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Re-irradiation in breast cancer

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Re-irradiation (ReRT) in breast cancer

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Conflicts of Interest Statement

- None to declare

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Re-irradiation in breast cancer

1 – Introduction

2 – Second breast conserving treatment

3 – Chest wall recurrence

4 – Conclusions

Gustavo Nader Marta

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Re-irradiation in breast cancer

1 – Introduction

2 – Second breast conserving treatment

3 – Cheat wall recurrence

4 – Conclusions

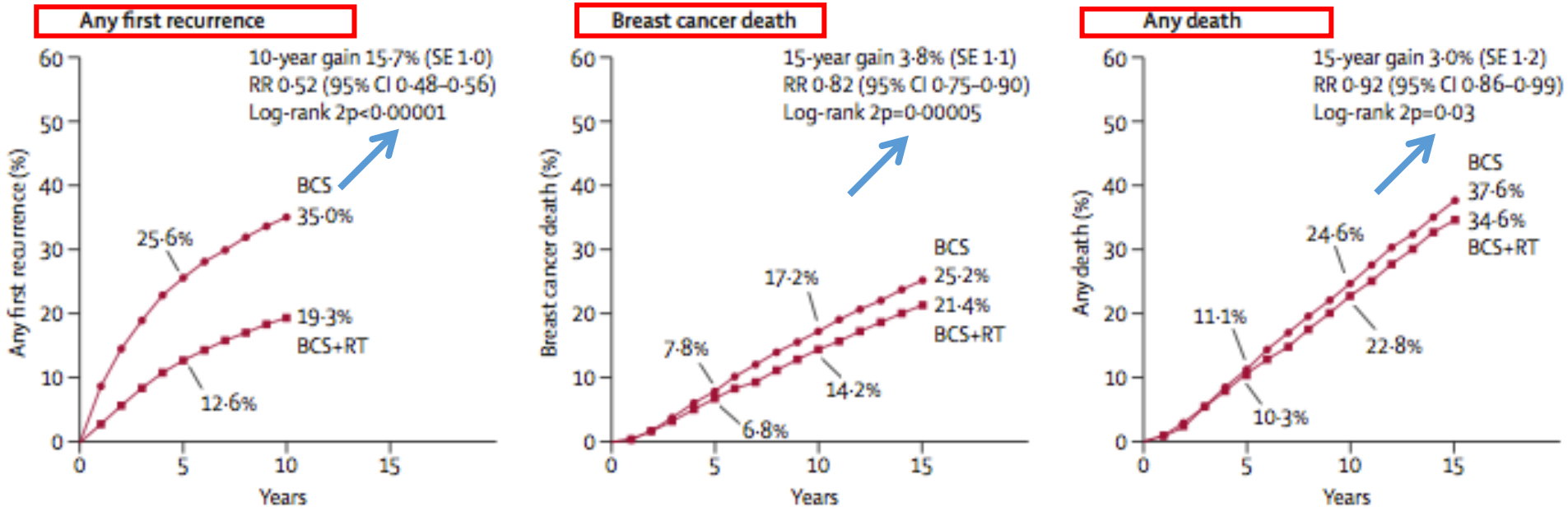
Gustavo Nader Marta

Introduction

- Radiotherapy (RT) is an integral part of breast conserving therapy

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)**

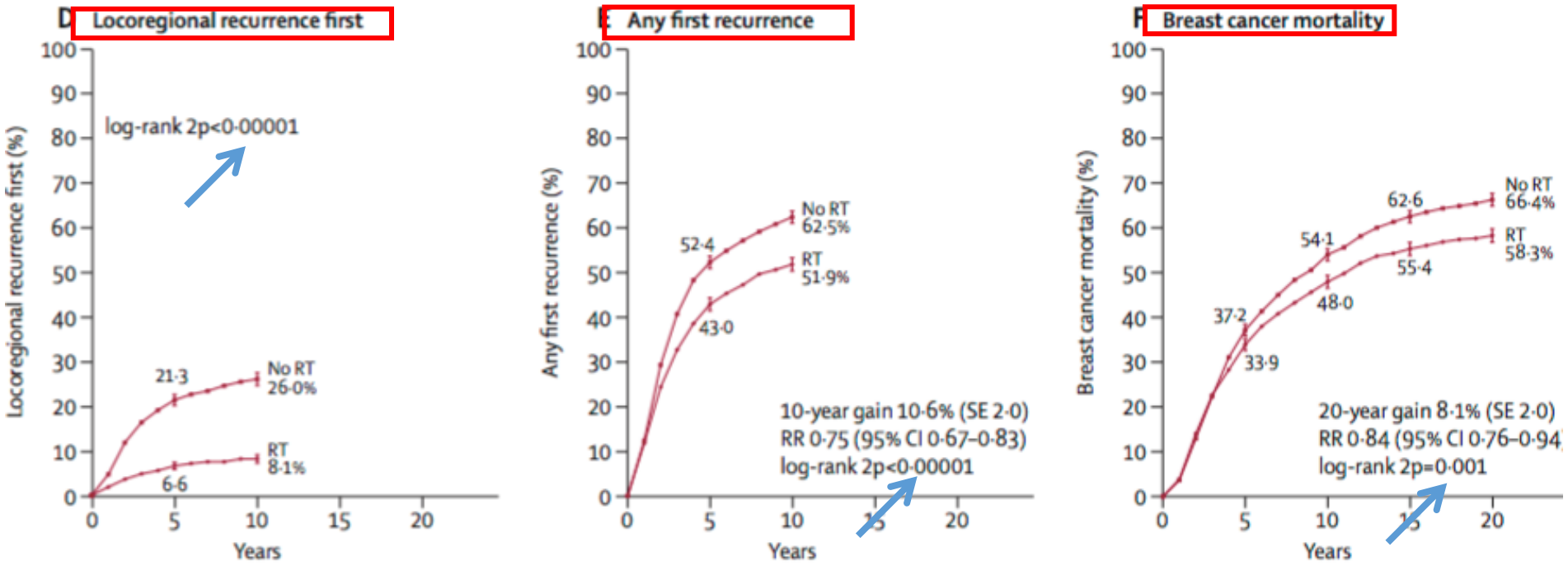


EBCTCG. Lancet 366:2087-2106, 2011

Introduction

Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials

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



EBCTCG, McGale P, et al. Lancet. 2014;383 (9935):2127–2135.

Introduction

- **Older series**: local ipsilateral breast tumour recurrence

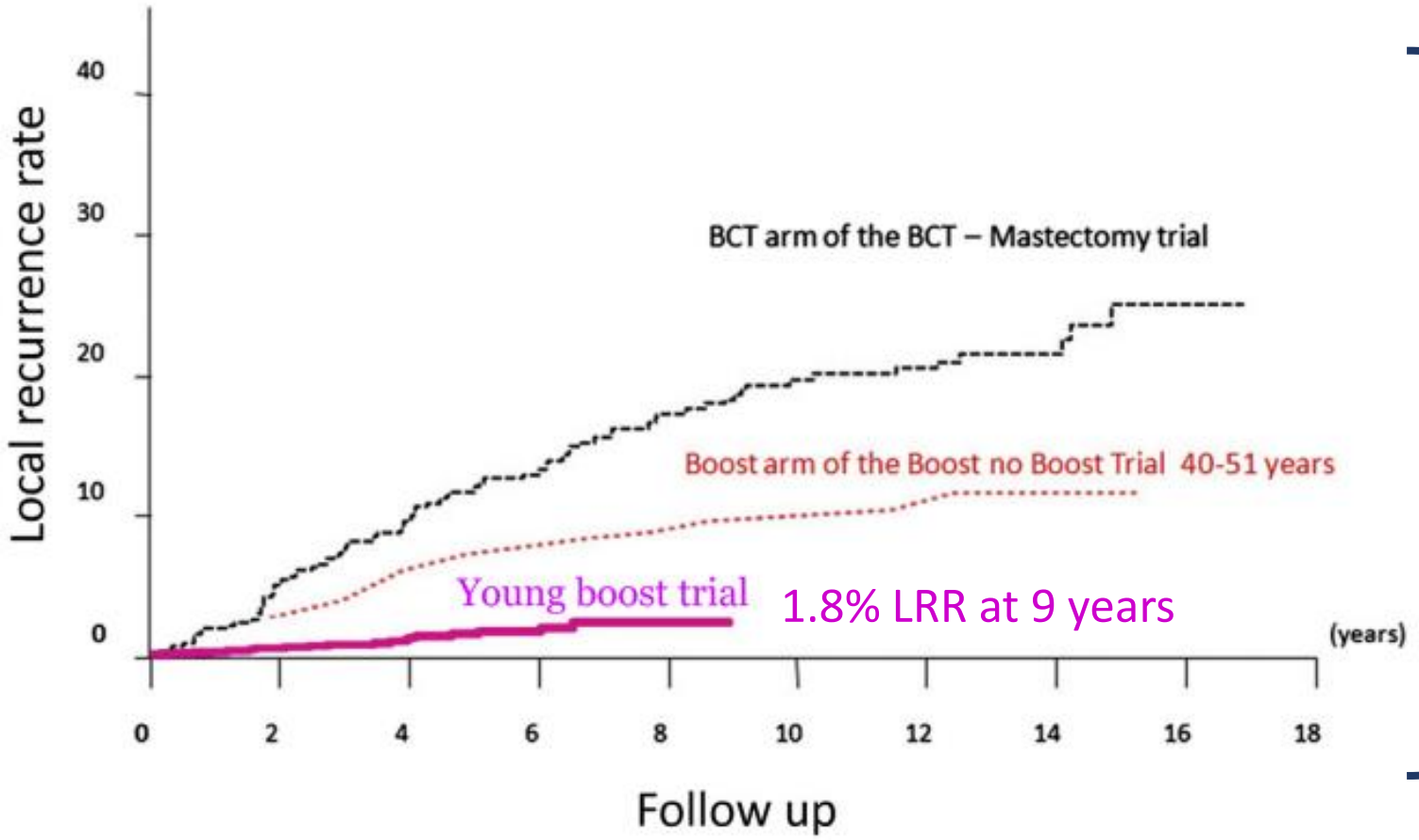
  - Breast-conserving therapy: 20-year incidence rate of **15 -20%**

  - Mastectomy: 10-year incidence rate of **10-20%**

Marta GN, et al. Breast J. 2017;23(1):26-33.

