperative irradiation.

3083 pts

PMRT: 1538 pts

No PMRT: 1545 pts

PMRT: 48–50 Gy in 22–25 fractions in 5 weeks to the chest wall and regional lymph nodes (internal mammary nodes, periclavicular nodes, and the axilla)

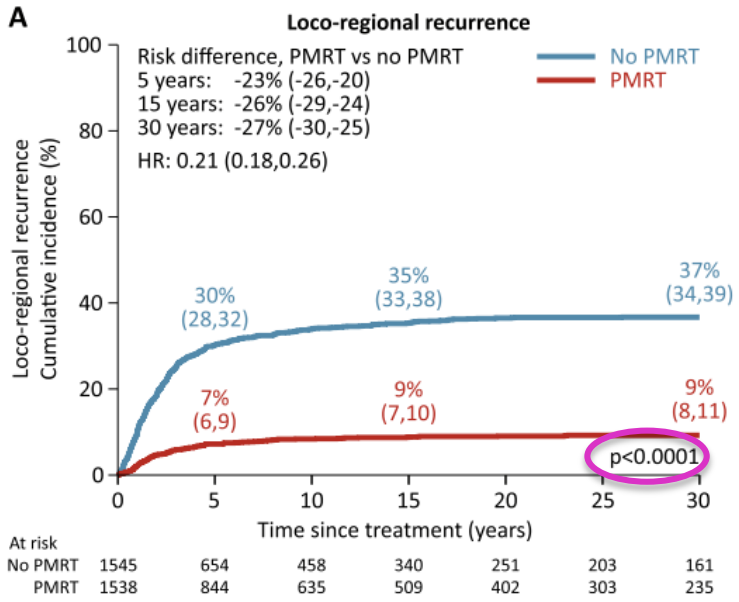
Primary endpoints : loco-regional recurrence (LRR) and overall mortality.

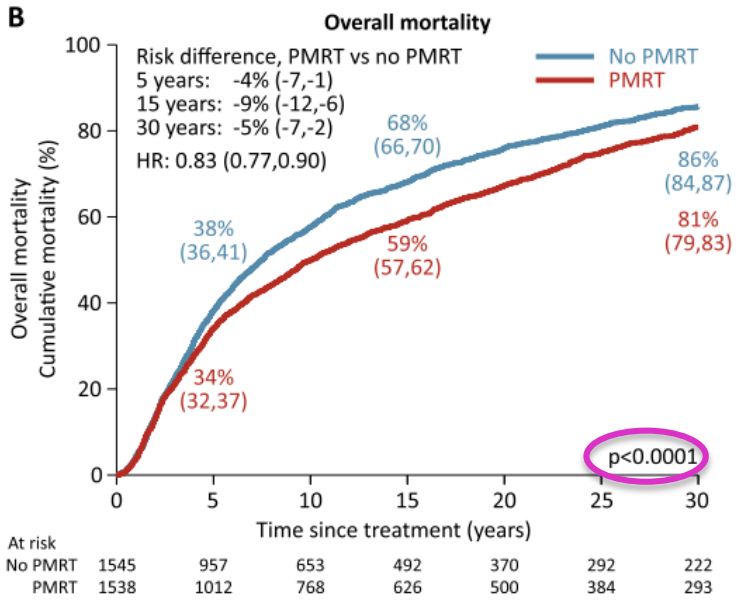
Secondary endpoints: distant metastasis, any recurrence (LRR or distant metastasis), contralateral BC, BC death, second malignant disease, ischemic heart disease and other causes of death.

Results: Overall the 30-year cumulative incidence of loco-regional recurrence was 9% in irradiated patients versus 37% in non-irradiated patients who received adjuvant systemic therapy alone (HR: 0.21 [95% cfl 0.18–0.26]). Distant metastasis probability at 30 years was 49% in irradiated patients compared to 60% in non-irradiated (HR: 0.77 [0.70–0.84]). Consequently, these figures resulted in a reduced breast cancer mortality: 56% vs 67% (HR: 0.75 [0.69–0.82], and overall mortality (81% vs 86% at 30 years ($p < 0.0001$), HR: 0.83 [0.77–0.90] in favor of irradiation. Radiotherapy did not result in any significant excess death of other courses, such as ischemic heart disease, HR: 0.82 [0.58–1.18]; nor secondary lung cancer HR: 1.44 [0.92–2.24], or other non-cancer related death HR: 1.15 [0.92–1.45].

Conclusion: The study definitely demonstrate that optimal long-term treatment benefit of high-risk breast cancer can only be achieved if both loco-regional and systemic tumor control are aimed for. Therefore, radiotherapy has an important role in the multidisciplinary treatment of breast cancer. The PMRT treatment did not result in excess ischemic heart damage, nor in other non-breast cancer related death.

