Outcome dei Ritrattamenti Mammari con IORT o dopo IORT full dose

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XXVI CONGRESSO NAZIONALE AIRO
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BREAST RE-IRRADIATION

Why?

Increase number of breast cancer survivors

When?

- Recurrent tumor
- New primary tumor, (hystology site, time to recurrence)
- Nodal disease

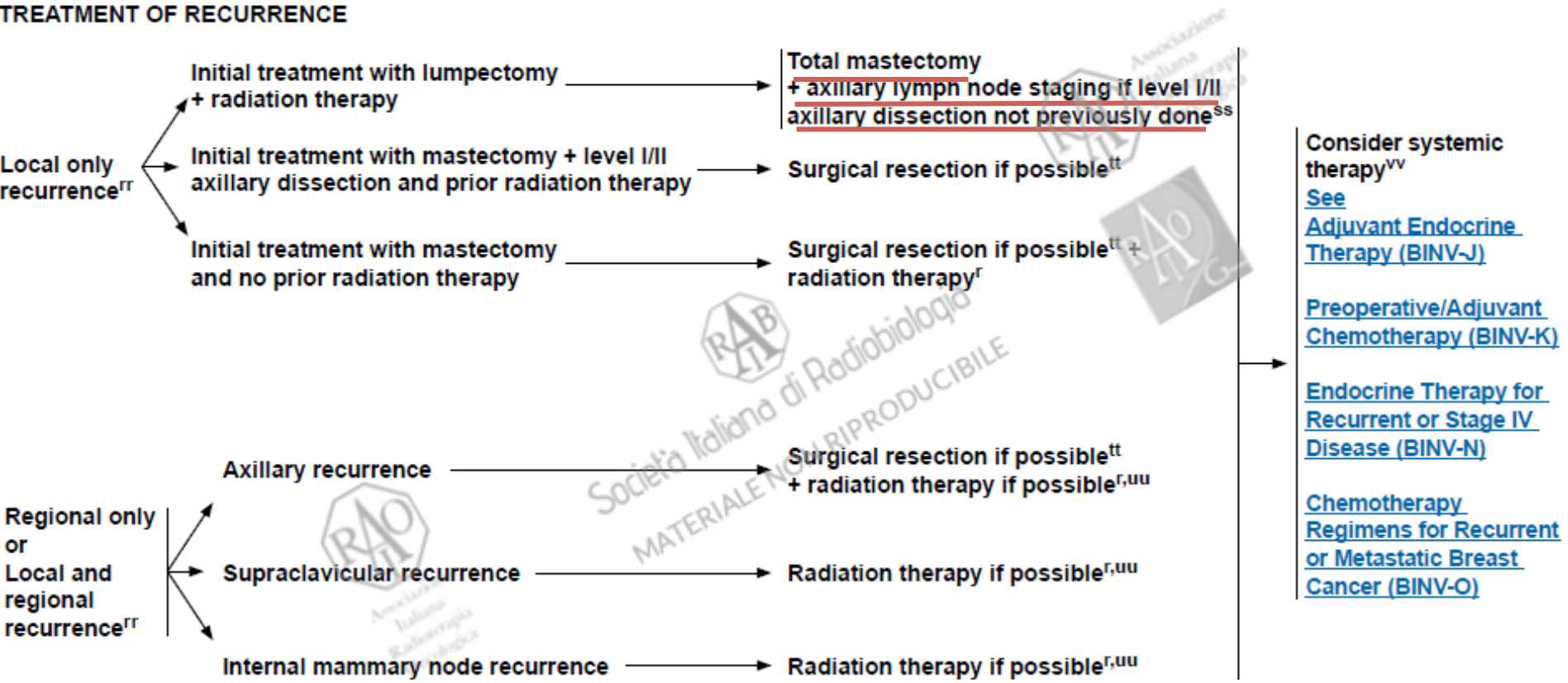
Treatment Guidelines after Breast Conserving Therapy
ACR Appropriatness Criteria