Introduction

Local breast recurrence rate in three consecutive trials on breast-conserving therapy from 1980 till 2012

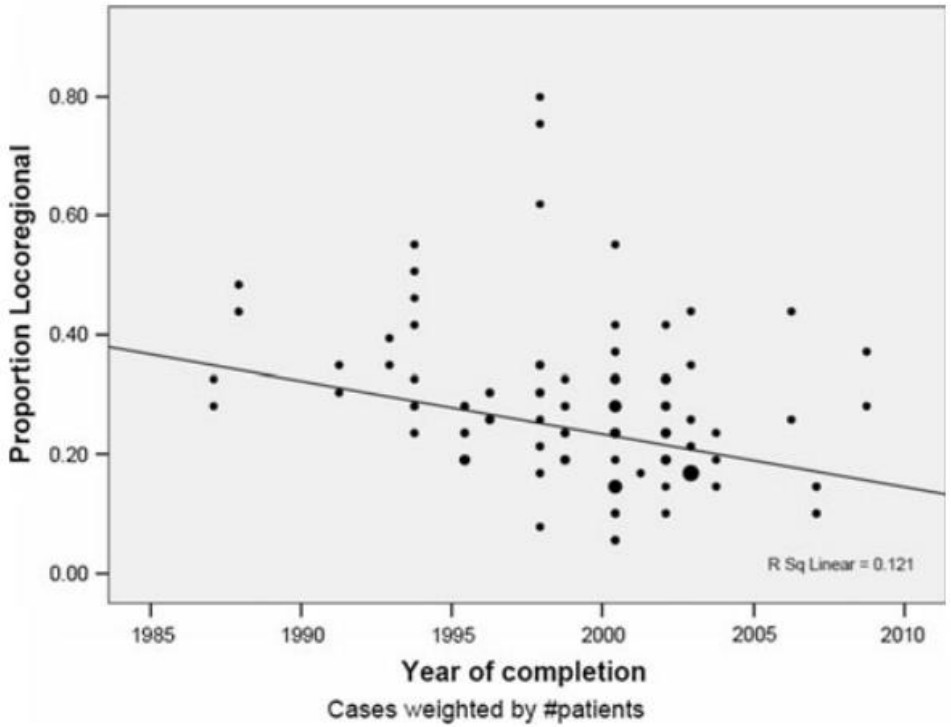


Better diagnostic test, local and systemic therapies

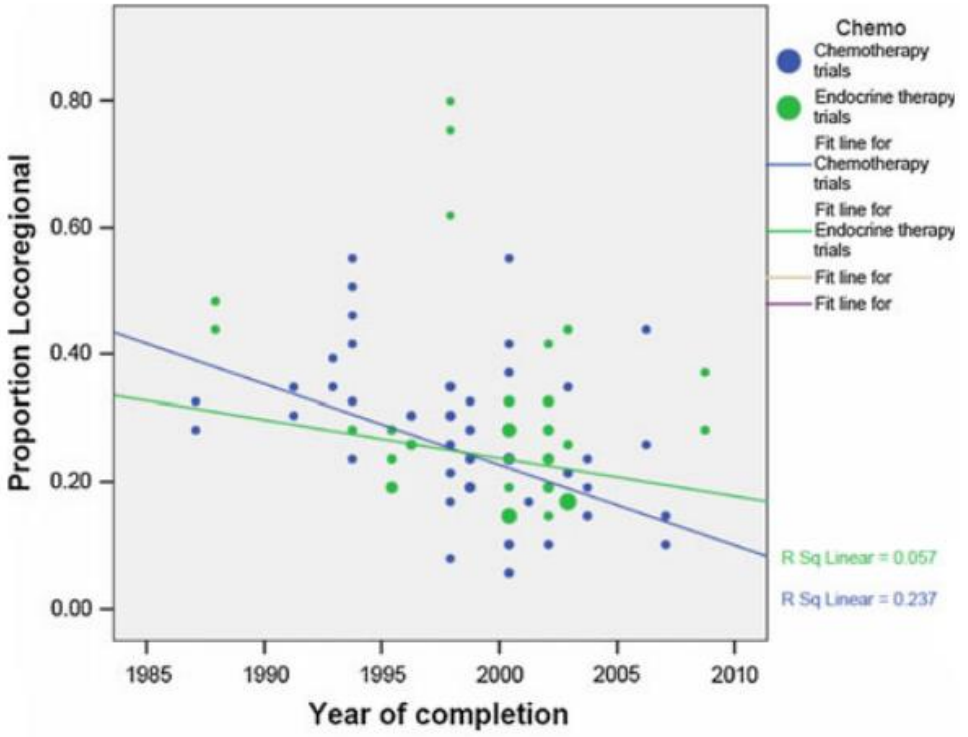
Poortmans P, et al. Breast. 2017;31:295-302.

Introduction

Proportion of locoregional recurrences over time



Proportion of locoregional recurrences for endocrine and chemotherapy over time



Over the last 20 years -> Down to 10-15% of all recurrences

Bouganim N, et al. Breast Cancer Res Treat 2013;139:603–6.

Introduction

Estimated Number of US Cancer Survivors by Site – SEER database

2019	Female
Breast	3,861,520
Uterine corpus	807,860
Colon & rectum	768,650
Thyroid	705,050
Melanoma of the skin	672,140
Non-Hodgkin lymphoma	357,650
Lung & bronchus	313,140
Cervix	283,120
Ovary	249,230
Kidney & renal pelvis	227,510
All sites	**8,781,580**

2030	Female
Breast	4,957,960
Uterine corpus	1,023,290
Thyroid	989,340
Colon & rectum	965,590
Melanoma of the skin	888,740
Non-Hodgkin lymphoma	480,690
Lung & bronchus	398,930
Kidney & renal pelvis	316,620
Ovary	297,580
Uterine cervix	288,710
All sites	**11,174,200**

The number of breast cancer survivors will increase by **22%** between 2019 to 2030(**> 1 million**)

More patients with breast ipsilateral recurrence

More patients will need a second local treatment (ReRT)

Miller KD, et al. CA Cancer J Clin. 2019;69(5):363-385.

Introduction

Tumour recorrence

Tumours are heterogeneous
Patients are heterogeneous

Reirradiation

Therapeutic challenge

Side effects

Tumour control / quality of life

Treatment options for in-field relapse involve surgery, systemic therapy and ReRT

Introduction

- **Decision on ReRT needs to consider**:

1 - Localisation of the second tumour in relation to the initial radiation treatment volumes, and so the previuos exposure of organs at risk;

2 - Parameters of the initial radiotherapy: dose, fractionation and volume;

3 - Combination therapy for the first tumour (chemotherapy, 'biologicals');

4 - Time interval from the treatment of the first tumour with regard to potential tissue-specific morbidity after ReRT and its impact on the patient's quality of life.

Dörr W, et al. Clin Oncol (R Coll Radiol). 2018;30(2):67-72.

Introduction

- **ReRT aspects**:

1 - Different techniques can be used for ReRT. The largest experience comes from brachytherapy, but external-beam irradiation is a well-documented option for ReRT. However, the clinical indications for ReRT, techniques, ideal doses and fractionation schemes have not yet been clearly defined.

Marta GN, et al. Breast. 2017;33:159-165.

Introduction

- **ReRT aspects**

Several studies have reported using hyperthermia with ReRT for the management of breast cancer recurrence. Hyperthermia is a radiosensitizer that increases tumour temperature, decreasing intratumoral hypoxia and reducing sublethal damage repair in the malignant cells.

Oliver J. Ott and Manfred Schmidt.
Hyperthermia and Reirradiation, 2017

Marta GN, et al. Breast. 2017;33:159-165.

Introduction

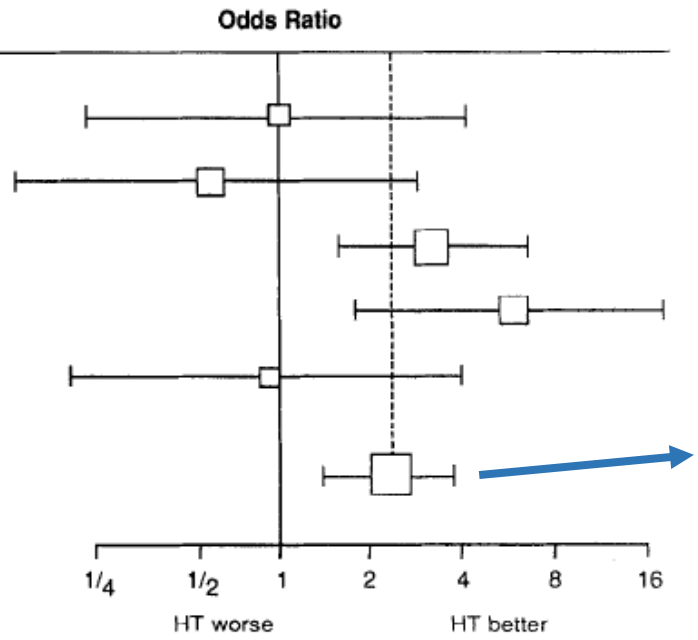
- ReRT with hyperthermia

RADIOTHERAPY WITH OR WITHOUT HYPERTHERMIA IN THE TREATMENT OF SUPERFICIAL LOCALIZED BREAST CANCER: RESULTS FROM FIVE RANDOMIZED CONTROLLED TRIALS

1988 to 1991

Trial	No of CRs/No randomised RT	RT+HT	OR	95% CI
DHG	14/19	14/19	1.0	0.2 - 4.2
MRC Brl	8/12	10/18	0.6	0.1 - 2.9
MRCBrR	17/59	51/90	3.2	1.6 - 6.5
ESHO	11/29	21/27	5.7	1.8 - 19.0
PMH	5/16	5/17	0.9	0.2 - 4.0
ALL	55/135	101/171	2.3*	1.4 - 3.8

* obtained after stratification by trial



Overall complete response: 41% vs. 59%

Vernon CC, et al. Int J Radiat Oncol Biol Phys. 1996;35(4):731-44.

Introduction

- ReRT with hyperthermia

Hyperthermia and Radiation Therapy in Locoregional Recurrent Breast Cancers: A Systematic Review and Meta-analysis

34 studies

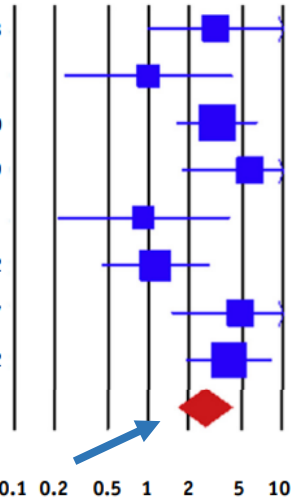
Eight were 2-arm (randomized, n=5; nonrandomized, n=3), whereas 26 were single-arm studies.