Modificato da Radiotherapy and Oncology 170 (2022) 4–13





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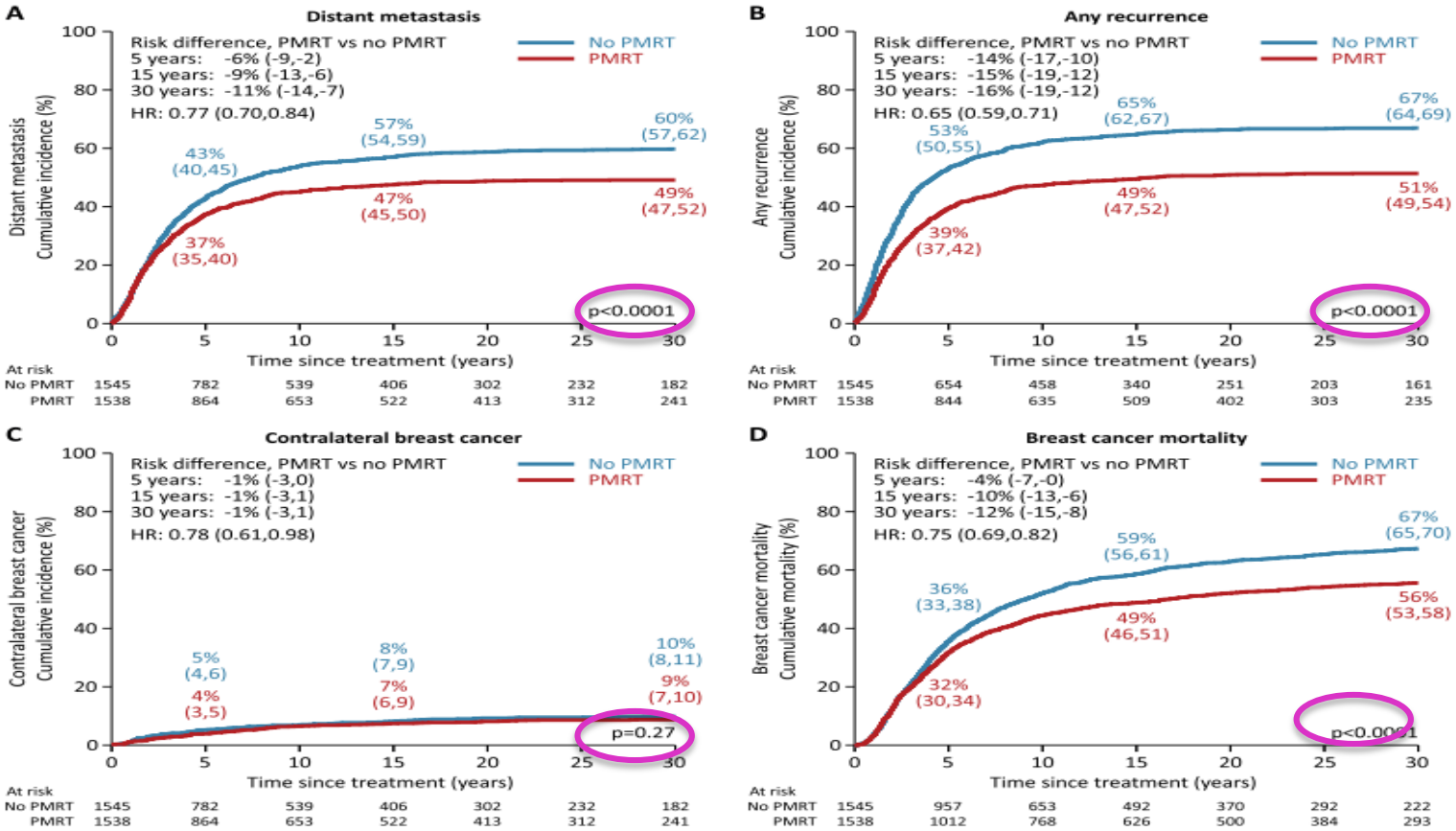

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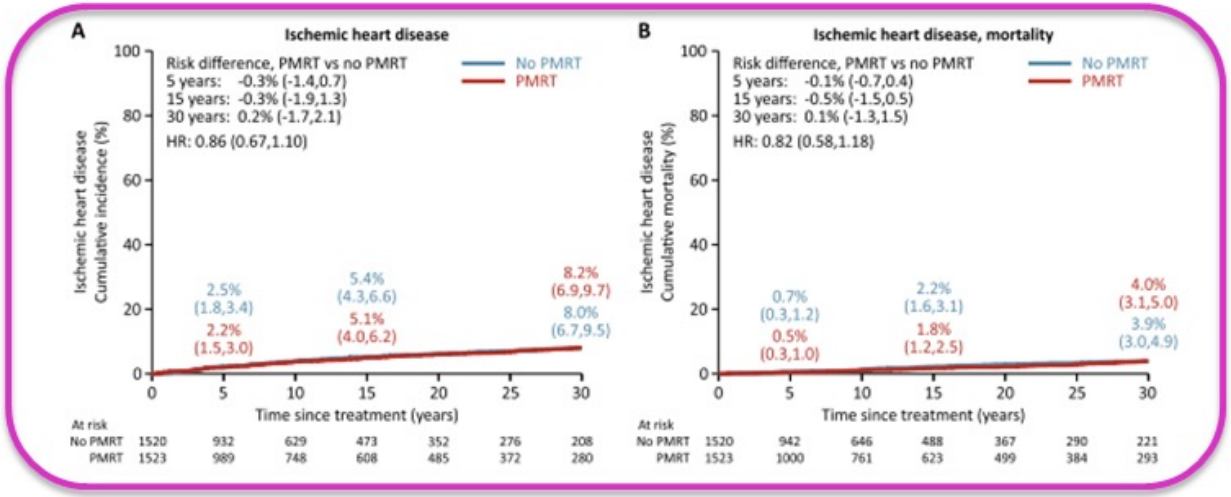
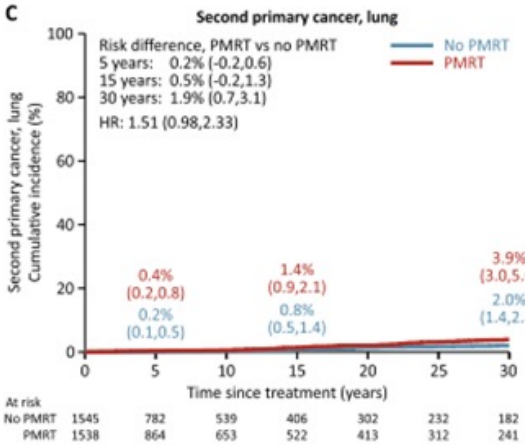
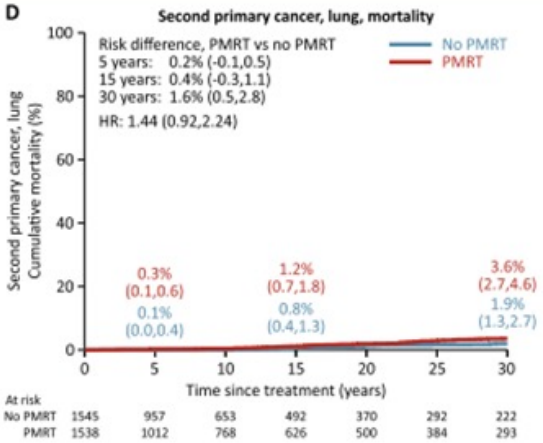
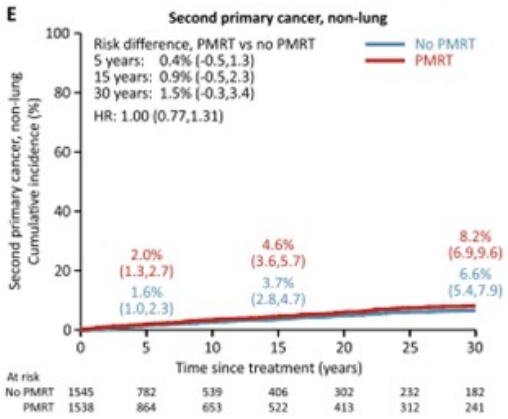
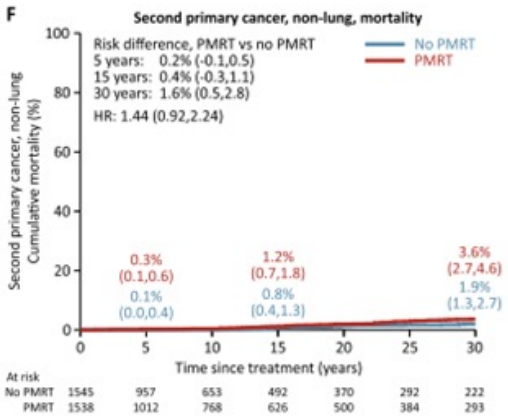