Recidiva locale dopo QUART

- Mastectomia è raccomandata come trattamento di scelta quando la recidiva è operabile e confinata alla mammella

- Escissione +/- RT: solo in trials clinici

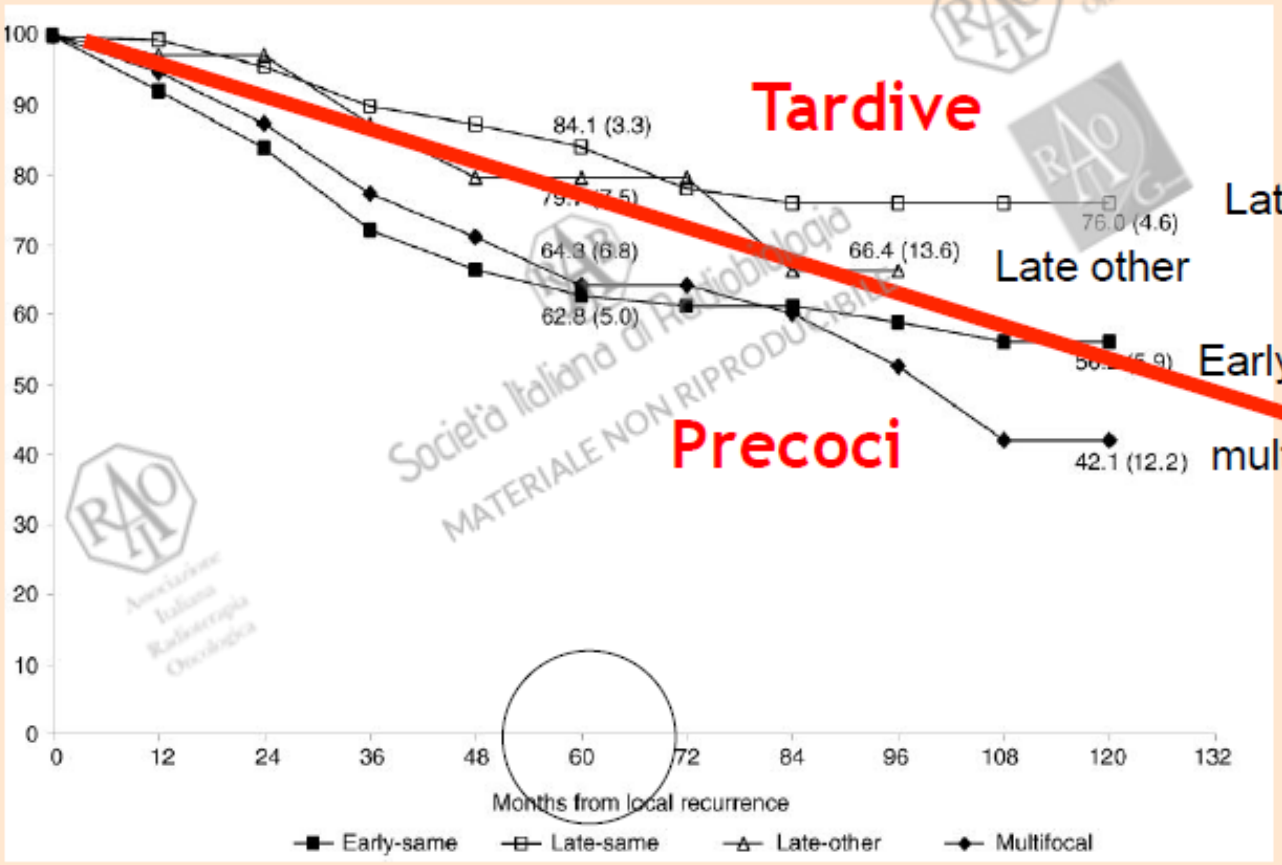
Am J Clin Oncol 2012; 35: 178



- repeat attempts at BCT may result in an unacceptable cosmetic outcome
- normal tissue toxicity concerns regarding re- RT limit second attempt at BCT
- But….reported **outcomes after salvage mastectomy** for IBTRs: chest wall recurrence rates from **7% to 25%**, highlighting the persistent risk of local recurrence