Median of 7 HT sessions (average temperature of 42.5°C)
Mean RT dose: 38.2 Gy (range, 26-60 Gy)

A Odds ratio (Hyperthermia + Radiation Therapy vs Radiation Therapy alone)

Study name	Odds ratio	Lower limit	Upper limit	Z value	P value	CR / Total RT+HT	CR / Total RT	Relative weight
Wahl et al, 2008	3.143	0.972	10.166	1.912	0.056	24 / 36	7 / 18	10.73
Vernon et al, 1996(DHG)	1.000	0.236	4.238	0.000	1.000	14 / 19	14 / 19	7.90
Vernon et al, 1996(MRO)	3.231	1.603	6.512	3.279	0.001	51 / 90	17 / 59	19.50
Vernon et al, 1996(ESHO)	5.727	1.765	18.587	2.906	0.004	21 / 27	11 / 29	10.69
Vernon et al, 1996(PMH)	0.917	0.208	4.048	-0.115	0.909	5 / 17	5 / 16	7.56
Perez et al, 1991	1.125	0.442	2.865	0.247	0.805	14 / 42	12 / 39	14.42
Li et al, 1990	4.813	1.468	15.774	2.594	0.009	22 / 30	8 / 22	10.57
Perez et al, 1986	3.953	1.892	8.257	3.657	0.000	35 / 48	47 / 116	18.62
Overall effect (Random effects model)	2.640	1.666	4.182	4.134	0.000	186 / 309	121 / 318	

(Test for Heterogeneity: I^2= 36.5, P=.122)



In the 2-arm studies
Complete response: 60.2% RT + HT versus 38.1% RT alone

Datta NR, et at. Int J Radiat Oncol Biol Phys. 2016;94(5):1073-87.

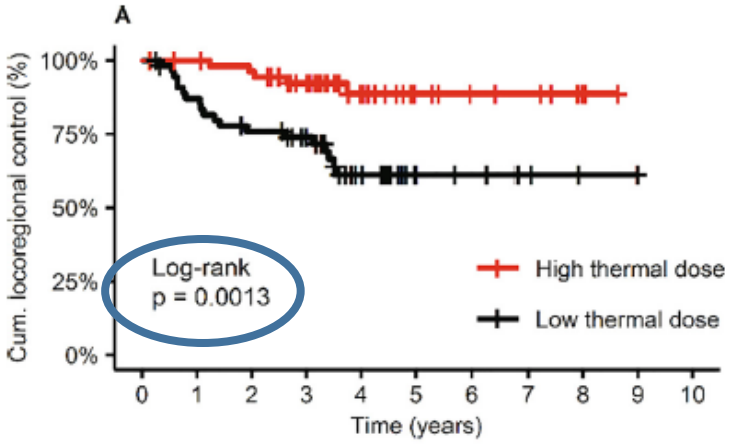
Introduction

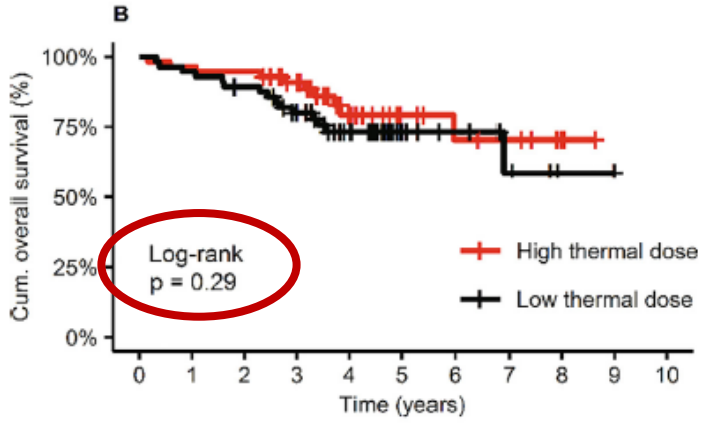
- ReRT with hyperthermia

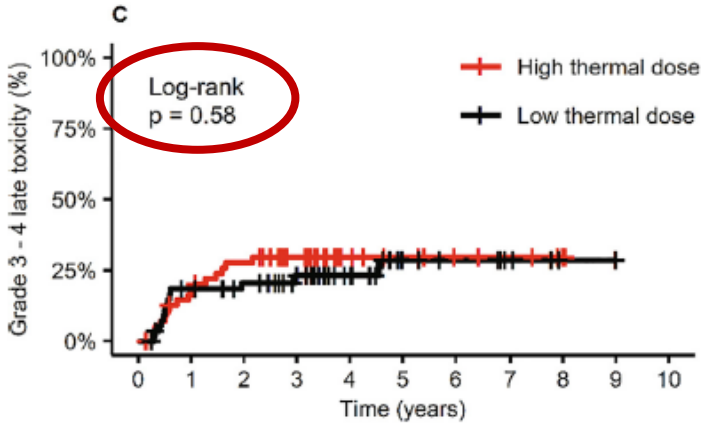
Post-operative re-irradiation with hyperthermia in locoregional breast cancer recurrence: Temperature matters

To assess the impact of hyperthermia thermal dose (TD)

Retrospective study (n = 112)
Resected locoregional recurrent breast cancer
ReRT 8frx4Gy (n = 34) or 23frx2Gy (n = 78)
4–5 weekly hyperthermia guided by invasive thermometry: ‘low’ (n = 56) and ‘high’ TD (n = 56)







Bakker A, et al. Radiother Oncol. 2022;167:149-157.

Reirradiation

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Review

Reirradiation for locally recurrent breast cancer

Gustavo Nader Marta, MD, PhD [a, *], Tarek Hijal, MDCM, MSc [b], Heloisa de Andrade Carvalho, MD, PhD [c]

Evidences for ReRT?

Marta GN, et al. Breast. 2017;33:159-165.

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Re-irradiation in breast cancer

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3 – Chest wall recurrence

4 – Conclusions

Reirradiation

- Second breast-conserving curative treatment and ReRT

BCS without RT *versus* mastectomy

							ear OS (%)
							MT
Milan (EIO)							-
Milan (EIO)							70
Budapest (NI							55
Dutch Grouc							NR
Yale-New Haven							58
Marseille Cance							NR
Univ. Pennsylvania	3.7	0	112	-	3	-	86

Rate of second local recurrence

- after mastectomy **~ 10%**

- after BCS without RT **> 20%**

Reirradiation

- Breast ReRT with brachytherapy (PBI – *Partial breast irradiation*)

Partial breast re-irradiation with brachytherapy.

Authors	Year of publication	# pts	MFU (months)	Irradiation techniques	Dose (Gy)		3rdIBTE-FS (%)	OS		≥ G3 tox. (%)
					Total (Gy)	Dose/f Dose rate		@	(%)	
Maulard C et al. [12]	1995	38	48	MIB LDR	30	–	a)	5 y	55	8
Resch A et al. [13]	2002	17	59	MIB PDR EBRT	12.5 30	0.5–1	b)	4 y	70	0
Hannoun-Levi JM et al. [14]	2004	69	50	MIB LDR	30–50	–	77.4	5 y	91.8	10.2
Niehoff P et al. [15]	2							1.5 y	68.7	3
Chadha M et al. [16]	2							3 y	100	0
Guix B et al. [17]	2							10 y	96.7	0
Hannoun-Levi JM et al. [18]	2							–	3	
Kauer-Dorner D et al. [19]	2							5 y	87	17
GEC-ESTRO [6]	2							5 y	88.7	11
								10 y	76.4	
Trombetta M et al. [23].	2							–	–	
Smanyko V et al. [20]	2							5 y	81	8
Montagne L et al. [21]	2							6 y	91.2	–
Forster T et al. [22]	2019	19	65	MIB PDR	49.8–50.4	0.5–0.7	100	5 y	100	0
				HDR	34.2–32	3.4–3.8				

Rate of second local recurrence

- after BCS + RT(brachy) **~ 10%**

pts: number of patients; MFU: median follow-up; Dose/f: dose per fraction; Dose rate in Gy per hour; BID: dose given twice a day; 3rdIBTE-FS: third ipsilateral breast tumor event free survival rate; 3rdIBTE: third ipsilateral breast tumor event rate; OS: overall survival; ≥ G3 tox.: grade 3 and higher toxicity rate; MIB: Mutlicatheter interstitial brachytherapy; LDR: low-dose rate; PDR: pulsed-dose rate; HDR: High-dose rate; EBRT: external beam radiation therapy.

a 21% of 3rdIBTE rate.

b 24% of 3rdIBTE rate.

c 3% of 3rdIBTE rate.

d 11% of 3rdIBTE rate.

Montagne L, et al. Breast. 2020;49:274-280.

Reirradiation

- 2nd BCT versus mastectomy

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RADIATION ONCOLOGY · BIOLOGY · PHYSICS ASTRO

Salvage Mastectomy Versus Second Conservative Treatment for Second Ipsilateral Breast Tumor Event: A Propensity Score-Matched Cohort Analysis of the GEC-ESTRO Breast Cancer Working Group Database

Jean-Michel Hannoun-Levi, MD, PhD,* Jocelyn Gal, PhD,† Erik Van Limbergen, MD, PhD,‡ Marie-Eve Chand, MD,* Renaud Schiappa, MSc,† Viktor Smanyko, MD,§ Daniela Kauer-Domer, MD,‖ David Pasquier, MD, PhD,¶ Claire Lemanski, MD,# Séverine Racadot, MD,** Gilles Houvenaeghel, MD,†† Benjamin Guix, MD, PhD,‡‡ Aurélie Belliere-Calandry, MD,§§ Kristina Loessl, MD,‖‖ Bulent Polat, MD, PhD,¶¶ Cristina Gutierrez, MD, PhD,## Razvan Galalae, MD, PhD,*** Csaba Polgar, MD, PhD,§,††† and Vratislav Strnad, MD, PhD‡‡‡

Hannoun-Levi JM, et al. Int J Radiat Oncol Biol Phys. 2021;110(2):452-461.