Modificato da Radiotherapy and Oncology 170 (2022) 4–13

Internal Mammary Node Irradiation in Patients With Node-Positive Early Breast Cancer: Fifteen-Year Results From the Danish Breast Cancer Group Internal Mammary Node Study

Lise B.J. Thorsen, MD, PhD[1,2]; Jens Overgaard, MD, DMSc[1]; Louise W. Matthiessen, MD, PhD[3]; Martin Berg, MSc[4]; Lars Stenbygaard, MD[5]; Anders N. Pedersen, MD, PhD[6]; Mette H. Nielsen, MD, PhD[7]; Marie Overgaard, MD[2]; and Birgitte Vrou Offersen, MD, PhD[1,2]; on behalf of the DBCG Radiotherapy Committee

PURPOSE The Danish Breast Cancer Group Internal Mammary Node study demonstrated improved 8-year overall survival (OS) with internal mammary node irradiation (IMNI) in patients with node-positive early breast cancer. Here, we present long-term results from the Danish Breast Cancer Group Internal Mammary Node study cohort.

PATIENTS AND METHODS This nationwide, prospective cohort study allocated patients with node-positive early breast cancer to adjuvant radiotherapy with or without IMNI depending on cancer laterality. Patients with right-sided cancer received IMNI. Patients with left-sided cancer were treated without IMNI because of risk of radiation-induced heart disease. Other treatment was independent of laterality. The primary study end point was OS. Secondary end points were distant recurrence and breast cancer mortality. Analyses were by intention to treat.

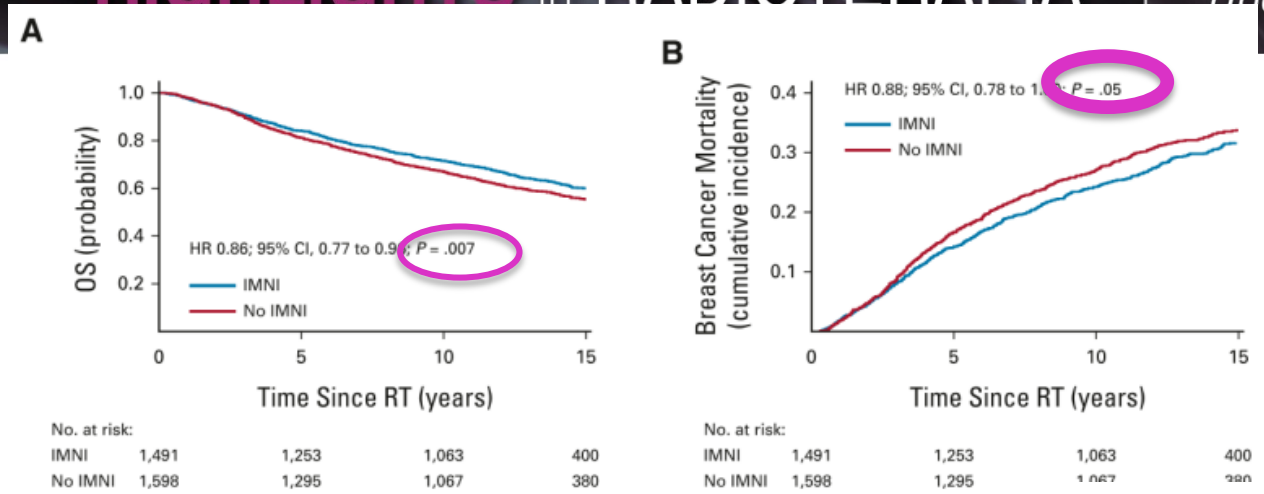
RESULTS During 2003-2007, 3,089 women were allocated to IMNI (right-sided, n = 1,491) or no IMNI (left-sided, n = 1,598). With a median follow-up of 14.8 years, 589 patients with and 701 patients without IMNI had died. The corresponding 15-year OS rates were 60.1% and 55.4%. The adjusted hazard ratio (HR) for death was 0.86 (95% CI, 0.77 to 0.96; $P = .007$) in favor of IMNI. The 15-year risk of developing distant recurrence was 35.6% (523 recurrences) and 38.6% (602 recurrences) with vs. without IMNI (adjusted HR, 0.88 [95% CI, 0.79 to 0.99; $P = .04$]). The 15-year breast cancer mortality with IMNI was 31.7% (467 deaths) compared with 33.9% (537 deaths) without IMNI (adjusted HR, 0.88 [95% CI, 0.78 to 1.00; $P = .05$]). The distribution of other deaths was similar across groups.