Quando possibile? Selezione dei pazienti

L'importanza dell'intervallo tra primitivo e recidiva

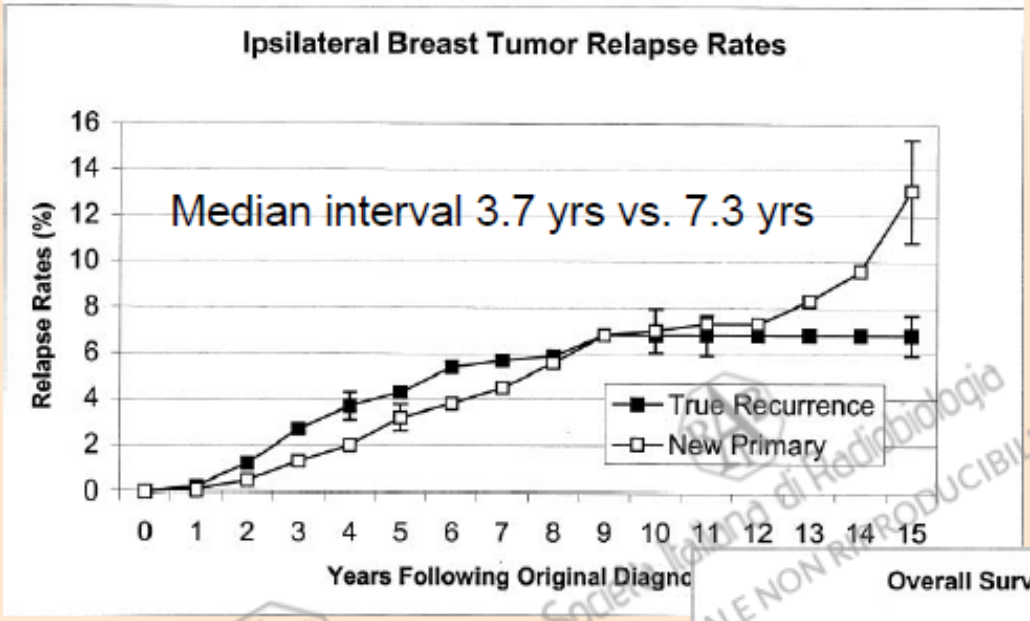


Life-table of BC-specific survival as measured from recurrence

Fredriksson 2002

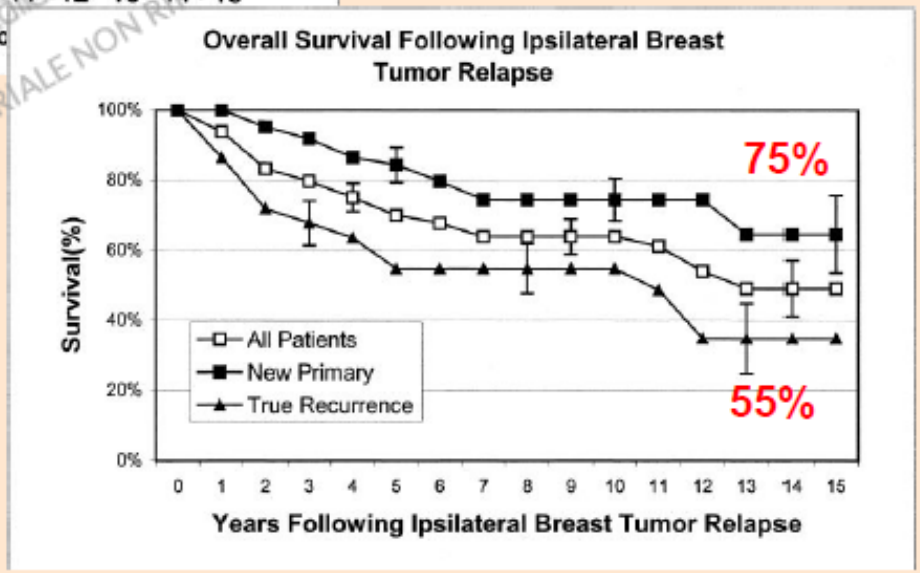
Smith JROBP2000

True vs. elsewhere