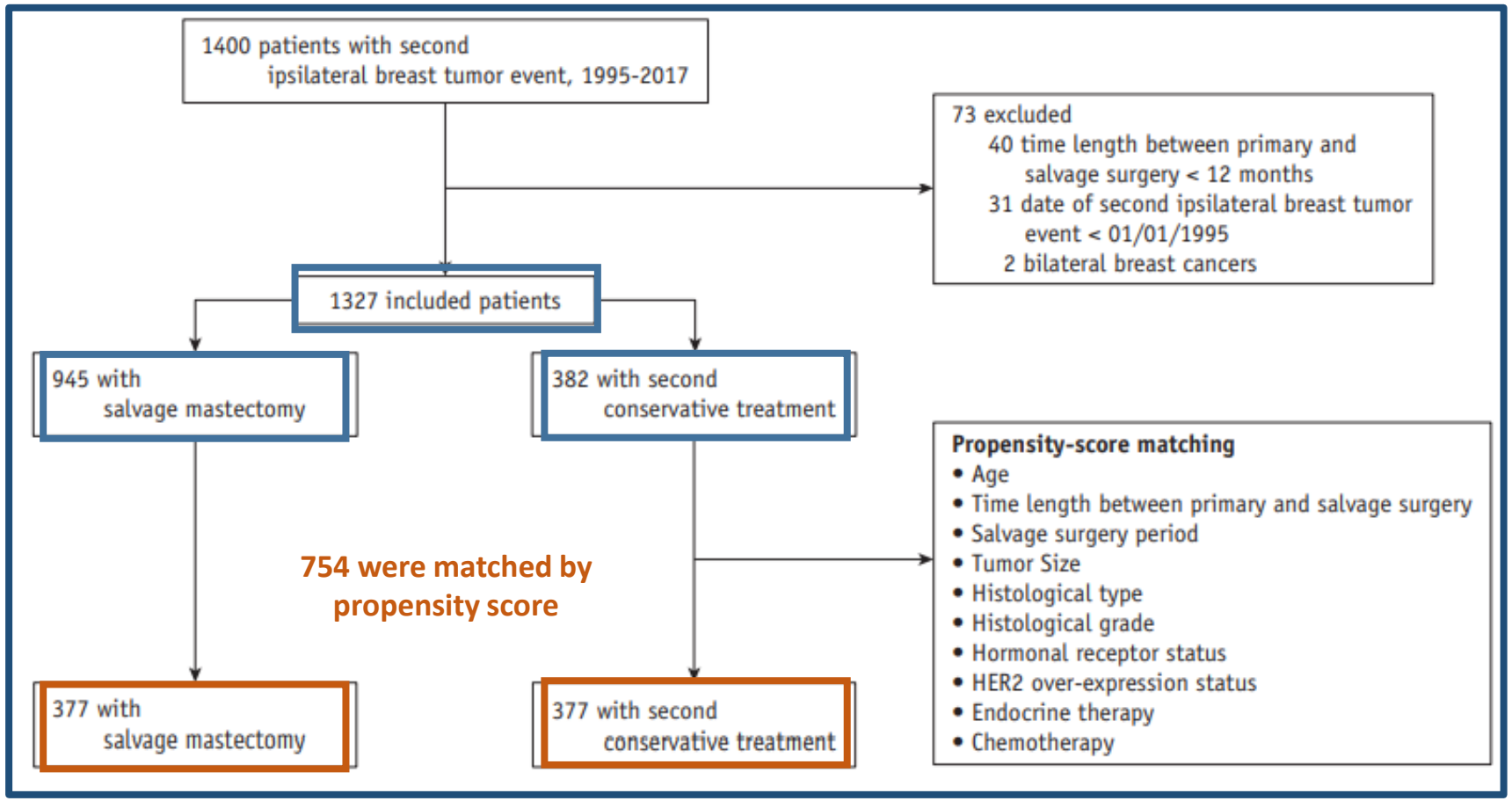
Reirradiation

- 2nd BCT versus mastectomy

GEC-ESTRO study

- 01/1995 to 06/2017
- 15 hospitals/cancer centers in 7 European countries

Patients were offered mastectomy or lumpectomy plus brachytherapy



Hannoun-Levi JM, et al. Int J Radiat Oncol Biol Phys. 2021;110(2):452-461.

Reirradiation

- 2nd BCT versus mastectomy

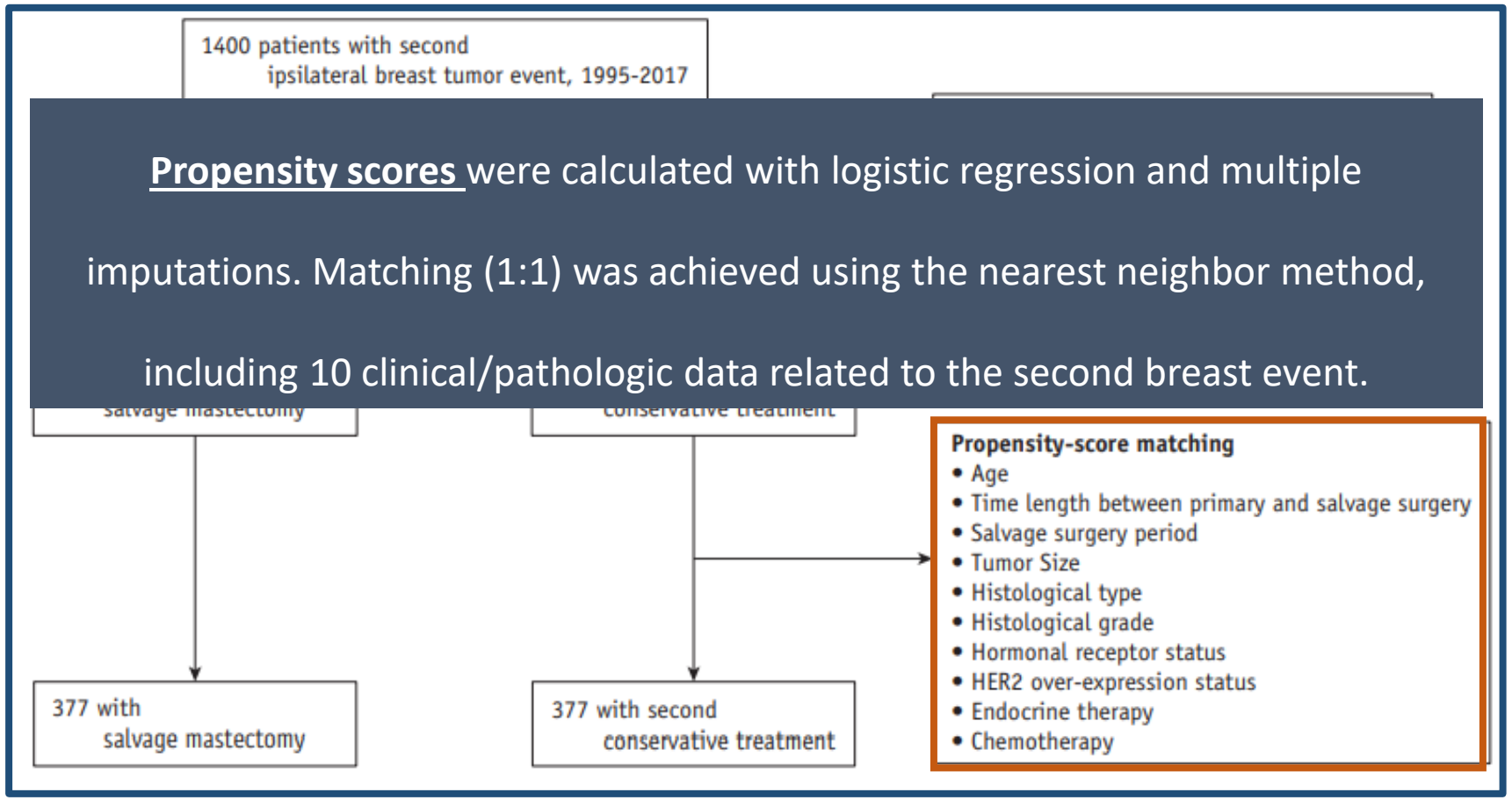
GEC-ESTRO study

Primary endpoint:

- 5-year OS from the salvage surgery date

Secondary endpoints:

- 5-year cumulative incidence of third breast event
- Regional relapse and distant metastasis
- Disease-free and specific survival.



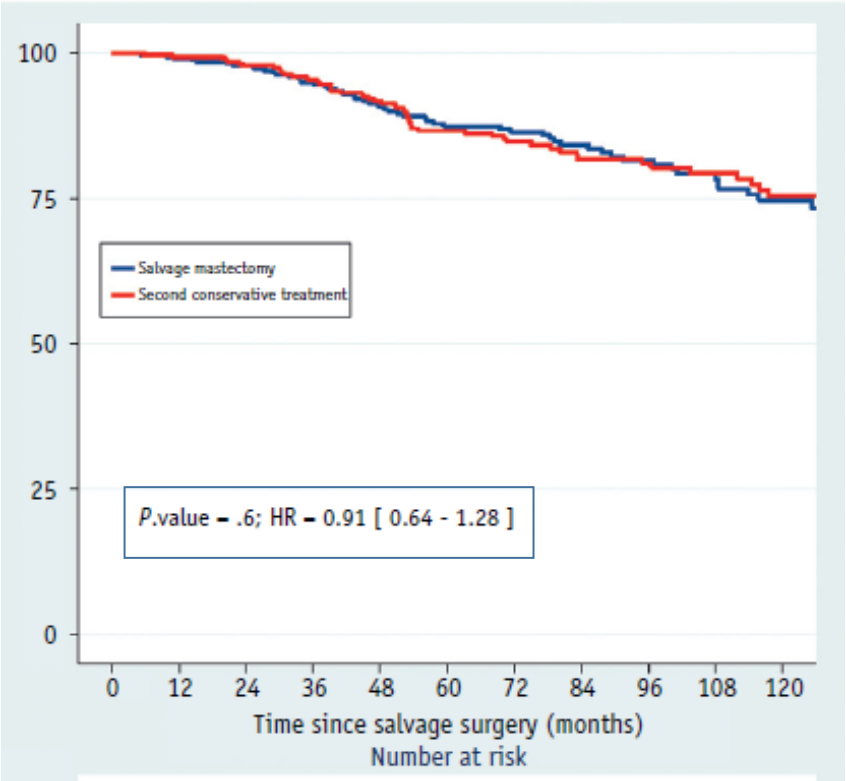
Hannoun-Levi JM, et al. Int J Radiat Oncol Biol Phys. 2021;110(2):452-461.