CONCLUSION In patients with node-positive early breast cancer treated with IMNI or without IMNI depending on breast cancer laterality, IMNI reduced the risk of distant recurrence and death from breast cancer, thereby improving long-term survival.

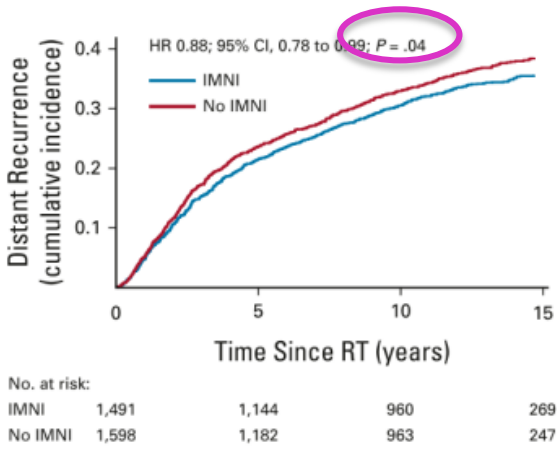
INTERNAL MAMMARY NODES RT

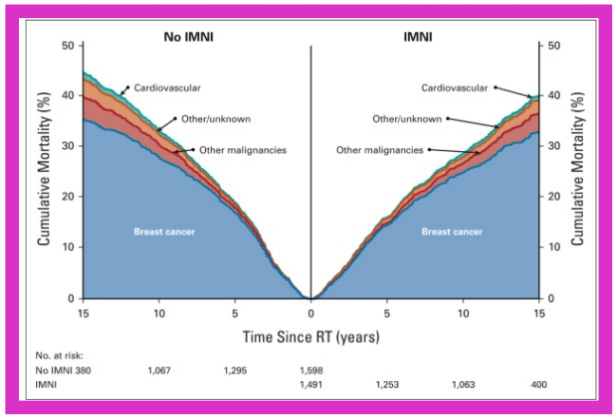
3089 pts
IMN RT (right side): 1491
no IMN RT (left side): 1598
median FUP 14 yrs
Enrollment: 2003-2007

Modificato da J Clin Oncol 40:4198-4206. © 2022 I



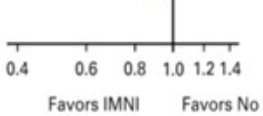
Kaplan-Meier estimates and associated HRs of (A) OS, (B) cumulated incidence of breast cancer mortality, and (C) distant recurrence in patients with IMNI and without IMNI. HR, hazard ratio; IMNI, internal mammary node irradiation; OS, overall survival; RT, radiotherapy.





Subgroup	IMNI Patients	IMNI Events	No IMNI Patients	No IMNI Events	HR (95% CI)	15-Year Survival Rate, % IMNI	No IMNI
Lateral 1-3 nodes	511	149	564	167	0.99 (0.80 to 1.24)	70.5	69.3
Medial/central 1-3 nodes	353	118	382	152	0.80 (0.63 to 1.01)	65.7	59.4
Lateral ≥ 4 nodes	392	186	384	210	0.78 (0.64 to 0.95)	53.0	44.9
Medial/central ≥ 4 nodes	223	132	260	168	0.91 (0.73 to 1.15)	39.4	34.9
All patients	1,479	585	1,590	697	0.86 (0.77 to 0.96)	60.1	55.4

Test for heterogeneity, $P = .351$



Overall survival rates and corresponding HRs with IMNI versus without IMNI within subgroups defined by tumor location and the number of axillary nodes involved. HR, hazard ratio; IMNI, internal mammary node irradiation.

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Effect of Elective Internal Mammary Node Irradiation on Disease-Free Survival in Women With Node-Positive Breast Cancer: A Randomized Phase 3 Clinical Trial

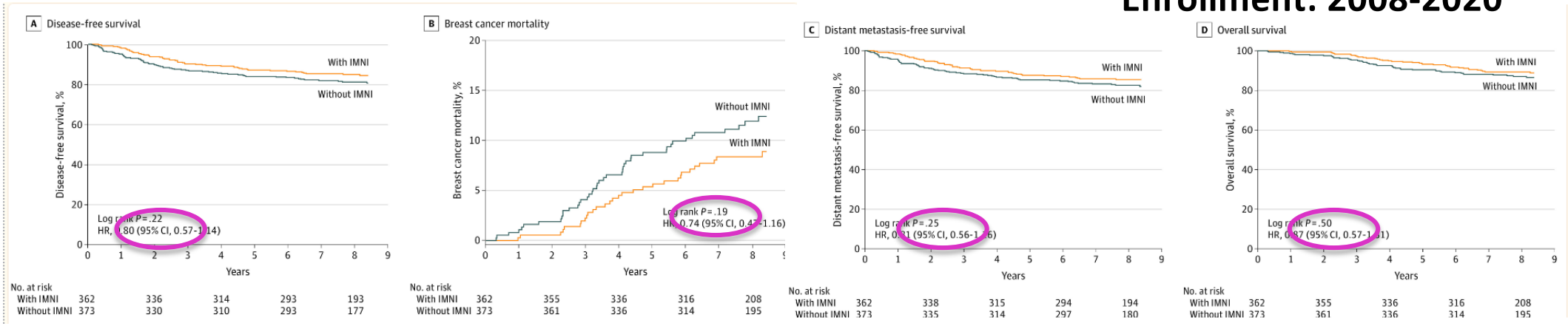
Yong Bae Kim , Hwa Kyung Byun , Dae Yong Kim , Sung-Ja Ahn , Hyung-Sik Lee , Won Park , Su Ssan Kim , Jin Hee Kim , Kyu Chan Lee , Ik Jae Lee , Won Taek Kim , Hyun Soo Shin , Kyubo Kim , Kyung Hwan Shin , Chung Mo Nam , Chang-Ok Suh