Differente storia naturale

differente prognosi e implicazioni



Criteri di differenziazione

Sede

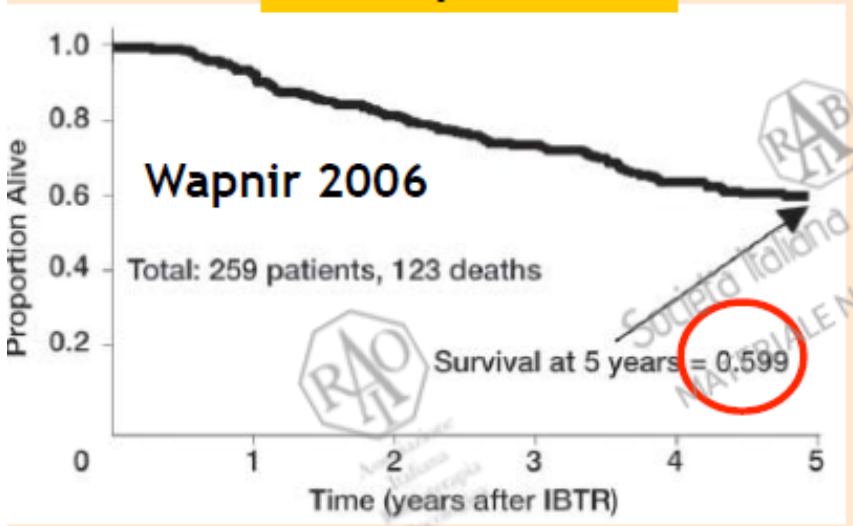
Istologia

Timing

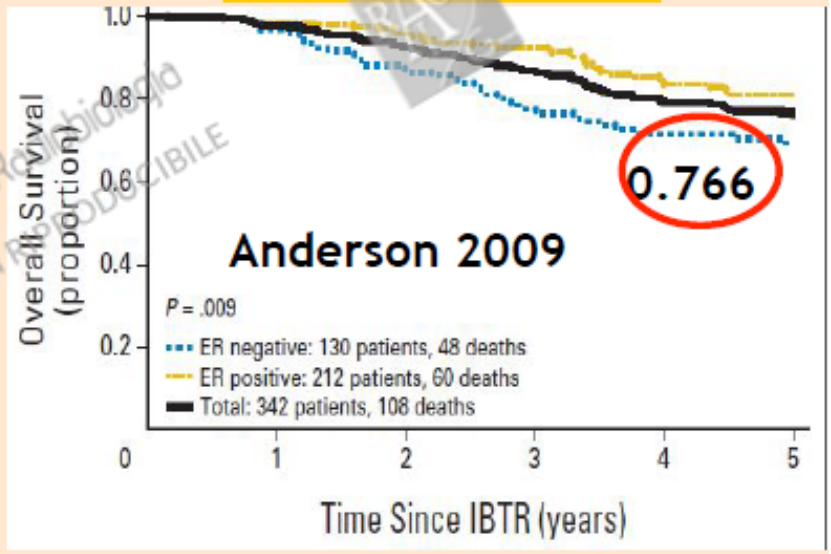
Clonalità

Lo stato linfonodale iniziale
Impatto sulla sopravvivenza e sull'intervallo tra primitivo e recidiva