Reirradiation

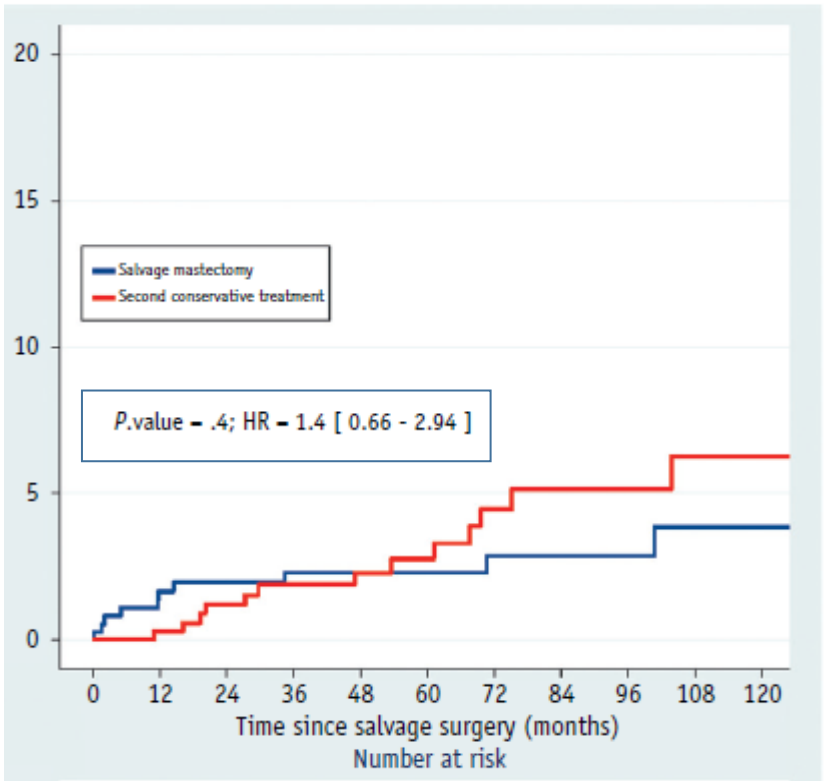
- 2nd BCT versus mastectomy

GEC-ESTRO study

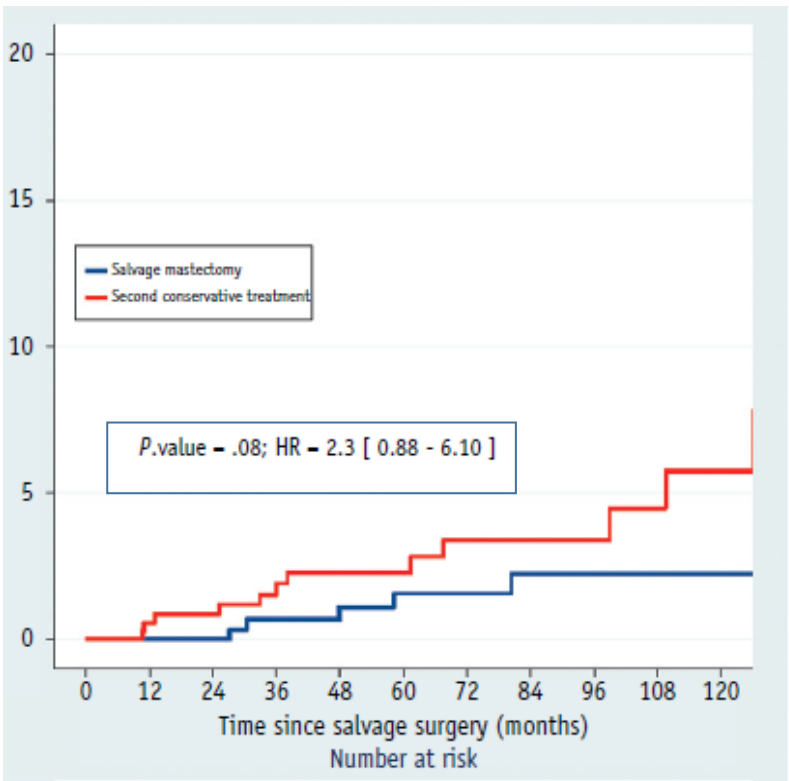
Overall survival



Incidence of third ipsilateral breast tumour event



Incidence of regional relapse



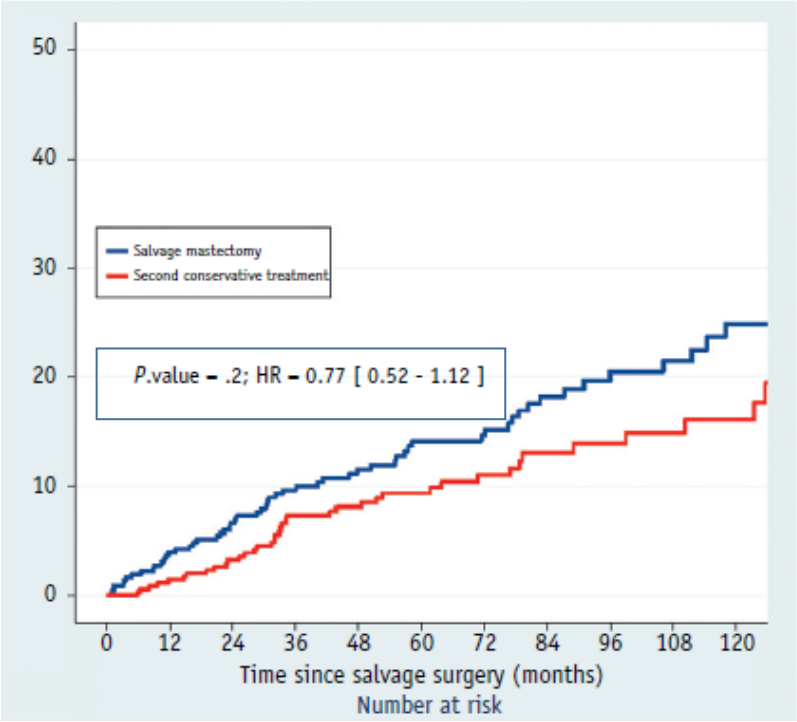
Hannoun-Levi JM, et al. Int J Radiat Oncol Biol Phys. 2021;110(2):452-461.

Reirradiation

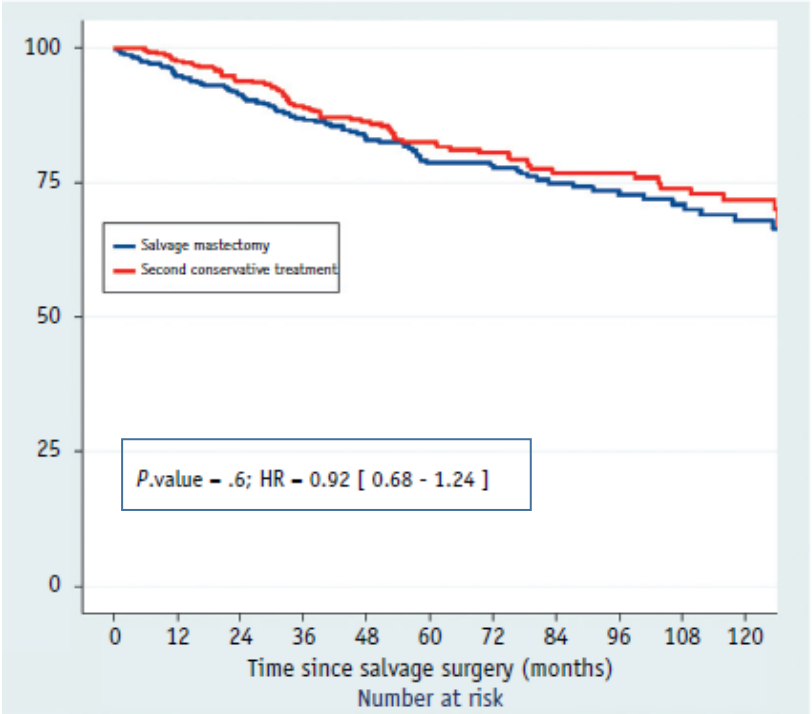
- 2nd BCT versus mastectomy

GEC-ESTRO study

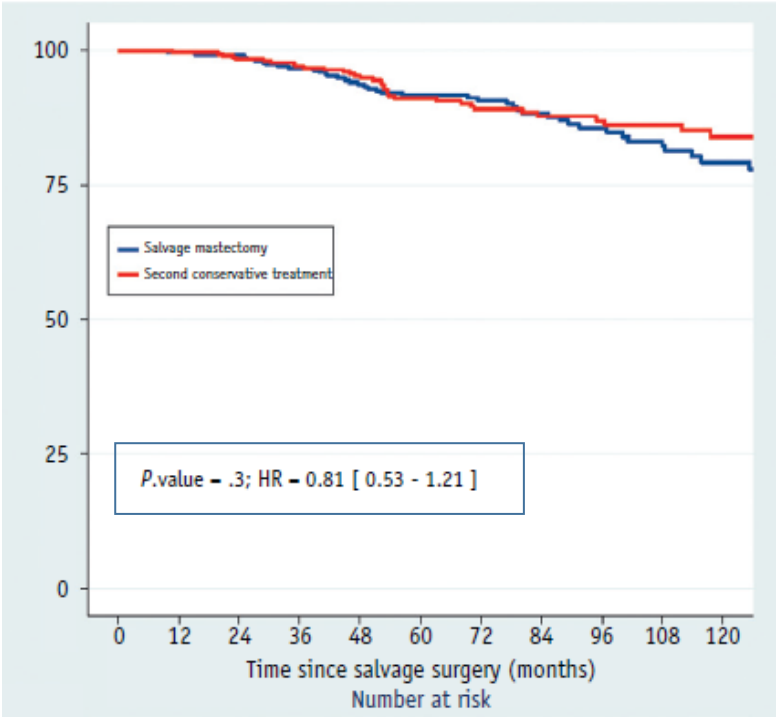
Incidence of distant metastasis



Disease-free survival rate



Specific survival



Hannoun-Levi JM, et al. Int J Radiat Oncol Biol Phys. 2021;110(2):452-461.

Reirradiation

- 2nd BCT versus mastectomy

GEC-ESTRO study

Table 3 Complications (type and grade) observed in the second conservative treatment cohort (283 complications observed for 377 patients)

Complications	Grade 1		Grade 2		Grade 3		Grade 4		Total	
	n	%	n	%	n	%	n	%	n	%
Cutaneous fibrosis	47	34.8	21	17.4	2	8.0	0	0.0	70	24.7
Sub-cutaneous fibrosis	38	28.1	67	55.4	13	52.0	1	50.0	119	42.1
Telangiectasia	15	11.2	9	7.4	1	4.0	0	0.0	25	8.8
Hyperpigmentation	21	15.6	7	5.8	1	4.0	0	0.0	29	10.2
Ulceration	1	0.7	0	0.0	3	12.0	1	50.0	5	1.8
Deformation	13	9.6	17	14.0	5	20.0	0	0.0	35	12.4
Total	135	47.7	121	42.8	25	8.8	2	0.7	283	100

Hannoun-Levi JM, et al. Int J Radiat Oncol Biol Phys. 2021;110(2):452-461.