INTERNAL MAMMARY NODES RT

All patients underwent regional nodal irradiation along with breast or chest wall irradiation. They were randomized 1:1 receive RT with or without IMNI
RT: 1.8-2 Gy up to 45-50 Gy

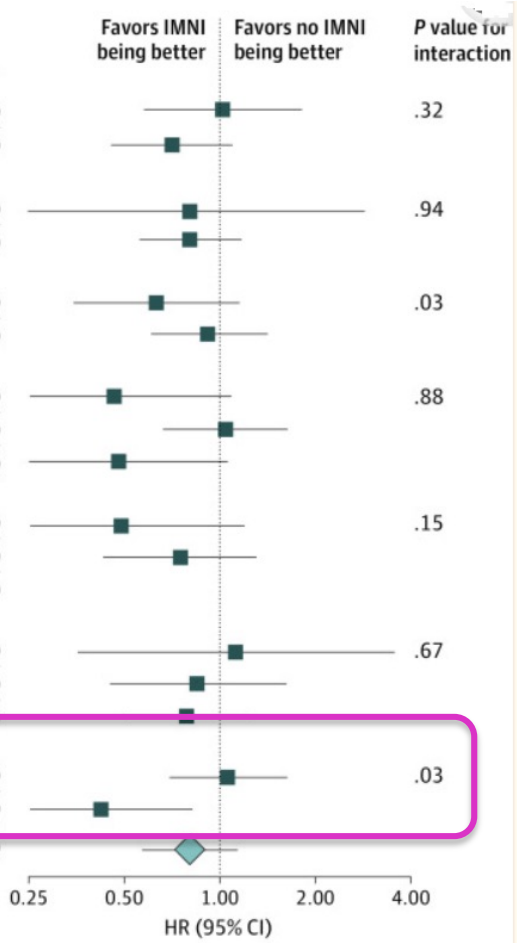
735 pts
RNI w/o IMN RT: 373 pts
RNI with IMN RT: 362 pts
Enrollment: 2008-2020

Primary end point: 7-year DFS. Secondary end points: overall survival, breast cancer–specific survival and toxic effects.



Modificato da JAMA Oncol. 2022 Jan 1;8(1):96-105.

Subgroup	No. of events	Total No.	No. of events	Total No.	HR (95% CI)	P value for interaction
Type of surgery						
BCS	23	187	23	180	1.02 (0.57-1.81)	.32
MRM	46	186	35	182	0.70 (0.45-1.09)	
Nodes removed						
<10	5	30	5	37	0.81 (0.23-2.84)	.94
≥10	64	343	53	324	0.81 (0.56-1.16)	
Hormone receptor						
ER and PR negative	28	108	17	82	0.63 (0.35-1.17)	.03
ER and/or PR positive	41	263	40	275	0.92 (0.60-1.42)	
T stage						
T1	14	111	9	119	0.46 (0.20-1.08)	.88
T2	40	218	36	194	1.04 (0.66-1.63)	
T3 or T4	15	44	13	49	0.48 (0.22-1.05)	
N stage						
N1	15	157	7	147	0.49 (0.20-1.19)	.15
N2	29	136	22	133	0.75 (0.43-1.30)	
N3	25	80	29	82	1.03 (0.60-1.76)	
Grade						
1	6	44	6	46	1.12 (0.35-3.52)	.67
2	20	144	18	148	0.85 (0.45-1.60)	
3	41	173	32	151	0.70 (0.43-1.24)	
Tumor location						
Lateral	41	220	43	208	1.05 (0.69-1.62)	.03
Medial or central	28	153	14	153	0.42 (0.22-0.82)	
All	69	373	58	362	0.80 (0.57-1.14)	



The trial was designed to detect a difference of 10 percentage points (70% with IMNI vs 60% without IMNI) in the 7-year DFS

No differences in the toxic effect rates were found between the groups treated with IMNI or without IMNI, including arm edema (24.0% vs 22.3%), brachial plexopathy (0.8% vs 0.5%), rib fracture (1.1% vs 0.3%), skin reaction (17.7% vs 18.2%), soft-tissue fibrosis and necrosis (1.4% vs 1.3%), and cardiac problems (2.2% vs 1.3%)

This randomized clinical trial found that including IMNI in regional nodal irradiation did not significantly improve the DFS in patients with node-positive breast cancer. However, patients with medially or centrally located tumors may benefit from the use of IMNI

Modificato da JAMA Oncol. 2022 Jan 1;8(1):96-105.

De-escalation of radiotherapy after primary chemotherapy in cT1–2N1 breast cancer (RAPCHEM; BOOG 2010–03): 5-year follow-up results of a Dutch, prospective, registry study

Sabine R de Wild, Linda de Munck, Janine M Simons, Janneke Verloop, Thijs van Dalen, Paula H M Elkhuizen, Ruud M A Houben, A Elise van Leeuwen, Sabine C Linn, Ruud M Pijnappel, Philip M P Poortmans, Luc J A Strobbe, Jelle Wesseling, Adri C Voogd, Liesbeth J Boersma

Methods In this prospective registry study (RAPCHEM, BOOG 2010–03), patients referred to one of 17 participating radiation oncology centres in the Netherlands between Jan 1, 2011, and Jan 1, 2015, with cT1–2N1 breast cancer (one to three suspicious nodes on imaging before primary chemotherapy, of which at least one had been pathologically confirmed), and who were treated with primary chemotherapy and surgery of the breast and axilla were included in the study. The study guideline comprised three risk groups for locoregional recurrence, with corresponding locoregional radiotherapy recommendations: no chest wall radiotherapy and no regional radiotherapy in the low-risk group, only local radiotherapy in the intermediate-risk group, and locoregional radiotherapy in the high-risk group. Radiotherapy consisted of a biologically equivalent dose of 25 fractions of 2 Gy, with or without a boost. During the study period, the generally applied radiotherapy technique in the Netherlands was forward-planned or inverse-planned intensity modulated radiotherapy. 5-year follow-up was assessed, taking into account adherence to the study guideline, with locoregional recurrence rate as primary endpoint. We hypothesised that 5-year locoregional recurrence rate would be less than 4% (upper-limit 95% CI 7·8%). This study was registered at ClinicalTrials.gov, NCT01279304, and is completed.