Node positive



Node negative

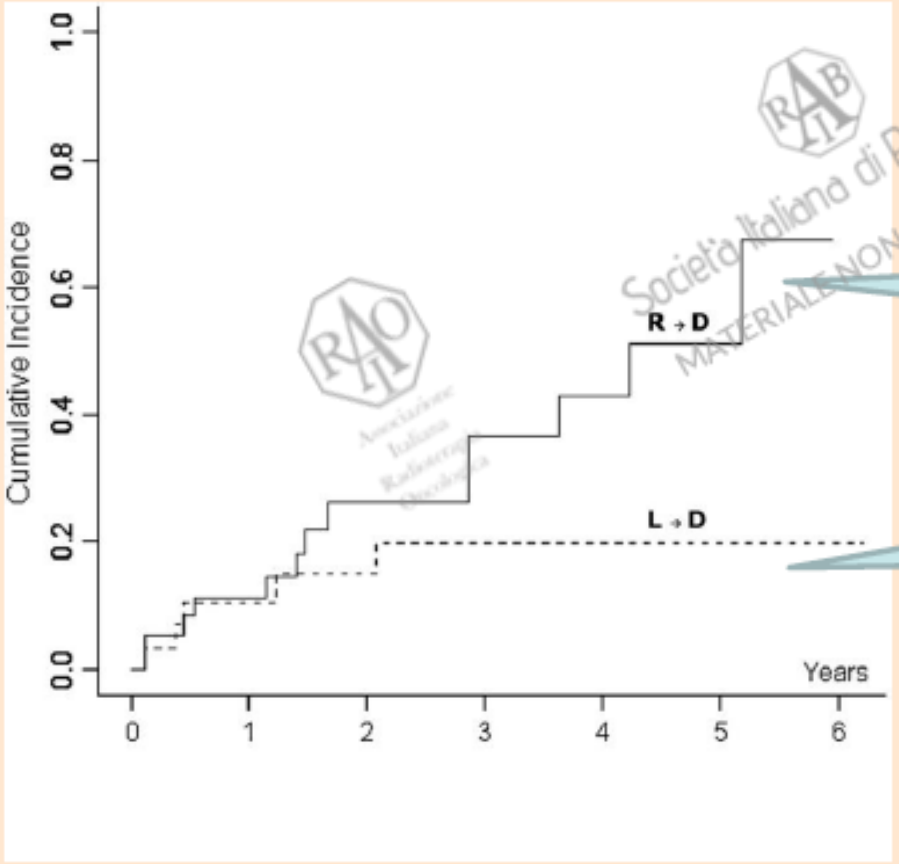


5 NSABP-B trials with BCS

N+: recidiva precoce

N-: recidiva tardiva

Lo stato linfonodale alla recidiva Incidenza cumulativa di metastasi o morte



dopo eventi linfonodali

dopo eventi locali

Botteri, Ann Oncol 2010

Mastectomy vs BCS

- Mastectomy associated with increased psychological distress compared to lumpectomy. The degree of difficulty with body image and clothing are more pronounced *(Ganz et al. 1992)*
- After mastectomy younger women may be more susceptible to increased psychological distress
- About 66% of mastectomy patients under age 40 had high-psychological distress compared to 13% of partial mastectomy patients, $p = 0.027$ (*Maunsell et al. 1989)*
- Lumpectomy has less negative impact on sex life compared to mastectomy, 30% versus 45% *(Rowland et al. 2000)*

Results of salvage BCS without repeat Radiotherapy

References	*N*	Follow up (years)	Local control (%)
Alpert et al. (2005)	30	13.8	93
Abner et al. (1993)	16	3.25	69
Kurtz et al. (1991)	50	4.25	62
Komoike et al. (2003)	30	3.6	70
Salvadori et al. (1999)	57	6.1	86
Dalberg et al. (1998)	14	13	50
Voogd et al. (1999)	16	4.3	62