Reirradiation

- Breast ReRT with brachytherapy (PBI)

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Radiotherapy and Oncology

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Original article

Accelerated partial breast irradiation with interstitial brachytherapy as second conservative treatment for ipsilateral breast tumour recurrence: Multicentric study of the GEC-ESTRO Breast Cancer Working Group

Jean-Michel Hannoun-Levi [a,*], Alexandra Resch [b], Jocelyn Gal [c], Daniela Kauer-Dorner [b], Vratislav Strnad [d], Peter Niehoff [e], Kristina Loessl [f], Gyoergy Kovács [g], Erick Van Limbergen [h], Csaba Polgár [i], On behalf of the GEC-ESTRO Breast Cancer Working Group

[a] Department of Radiation Oncology, Antoine Lacassagne Cancer Center, University of Nice-Sophia, France; [b] Department of Radiotherapy and Radiobiology, University of Vienna, Austria; [c] Biostatistic Unit, Antoine Lacassagne Cancer Center, Nice, France; [d] Department of Radiation Oncology, University Hospital Erlangen; [e] Department of Radiotherapy, City Hospital Cologne, Germany; [f] Department of Radiation Oncology, Bernes, Switzerland; [g] Interdisciplinary Brachytherapy Unit, University of Luebeck, Germany; [h] Department of Radiation Oncology, University Hospital Gasthuisberg, Leuven, Belgium; [i] Center of Radiotherapy, National Institute of Oncology, Budapest, Hungary

Hannoun-Levi JM, et al. Radiother Oncol. 2013;108(2):226-31.

Reirradiation

- Breast ReRT with brachytherapy (PBI)

GEC-ESTRO study

217 patients
breast tumour recurrence

→

Salvage lumpectomy
Multi-catheter brachytherapy
(low, pulsed, or high-dose rate)

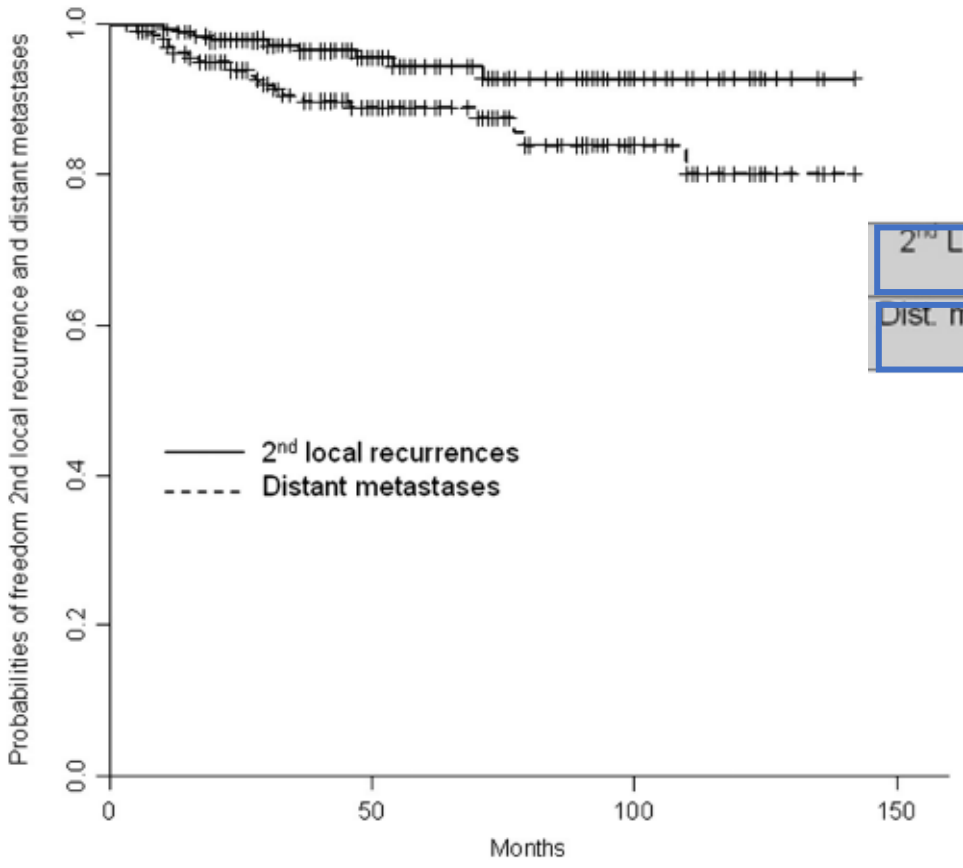
Time to IBTR (years)	10.1 [1.1–35.3]	
Median age (years)		
Primary	50	[19 - 83]
Recurrence	61	[28 - 85]
Recurence site		
Initial tumour bed (ITB)	111	51.2 %
Close to ITB	35	16.1 %
Other quadrant	45	20.7 %
Unknown	26	12.0 %
Median RT dose (Gy)	56	[30 - 69.6]
Technique		
LDR	27	12%
PDR	88	41%
HDR	102	47%

Hannoun-Levi JM, et al. Radiother Oncol. 2013;108(2):226-31.

Reirradiation

- Breast ReRT with brachytherapy (PBI)

GEC-ESTRO study



Median follow-up (years) from the recurrence: 3.9 (1.1 – 10.3)

	Time	0	12	24	36	48	60	120	
2nd LR	# pts @ risk	217	200	165	129	97	69	11	9 pts (4.1%)
	# events	0	1	3	2	1	1	1	
Dist. met.	# pts @ risk	217	195	159	122	93	70	12	22 pts (10.1%)
	# events	0	8	4	5	2	0	4	

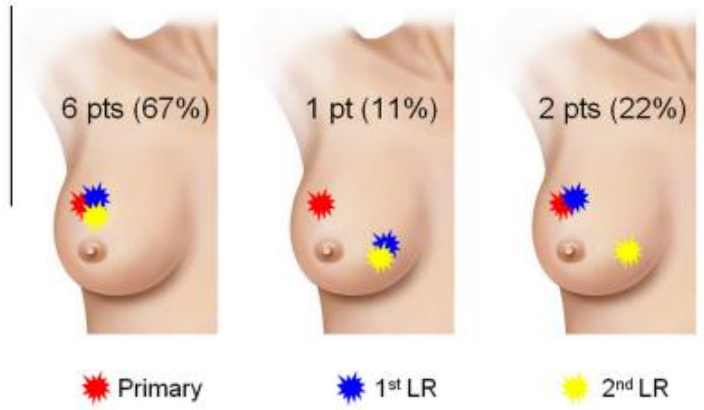


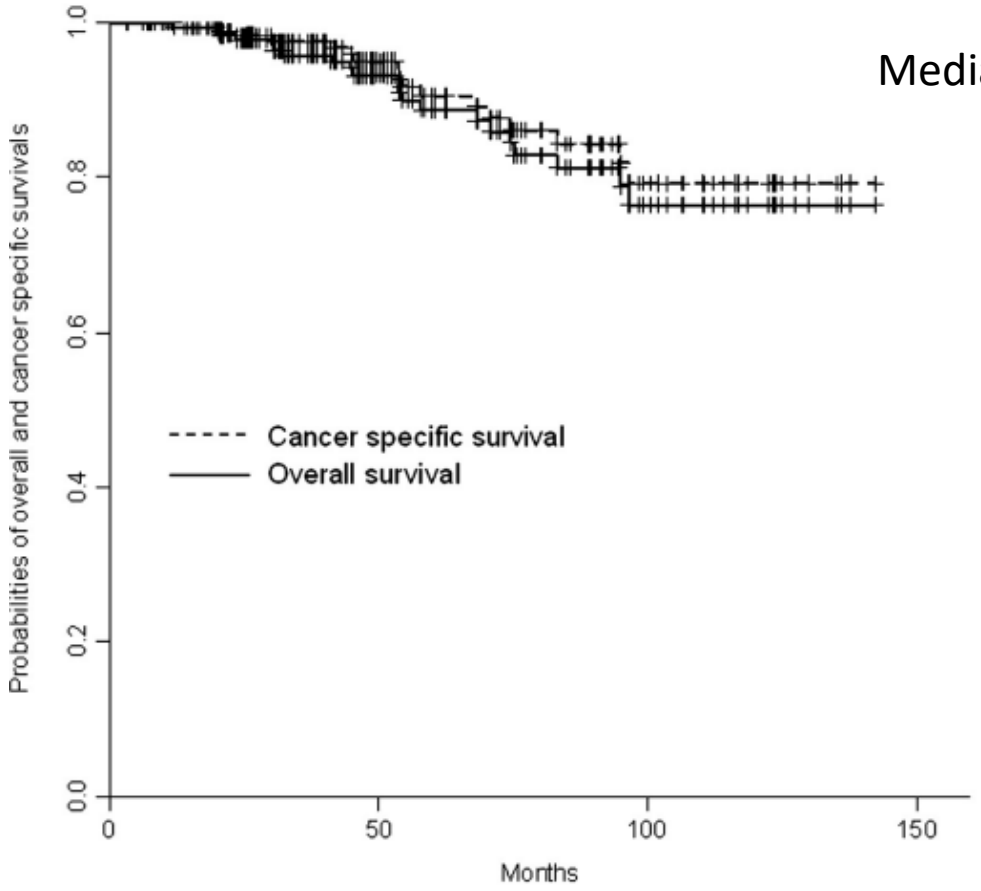
Fig. 2. Sites of 2nd local recurrence with primary tumour in red, 1st local recurrence (i.e. IBTR) in blue and 2nd local recurrence in yellow.

Hannoun-Levi JM, et al. Radiother Oncol. 2013;108(2):226-31.

Reirradiation

- Breast ReRT with brachytherapy (PBI)

GEC-ESTRO study



Median follow-up (years) from the recurrence: 3.9 (1.1 – 10.3)

5-year OS: 88.7% [83.1–94.8]
10-year OS: 76.4% [66.9–87.3]

Hannoun-Levi JM, et al. Radiother Oncol. 2013;108(2):226-31.

Reirradiation

- Breast ReRT with brachytherapy (PBI)

GEC-ESTRO study

Late side effects: 141 patients with 193 events

- Cutaneous and sub-cutaneous fibrosis (67%)
- Telangiectasia (16%)
- Hyperpigmentation (9%)
- Ulceration (1%)

Late side effects: Grade

- G1 50%
- G2 39%

89%

- G3 10 %
- G4 1%

Cosmetic assessment

- Excellent 48%
- Good 37%

85%

- Fair 14 %
- Poor 2%

Hannoun-Levi JM, et al. Radiother Oncol. 2013;108(2):226-31.

Reirradiation

- Breast ReRT with IORT (PBI)

Table 2
Partial breast re-irradiation with IORT.

Authors	Year of publication	# pts	MFU (months)	Irradiation technique	Median Dose (Gy)	3rd IBTE-FS (%)	5-y OS (%)	≥ G3 tox. (%)
Kraus-Tiefenbacher U et al. [26]	2007	17	26	50 kV X-rays	20	100	–	–
Chin C et al. [27]	2017	12	14	50 kV X-rays	20	100	–	0
Blandino G et al. [27]	2017	30	47	Electron beam	18	92.3	91.2	21
Thangarajah F et al. [24]	2018	41	58	50 kV X-rays	20	89.7	82	0

pts: number of patients; MFU: median follow-up; 3rd IBTE-FS: third ipsilateral breast tumor event free survival rate; OS: overall survival; ≥ G3 tox.: grade 3 and higher toxicity rate.