Findings 838 patients were eligible for 5-year follow-up analyses: 291 in the low-risk group, 370 in the intermediate-risk group, and 177 in the high-risk group. The 5-year locoregional recurrence rate in all patients was 2·2% (95% CI 1·4–3·4). The 5-year locoregional recurrence rate was 2·1% (0·9–4·3) in the low-risk group, 2·2% (1·0–4·1) in the intermediate-risk group, and 2·3% (0·8–5·5) in the high-risk group. If the study guideline was followed, the locoregional recurrence rate was 2·3% (0·8–5·3) for the low-risk group, 1·0% (0·2–3·4) for the intermediate-risk group, and 1·4% (0·3–4·5) for the high-risk group.

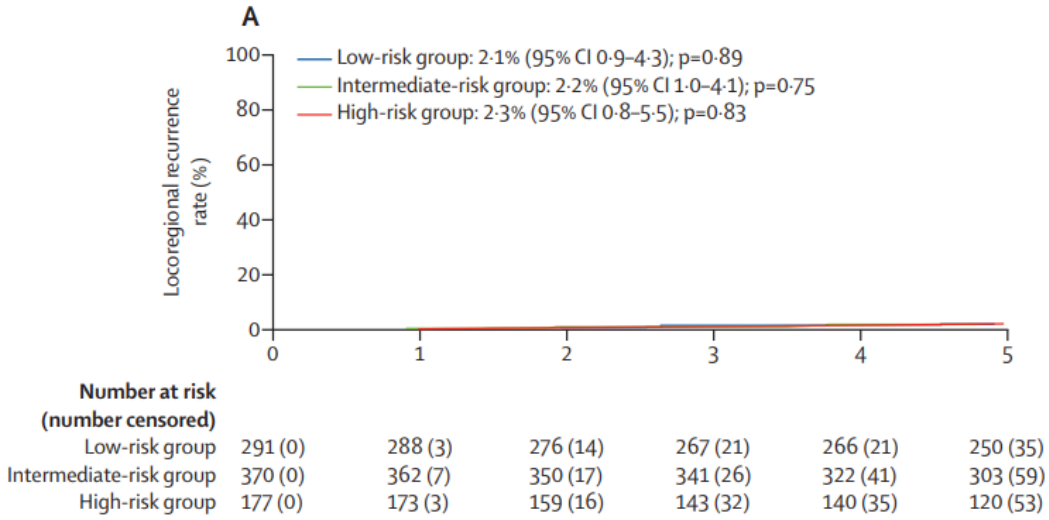
Primary endpoint: **5-year locoregional recurrence rate**

5-yrs LRR<4% support the hypothesis that is safe to DE-ESCALATE RT based on LRR risk in cT1-2 N1 pts treated with PST

RT after PST

	Radiotherapy after breast conserving therapy	Radiotherapy after mastectomy
Low-risk group		
ypN0 (ALND)	Whole breast radiotherapy	–
If SLNB before primary chemotherapy and no ALND: cN1mi (SLNB), no risk factor*; or if SLNB after primary chemotherapy and no ALND: ypN0 (SLNB)	Whole breast radiotherapy	–
Intermediate-risk group		
ypN1 (ALND)	Whole breast radiotherapy	Chest wall radiotherapy
If SLNB before primary chemotherapy and no ALND†: cN1mi (SLNB), ≥1 risk factor*, or cN1 (SLNB), ≤2 macrometastases, no risk factor*; or if SLNB after primary chemotherapy and no ALND†: ypN1mi (SLNB), no risk factor*	Whole breast radiotherapy; in addition axilla level I and II†	Chest wall radiotherapy; in addition axilla level I and II†
High-risk group		
ypN2–3 (ALND)	Whole breast radiotherapy; axilla level III and IV	Chest wall radiotherapy; axilla level III and IV
If SLNB before primary chemotherapy and no ALND†: cN1 (SLNB), with ≤2 macrometastases and ≥1 risk factor*, or ≥3 macrometastases; or if SLNB after primary chemotherapy and no ALND†: ypN1mi (SLNB), ≥1 risk factor*, or ypN1 (SLNB)	Whole breast radiotherapy; axilla level III and IV; in addition axilla level I and II†	Chest wall radiotherapy; axilla level III and IV; in addition axilla level I and II†

Modificato da Lancet Oncol 2022; 23: 1201–10



Number at risk (number censored)						
Low-risk group	291 (0)	288 (3)	276 (14)	267 (21)	266 (21)	250 (35)
Intermediate-risk group	370 (0)	362 (7)	350 (17)	341 (26)	322 (41)	303 (59)
High-risk group	177 (0)	173 (3)	159 (16)	143 (32)	140 (35)	120 (53)

To our knowledge, this is the first prospective study developed to evaluate the oncological safety of de-escalated locoregional radiotherapy in patients with cT1–2N1 breast cancer, according to a predefined consensus-based study guideline. Results from this study suggest that it is oncologically safe to de-escalate locoregional radiotherapy in this group, based on ypN-status, following axillary lymph node dissection (ALND). This study supports the hypothesis that locoregional radiotherapy can be omitted in selected patients in whom ALND is performed (ie, no chest wall radiotherapy and no regional radiotherapy in case of ypN0, and no regional radiotherapy in case of ypN1).