N number of patients

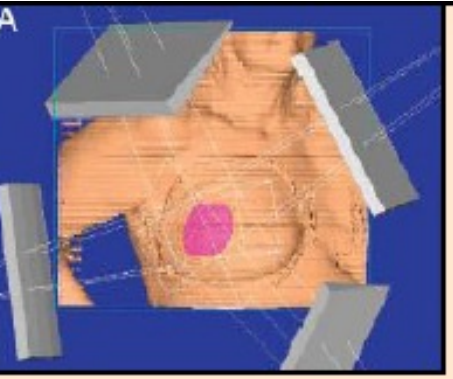
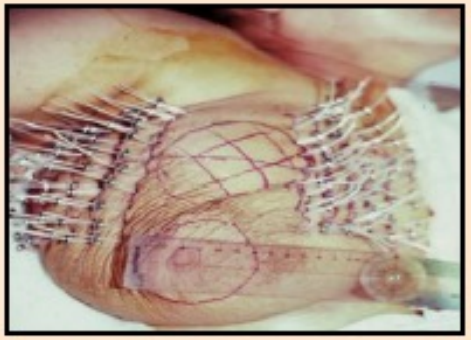
LR rates following repeat BCS in most reports range 30–35%

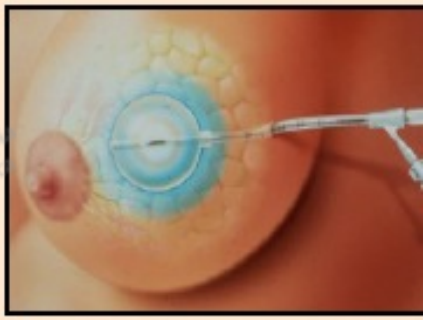
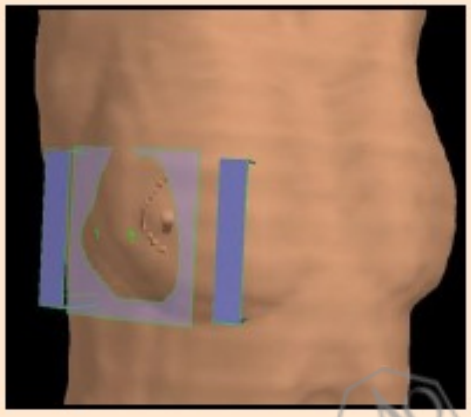
Breast imaging (?) and margin status (?).

Local control similar trials of newly diagnosed breast cancer patients treated with BCS and NO RT. The addition of repeat RT may decrease local failure rate to that seen at initial treatment.

Ritrattamenti Mammari con IORT

- Reirradiation is probably the most challenging treatment in the radio-oncological field.
- Tolerance of normal tissue is reduced compared with the first radiotherapy unless complete repair of the radiation damage has occurred
- To reduce the risk of toxicity one could either reduce the maximum dose or reduce the irradiated volume of normal tissue and maximizing the conformity of the dose distributions.

Esperienze limitate sull'utilizzo della APBI nelle pazienti precedentemente irradiate

reAPBI: teoricamente appropriata

Results of salvage BCS with (PB) Re-irradiation

partial breast irradiation or accelerated partial breast irradiation

References	*N*	Technique	Prior RT dose (Gy)	Re-RT dose (Gy)	Local control (%)
Chadha et al. (2008)	15	LDR	60	30–45	89
Hannoun-Levi et al. (2004)	69	LDR	60.5	30–50	77
Maulard et al. (1995)	38	LDR	65	30–70	79
Resch et al. (2002)	17	EBRT/PDR	50–60	40–50	76
Trombetta et al. (2009)	26	LDR/HDR	45–60.4	45–50 LDR; 34 HDR	96

- Experience on PBRI is confined to recurrences occurring at least 12 months after first treatment. It seems feasible to doses of 50 Gy EQD2 to a partial breast volume of 80-100 ccm with brachytherapy, IORT or EBRT.
- The prospective RTOG trial will probably reveale outcome and and related effects beyond these dimensions at least for EBRT

Activation Date: June 4, 2010
Version Date: May 21, 2010
Update Date: July 29, 2010