Montagne L, et al. Breast. 2020;49:274-280.

Reirradiation

- Breast ReRT with EBRT (PBI)

Table 3
Partial breast re-irradiation with external beam radiotherapy.

Authors	Year of publication	# pts	MFU (months)	Irradiation techniques	Dose (Gy)		3rd IBTE rate (%)	5-y OS (%)	≥ G3 tox. (%)
					Total (Gy)	Dose/f			
Mullen E et al. [28]	1997	17	75	Cobalt + Electron	50	2	–	–	–
Deutsch M et al. [29]	2002	39	51.5	Electron	50	2	–	–	–
Janssen S et al. [30]	2018	83	35	3D CRT	45	1.8	14.5[a]	76	0
Thorpe CS et al. [32]	2019	50	12.7	Proton	45–76	–	–	97	16
Arthur DW et al. [33]	2019	58	66	3D CRT	45	1.5 BID	5.2	95	7

pts: number of patients; MFU: median follow-up; Dose/f: dose per fraction; 3rd IBTE: third ipsilateral breast tumor event rate; OS: overall survival; ≥ G3 tox.: grade 3 and higher toxicity rate; 3DCRT: 3D conformal radiation therapy.
[a] At 21 months.

Montagne L, et al. Breast. 2020;49:274-280.

Reirradiation

- Breast ReRT with EBRT (PBI)

Research

JAMA Oncology | Original Investigation

Effectiveness of Breast-Conserving Surgery and 3-Dimensional Conformal Partial Breast Reirradiation for Recurrence of Breast Cancer in the Ipsilateral Breast

The NRG Oncology/RTOG 1014 Phase 2 Clinical Trial

Douglas W. Arthur, MD; Kathryn A. Winter, MS; Henry M. Kuerer, MD, PhD; Bruce Haffty, MD; Laurie Cuttino, MD; Dorin A. Todor, PhD; Pramila Rani Anne, MD; Penny Anderson, MD; Wendy A. Woodward, MD; Beryl McCormick, MD; Sally Cheston, MD; Walter M. Sahijdak, MD; Daniel Canaday, MD; Doris R. Brown, MD, PhD; Adam Currey, MD; Christine M. Fisher, MD, MPH; Reshma Jagsi, MD, DPhil; Jennifer Moughan, MS; Julia R. White, MD

Arthur DW, et al. JAMA Oncol. 2020;6(1):75-82.

Reirradiation

- Breast ReRT with EBRT (PBI)

RTOG 1014

58 patients
In-breast recurrence
Tumor ≤ 3 cm
1 year or more after initial
Unicentric (by MRI)
No skin involvement

June 4, 2010 to June 18, 2013

Histologic subtype	
DCIS	23 (40)
Invasive histologic subtypes	35 (60)

Salvage lumpectomy
1.5 Gy twice daily during 15 days (45 Gy)
Each fraction separated by a minimum of 6 h
3-D conformal technique

Median time from previous RT 13.4 years
(range, 1.6 – 27.7 years)

Table 3. The 3- and 5-Year Efficacy Results (Median Follow-up of 5.5 Years)

		3 y		5 y	
End Points	No. of Events	Estimate, % (95% CI)	No. at Risk	Estimate, % (95% CI)	No. at Risk
IBR[a]	4	3.4 (0.6-10.7)	52	5.2 (1.4-13.2)	46
MF[b]	7	5.2 (1.3-13.1)	51	10.5 (4.2-20.1)	43
DMFS	3	94.8 (84.8-98.3)	53	94.8 (84.8-98.3)	48
OS	3	94.8 (84.8-98.3)	53	94.8 (84.8-98.3)	48

IBR, in-breast recurrence; MF, mastectomy failure; DMFS, distant metastasis–free survival; OS, overall survival

Arthur DW, et al. JAMA Oncol. 2020;6(1):75-82.

Reirradiation

- Breast ReRT with EBRT (PBI)

RTOG 1014

Table 2. Characteristics of the Patients With an In-Breast Recurrence

Location	Histologic Subtype	Grade	Stage	Tumor Size, cm	ER Positive	PR Positive	*ERBB2* Positive	Dissection/Biopsy	Time From Registration to Failure, y
Outside treatment field	DCIS	Intermediate	0	1.3	No	No	ND	No SLNB/no ALND[a]	2.6
Within treatment field	DCIS	Intermediate	0	1.5	Yes	Yes	No	No SLNB/no ALND[a]	2.9
Within treatment field	DCIS	High	0	1.0	Yes	Yes	No	SLN not identified/no ALND	4.1
Outside treatment field	DCIS	Intermediate	0	0.2	Yes	Yes	No	No SLNB/yes ALND	5.1

Abbreviations: ALND, axillary lymph node dissection; DCIS, ductal carcinoma in situ; ER, estrogen receptor; ND, not done; PR, progesterone receptor; SLNB, sentinel lymph node biopsy.

[a] Not applicable or not performed counted as no ALND.

Arthur DW, et al. JAMA Oncol. 2020;6(1):75-82.

Reirradiation

- Breast ReRT with EBRT (PBI)

RTOG 1014

Table 4. Distribution of Patients by Highest-Grade Adverse Event by Specific Adverse Event Term Occurring More Than 1 Year From Completion of Partial Breast Reirradiation[a]

	Adverse Event Grade, No.				
System Organ Class or Term	1	2	3	4	5
Infections and infestations					
Total	0	1	1	0	0
Breast infection	0	0	1	0	0
Musculoskeletal and connective tissue disorders					
Total	17	5	1	0	0
Fibrosis deep connective tissue	9	3	1	0	0
Reproductive system and breast disorders					
Total	9	6	3	0	0
Breast atrophy	4	5	1	0	0
Breast pain	9	1	1	0	0
Other[b]	2	0	1	0	0
Skin and subcutaneous tissue disorders					
Total	12	9	1	0	0
Skin induration	4	4	1	0	0
Overall highest grade, No. (%)	14 (24.6)	15 (26.3)	4 (7.0)	0	0

Arthur DW, et al. JAMA Oncol. 2020;6(1):75-82.

Reirradiation

- Breast ReRT with PBI

Available online at www.sciencedirect.com

Reports of Practical Oncology and Radiotherapy

journal homepage: http://www.elsevier.com/locate/rpor

Technical note

Apples and oranges: comparing partial breast irradiation techniques

Orit Kaidar-Person [a,⁎,1], Icro Meattini [b,c,1], Douglas Zippel [d], Philip Poortmans [e,f,1]

What is the best PBI technique for ReRT?

Kaidar-Person O, et al. Rep Pract Oncol Radiother. 2020;25(5):780-782.

Reirradiation

- Breast ReRT with PBI

Different doses

Main partial breast irradiation techniques.

	EBRT	Interstitial Brachytherapy PDR, HDR, LDR	Endocavitary balloon[a]	IORT	IOeRT
Type of treatment	Non-invasive	Invasive	Invasive	Invasive	Invasive
Time of RT	Postoperative	Intraoperative/ postoperative	Postoperative	Intraoperative/ postoperative	Intraoperative
Specialized device/specialized centre	No	yes	yes	yes	yes
Type of RT	High-energy photons	Nuclide, mostly ^{192}Ir	Nuclide, mostly ^{192}Ir	50-kV photons	High-energy electrons
Coverage of clinical target volume	Best	Good	Fair to poor	Poor	Good
RT volume prescription	~ Tumour bed+20 mm to CTV; +5 mm to PTV	~ Tumour bed+20 mm	Dose prescribed 10 mm from applicator surface	Dose prescribed 1 mm from applicator surface	Tumour bed+20 mm determined at time of surgery
Number of treatment days	Different protocols: 5-15	Different protocols: 1-10	5	one	one
Dose homogeneity	Best	Fair	Poor	Poor	Good
Sparing of normal tissue excluding skin	Least	Good	Good	Good	Good
Skin dose	Low	Low	Variable	Variable	Lowest
Technical feasibility for various size/shape/location	Best	Good	Poor	Poor	Good
Draw backs	Dose to normal tissues; Variability in determining tumour bed especially after oncoplastic surgery	Specialized centres; dependent on tumour location within breast; invasive	Low dose at >10 mm from applicator surface; Specialized centres; dependent on tumour location within breast; invasive	Very low dose at >5 mm from applicator surface; Time added to surgery; No final histology available; Specialized centres; dependent on tumour location within breast; invasive	Time added to surgery; No final histology available; Specialized centres; dependent on tumour location within breast; invasive

IORT – intraoperative radiation using 50 kV X-ray device.
EBRT – external beam radiation therapy; PDR- pulse dose rate; HDR-high dose rate; LDR-low dose rate; IOeRT- intraoperative electron radiation therapy.
[a] Example: MammoSite (Hologic, Marlborough, MA).

Kaidar-Person O, et al. Rep Pract Oncol Radiother. 2020;25(5):780-782.

Reirradiation

- Breast ReRT – Normal tissue dose constraints

Two prospective phase II trials – EBRT

Table 1
Normal tissue dose constraints used in RTOG 1014* for partial breast re-irradiation

Normal tissue	Constraint for the re-irradiation
Uninvolved ipsilateral breast	<60% of whole breast receive ≥ of prescribed dose <35% of whole breast receive prescribed dose
Contralateral breast	<3% receive prescribed dose
Ipsilateral lung	<15% receive 30% of the prescribed dose
Contralateral lung	<15% receive 5% of the prescribed dose
Heart	
Right side RT	<5% receive 5% of the prescribed dose
Left side RT	<5% receive 5% of the prescribed dose
Thyroid	Maximum point dose of 3% of the prescribed dose

Table 2
Current normal tissue dose constraints adapted from NL31630.018.10* for chest wall/breast re-irradiation

Normal tissue	Constraint
Spinal cord	Dmax < 50 Gy in EQD2
Whole heart	Minimise mean
Mean lung dose (both lungs)	<16 Gy
V20 lung dose	<35%
V10 lung dose	<50%

Kaidar-Person O, et al. Clin Oncol (R Coll Radiol). 2018;30(2):73-84.