5-yrs LRR RATE: WHOLE SERIES 2.2%

LOW RISK 2.1 %

INTERMEDIATE RISK 2.2%

HIGH RISK 2.3%

RT Omission in selected pts: low-risk – ALND

Modificato da Lancet Oncol 2022; 23: 1201–10

Safety of pre- or postoperative accelerated radiotherapy in 5 fractions: A randomized pilot trial

Vakaet Vincent, MD [a, b], Van Hulle Hans, PhD [a, *], Van de Vijver Koen [c, d], Hilderson Ingeborg [e], Naert Eline [e, f], De Neve Wilfried [a], Vandorpe Jo [c, d], Hendrix An [a], Göker Menekse [g], Depypere Herman [a, g], Vergauwen Glenn [g], Van den Broecke Rudy [a, g], De Visschere Pieter [d, h], Braems Geert [a, g], Vandecasteele Katrien [a, b], Denys Hannelore [e, f], Veldeman Liv [a, b]

Objective: Neo-adjuvant radiotherapy (NART) for breast cancer has shown promising survival results in retrospective trials. However, there are some obstacles such as a chemotherapy delay, an increased overall treatment time (OTT) and the risk of increasing surgical morbidity. Accelerated radiotherapy (RT) in 5 fractions allows to deliver NART in a very short time span and minimizes the delay of surgery and chemotherapy. This trial investigates this NART schedule for safety, feasibility and OTT.

Material and methods: Twenty patients eligible for neo-adjuvant chemotherapy (NACT) and breast conserving surgery, were randomized between NART before NACT or NACT and postoperative RT. In both arms, RT treatment was given in 5 fractions to the whole breast with a simultaneously integrated boost (SIB) on the tumor(bed). Lymph node irradiation was given concomitantly in case of lymph node involvement. OTT was defined as the time from diagnosis to last surgery in the intervention group, while in the control group the time between diagnosis and last RT-fraction was used. In the intervention group NACT-delay was defined as time between diagnosis and start of chemotherapy.

Results: 20 patients were included, and 19 patients completed treatment. OTT was significantly shorter in the intervention group (mean 218 days, range 196–253) compared to the control group (mean 237, range 211–268, $p = 0.001$). The difference in mean duration from diagnosis to the first treatment was a non-significant 4 days longer (31 vs 27 days, $p = 0.28$), but the start of NACT after diagnosis was delayed by 21 days (48 vs 27 days, $p < 0.001$). NART did not result in additional surgery complications.

Conclusion: This pilot trial is the first to report on accelerated NART in 5 fractions with SIB. NART before NACT resulted in a shorter OTT with good safety results.

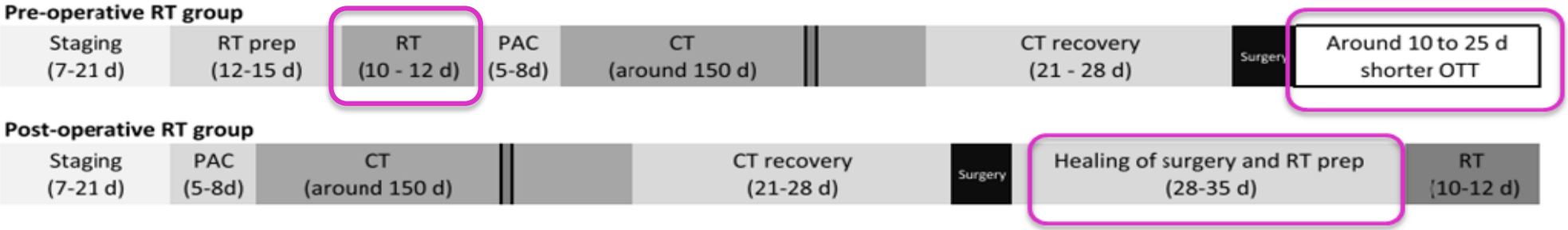
PREOPERATIVE RT

WBI

Ultra-hypofractionation+ SIB

Modificato da The Breast 62 (2022) 10–15

ULTRA- HYPOFRACTIONATED PREOPERATIVE RT



CT chemotherapy; RT radiotherapy; PAC port-a-cath; RT prep radiotherapy preparation; OTT overall treatment time

	Intervention group	Control group	P-value
Pathological complete response	N = 10	N = 9	
Yes	6 (60%)	6 (67%)	1.0
No	4 (40%)	3 (33%)	
Chemotherapy			
Finished all EC and Taxol treatments			
Yes	7 (70%)	4 (44%)	0.37
No	3 (30%)	5 (56%)	
Surgery			
Mastectomy rate			
Yes	1 (10%)	2 (22%)	0.58
No	9 (90%)	7 (78%)	
Second surgery			
Yes	2 (20%)	2 (22%)	1.0
No	8 (80%)	7 (78%)	
Use of antibiotics 3 weeks after surgery			
Yes	3 (30%)	0 (0%)	0.21
No	7 (70%)	9 (100%)	
Radiotherapy			
CTV boost volume in CC (mean (sd))	38 (25)	33 (11)	0.59
PTV WBI-volume in CC (mean (sd))	713 (333)	793 (304)[a]	0.62

RT was given in 5 fractions up to a total dose of 28.5Gy (5.7Gy per fraction) to the whole affected breast with a SIB up to 31 Gy (6.2Gy per fraction) on the tumor(bed). In case of pathologically confirmed lymph node involvement (either on SNB or FNAC), the level I-IV axillary lymph nodes were irradiated to 27 Gy (5.4 Gy per fraction). RT was delivered over 10–12 days with at least one day interval between fractions.

The primary endpoints of the trial are: 1) safety, 2) feasibility, and 3) overall treatment time (OTT). Secondary endpoints include tumor response, therapy compliance, and treatment complications.

NART did not result in additional surgery complications.