RADIATION THERAPY ONCOLOGY GROUP

RTOG 1014

A Phase II study of Repeat Breast Preserving Surgery and 3D-Conformal Partial Breast Re-Irradiation (PBrI) for Local Recurrence of Breast Carcinoma

SCHEMA

REGISTER	Partial Breast Re-Irradiation (PBrI) 3D-Conformal External Beam 1.5 GY x 15 (BID) to 45 Gy Total

OBJECTIVES

2.1 Primary

To evaluate skin, breast, and chest wall adverse events occurring within 1 year from the completion of reirradiation.

precedente RT > 1 anno, ≤ 3 cm , invasivo o noninvasivo, margini negativi ascella negativa o ≤ 3 N+

RTOG 1014 Norm. Tiss. Constr for repeat PBI

Normal tissue	Constraint
Uninvolved normal breast	<60% of whole breast receives ≥50% of prescription dose and <35% of whole breast receives prescribed dose
Contralateral breast	<3% receives prescription dose
Ipsilateral lung	<15% receives 30% of prescription dose
Contralateral lung	<15% receives 5% of prescription dose
Heart (right-sided recurrence)	<5% receives 5% of prescription dose
Heart (left-sided recurrence)	Volume of receiving 5% of prescription dose <40%
Thyroid	Maximum point dose of 3% of prescription dose

This study will provide the first cooperative group evaluation of salvage breast conserving surgery and PB re-irradiation adding information to the limited literature of repeat breast radiation therapy using ERT

Radiotherapy and Oncology 108 (2013) 226–231

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

- European multicentric, retrospective study on outcome of 217 women with IBTR after a previous radio-surgical conservative treatment and who underwent a 2nd BCT combining salvage lumpectomy and post-operative re-RT using interstitial implants

Characteristic		Primary		IBTR	
		#	Median % [range]	#	Median % [range]
#Patients				217	
Age (years)			50.3 [19–83]		60.6 [28–85]
Time to IBTR (years)					10.1 [1.1–35.3]
IBTR site	ITB			111	51.2
	Close to ITB			35	16.1
	Other quadrant			45	20.7
	Unknown			26	12.0
pT size (mm)			15.4 [1–60]		12.4 [1–55]
pLN status	Negative	141	65.0	59	27.2
	Positive	35	16.1	8	3.7
	Unknown	41	18.9	150	69.1
HG	1	36	16.6	34	15.7
	2	60	27.6	81	37.3
	3	40	18.4	58	26.7
	Unknown	81	37.3	44	20.3
HR status	Positive	93	42.9	158	72.8
	Negative	34	15.6	43	19.8
	Unknown	90	41.5	16	7.4
Her2 status	Negative	39	18.0	122	56.2
	+	7	3.2	28	12.9
	++	9	4.1	13	6.0
	+++	11	5.1	28	12.9
	Unknown	151	69.6	26	12.0
Hormonal therapy	Yes	84	38.7	141	65.0
	No	103	47.5	71	32.7
	Unknown	30	13.8	5	2.3
Chemotherapy	Yes	76	35.1	43	19.8
	No	137	63.1	171	78.8
	Unknown	4	1.8	3	1.4
Trastuzumab	Yes	3	1.4	4	1.8
	No	214	98.6	213	98.2
WBI dose (Gy)			56.0 [30–69.6]		