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Re-irradiation in breast cancer

1 – Introduction

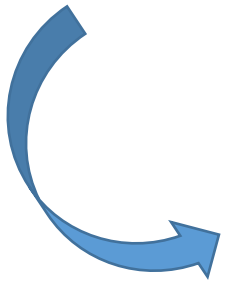
2 – Second breast conserving treatment

3 – Chest wall recurrence

4 – Conclusions

Chest wall recurrence and ReRT

- Treatment for chest wall recurrences after primary mastectomy is surgical resection
  - Local failure rates of up to 70% after surgery alone

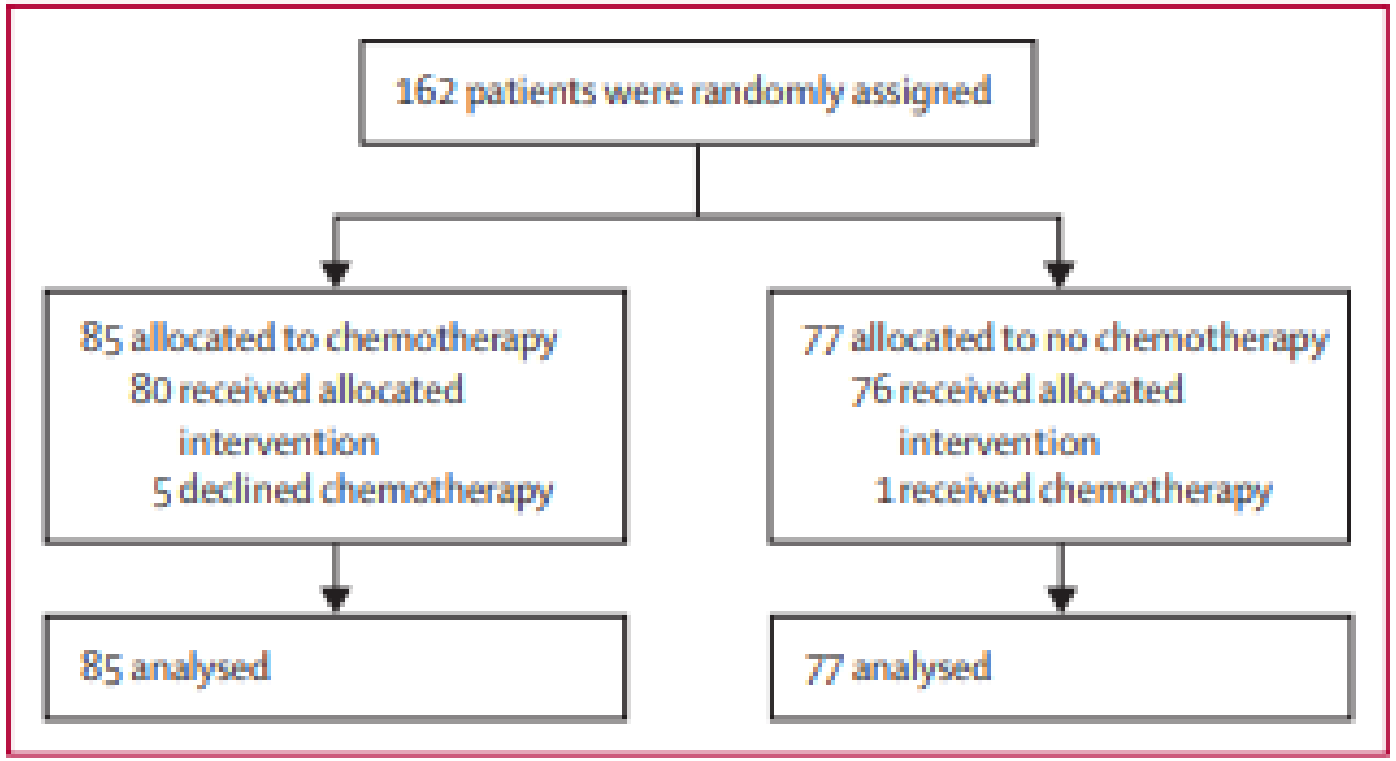


Systemic therapy after local treatment can improve outcomes!

Dahlstrom KK, et al. Cancer 1993;72:774-777.
Beck TM, et al . J Clin Oncol 1983;1:400-5.

Chest wall recurrence and ReRT

Chemotherapy for isolated locoregional recurrence of breast cancer (CALOR): a randomised trial

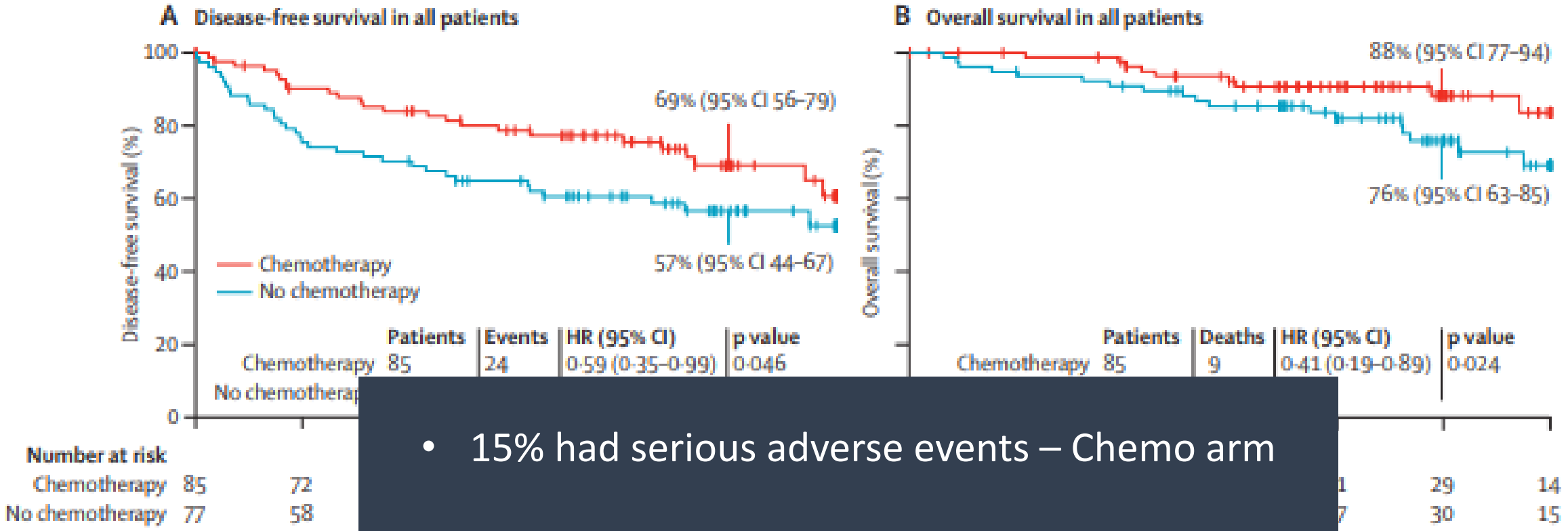


Completely excised after LR (mastectomy or lumpectomy) with clear surgical margins

Aebi S, ei al. Lancet Oncol. 2014;15(2):156-63.

Chest wall recurrence and ReRT

Chemotherapy for isolated locoregional recurrence of breast cancer (CALOR): a randomised trial



- 15% had serious adverse events – Chemo arm
- Only 19% of the patients were treated with ReRT

Aebi S, ei al. Lancet Oncol. 2014;15(2):156-63.

Chest wall recurrence and ReRT

Reirradiation (Re-RT) of resected or unresected breast/chest wall recurrence.

Study	Re-RT modality	Number of patients	Median follow-up (months)	First RT (Gy)	Second RT (Gy)	Cumulative dose (Gy)	Interval between RT courses (months)	Local control	Complete response	Overall survival	Toxicity
Harms et al. 2001 [29]	BT	30 (macro) 28 (micro)	18	52 56	2 × 20 Gy PDR	76–92 85–110	23 44	71% 75% (3-year)	93% –	17% 48% (5 years)	Acute G3 16% Late G3 60% G4 7%
Niehoff et al. 2006 [30]	BT	17 (R1) 15 (R0)	19	59 57	28 Gy HDR (15 pts) 30 Gy PDR (17 pts)	70–103	80 87	59% 67% (1 year)	–	75% (1 year)	G3 skin ulceration (1 pt)
Merino et al. 2015 [31]	EBRT	47 (6 macro)	17.4	50	50 (25 × 2Gy)	100	41	62% (1-year) 50% (2-year)	–	67% (2 years)	G3 fibrosis (4 pts) Telangiectasis (3 pts).

RT, radiotherapy; EBRT, external-beam radiation therapy; BT, brachytherapy; HDR, high dose rate; PDR, pulse dose rate; G, grade; pts, patients; macro, macroscopic disease present; micro, treated for microscopic disease only; R1, resected with residual disease; R0, resected with clear margins.

Marta GN, et al. Breast. 2017;33:159-165.

Chest wall recurrence and ReRT

Clinical practice

- **No standard approach**
- **To be individualised**
  - Prognosis
  - Time interval
  - Side effects of primary RT

- **ReRT to chest wall can be considered:**
  - For macroscopic disease, if surgery is not feasible
  - For microscopic disease after resection
  - For microscopic disease after systemic therapy

Courtesy of Philip Poortmans

Chest wall recurrence and ReRT

Clinical practice

Setting 1

- **Complete resection, no risk factors**
  - Follow-up

Setting 2

- **Complete resection, with risk factors**
  - No other or controlled disease elsewhere
  - Favourable tumour biology
  - Long life expectancy
  - No / limited side effects for earlier RT

Courtesy of Philip Poortmans

Chest wall recurrence and ReRT

Clinical practice

Setting 3

- **Micoscopically incomplete resection**
  - Strongly consider ReRT if
    - No other or controlled disease elsewhere
    - Unfavourable tumour biology
    - Long life expectancy
    - No / limited side effects for earlier RT

Setting 4

- **Macroscopically incomplete resection**
  - Strongly consider ReRT if
    - No other or controlled disease elsewhere
    - Unfavourable tumour biology
    - (Expected) symptomatic disease

Courtesy of Philip Poortmans

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Re-irradiation in breast cancer

1 – Introduction

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4 – Conclusions

Conclusions

- Locoregional recurrence rates after RT for breast cancer went down a lot (but breast cancer survivors will increase)
- Assess carefully physical + physiological +(radio)biological parameters of past RT
- ReRT is ofte tment
- Hypertherm
- Second BCT
  - ... for well-

Unicentric, without skin involvement

Isolated recurrence (no concurrent regional and distant relapse)

Tumour size ≤ 3 cm

Preferably: time to IBTR ≥ 3 years

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Conclusions

- Multi-disciplinary tumour board -> individualize therapeutic approach
- Systemic therapy added to adequate locoregional treatment -> can improve survival
- Further prospective studies are required to evaluate 2nd BCS ± ReRT vs. mastectomy and ReRT for chest wall recurrence
  - including the RT-technique and treatment dose!

No randomized phase III trials to suppot second BCT

and ReRT after salvage mastectomy!!

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Thank for your attention

Thanks to my colleagues

Philip Poortmans

Icro Meattini

Orit Kaidar-Person

Pierfrancesco Franco

Re-irradiation in breast cancer

Gustavo Nader Marta

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