Modificato da The Breast 62 (2022) 10–15

Single fraction ablative preoperative radiation treatment for early-stage breast cancer: the CRYSTAL study – a phase I/II clinical trial protocol

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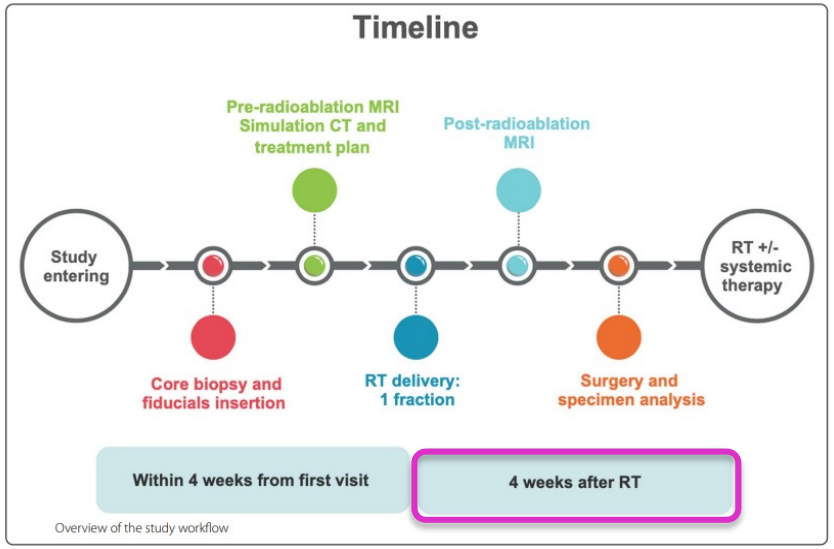
Background: Breast-conserving surgery (BCS) and whole breast radiation therapy (WBRT) are the standard of care for early-stage breast cancer (BC). Based on the observation that most local recurrences occurred near the tumor bed, accelerated partial breast irradiation (APBI), consisting of a higher dose per fraction to the tumor bed over a reduced treatment time, has been gaining ground as an attractive alternative in selected patients with low-risk BC. Although more widely delivered in postoperative setting, preoperative APBI has also been investigated in a limited, though increasing, and number of studies. The aim of this study is to test the feasibility, safety and efficacy of preoperative radiotherapy (RT) in a single fraction for selected BC patients.

Methods: This is a phase I/II, single-arm and open-label single-center clinical trial using CyberKnife. The clinical investigation is supported by a preplanning section which addresses technical and dosimetric issues. The primary endpoint for the phase I study, covering the 1st and 2nd year of the research project, is the identification of the maximum tolerated dose (MTD) which meets a specific target toxicity level (no grade 3–4 toxicity). The primary endpoint for the phase II study (3rd to 5th year) is the evaluation of treatment efficacy measured in terms of pathological complete response rate.

Discussion: The study will investigate the response of BC to the preoperative APBI from different perspectives. While preoperative APBI represents a form of anticipated boost, followed by WBRT, different are the implications for the scientific community. The study may help to identify good responders for whom surgery could be omitted. It is especially appealing for patients unfit for surgery due to advanced age or severe co-morbidities, in addition to or instead of systemic therapies, to ensure long-term local control. Moreover, patients with oligometastatic disease synchronous with primary BC may benefit from APBI on the intact tumor in terms of tumor progression free survival. The study of response to RT can provide useful information about BC radiobiology, immunologic reactions, genomic expression, and radiomics features, to be tested on a larger scale.



Overview of the study workflow

Phase I: **dose escalation 18-21-24 Gy**

Phase II- Primary Outcome: **rate of pathological complete response**

Modificato da Zerella *et al. BMC Cancer* (2022) 22:358

Preoperative robotic radiosurgery for early breast cancer: Results of the phase II ROCK trial (NCT03520894)

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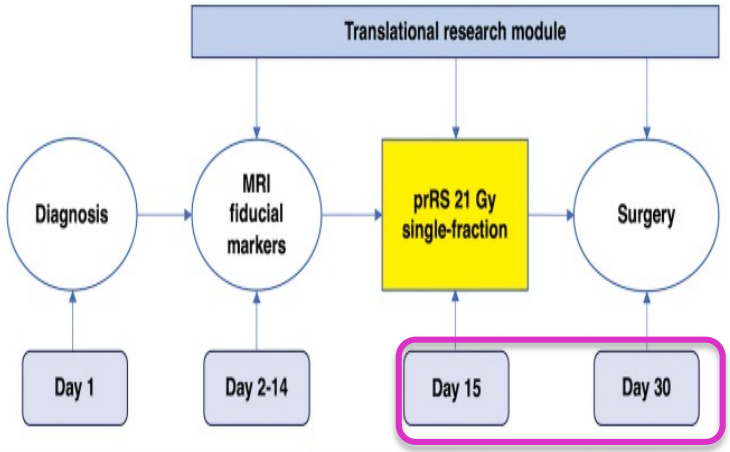
Background and purpose: Preoperative partial breast irradiation (PBI) has got the advantage of treating a well-defined target. We report the results of the phase II ROCK trial (NCT03520894), enrolling early breast cancer (BC) patients treated with preoperative robotic radiosurgery (prRS), in terms of acute and early late toxicity, disease control, and cosmesis.

Material and methods: The study recruited between 2018 and 2021 at our Radiation Oncology Unit. Eligible patients were 50 + years old BC, hormonal receptors positive/human epidermal growth factor receptor 2 negative (HR+/HER2-), sized up to 25 mm. The study aimed to prospectively assess the toxicity and feasibility of a robotic single 21 Gy-fraction prRS in preoperative setting.

Results: A total of 70 patients were recruited and 22 patients were successfully treated with pRS. Overall, three G1 adverse events (13.6 %) were recorded within 7 days from prRS. Three events (13.6 %) were recorded between 7 and 30 days, one G2 breast oedema and two G1 breast pain. No acute toxicity greater than G2 was recorded. Five patients experienced early late G1 toxicity. One patient reported G2 breast induration. No early late toxicity greater than G2 was observed. At a median follow up of 18 months (range 6–29.8), cosmetic results were scored excellent/good and fair in 14 and 5 patients, respectively, while 3 patients experienced a poor cosmetic outcome.

Conclusions: ROCK trial showed that a single 21 Gy dose prRS represents a feasible technique for selected patients affected by early BC, showing an acceptable preliminary toxicity profile.



Study overview: a step-by-step overview of ROCK trial. Abbreviations: MRI, magnetic resonance imaging; prRS, preoperative radiosurgery.

Primary Outcome: Rate of acute skin toxicity events (RTOG/EORTC scale)

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IN CONCLUSION…

Editorial

Personalised radiation therapy taking both the tumour and patient into consideration

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DE-ESCALATION

INTENSIFICATION

The future demands personalized radiation therapy taking both the tumour, the healthy tissues, and the individual patient into consideration.

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