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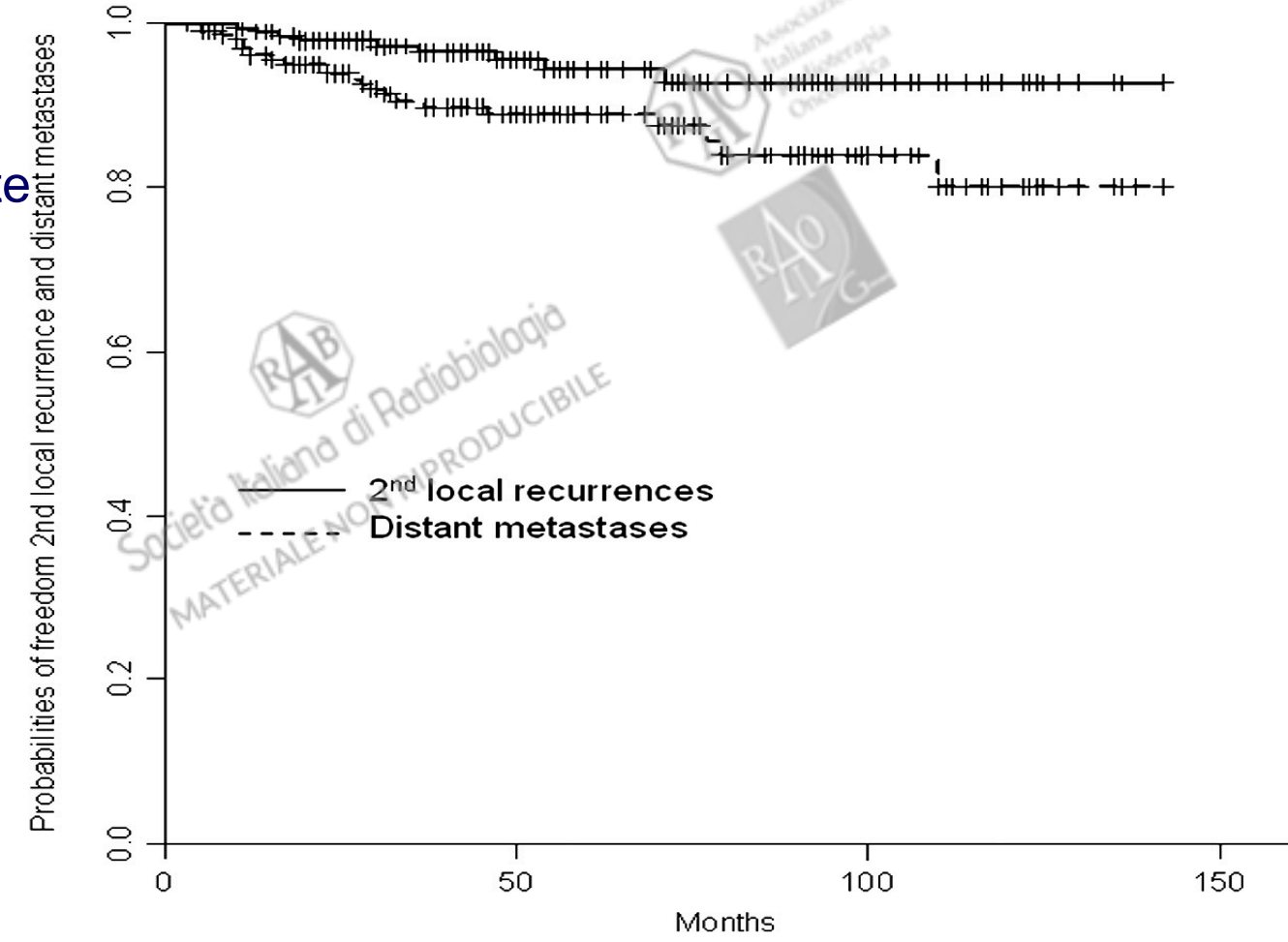
- Re RT with BRT
- Median CTV 52 cc LDR, 68 cc PDR and 62 cc HDR
- Median total dose 46 Gy LDR, 50.4 Gy PDR, and 32 Gy (EQD2 43 Gy4) in 5–10 fx (twice daily) for HDR
- End point: survival rates without second LR, DM and OS as well as late effects and cosmetic result
- Median FU: 14.5 years (3.5-38.2)

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

Freedom from LR act. rate

5 yrs FLR: 94.4 %

10-yrs: FLR: 92.8 %



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

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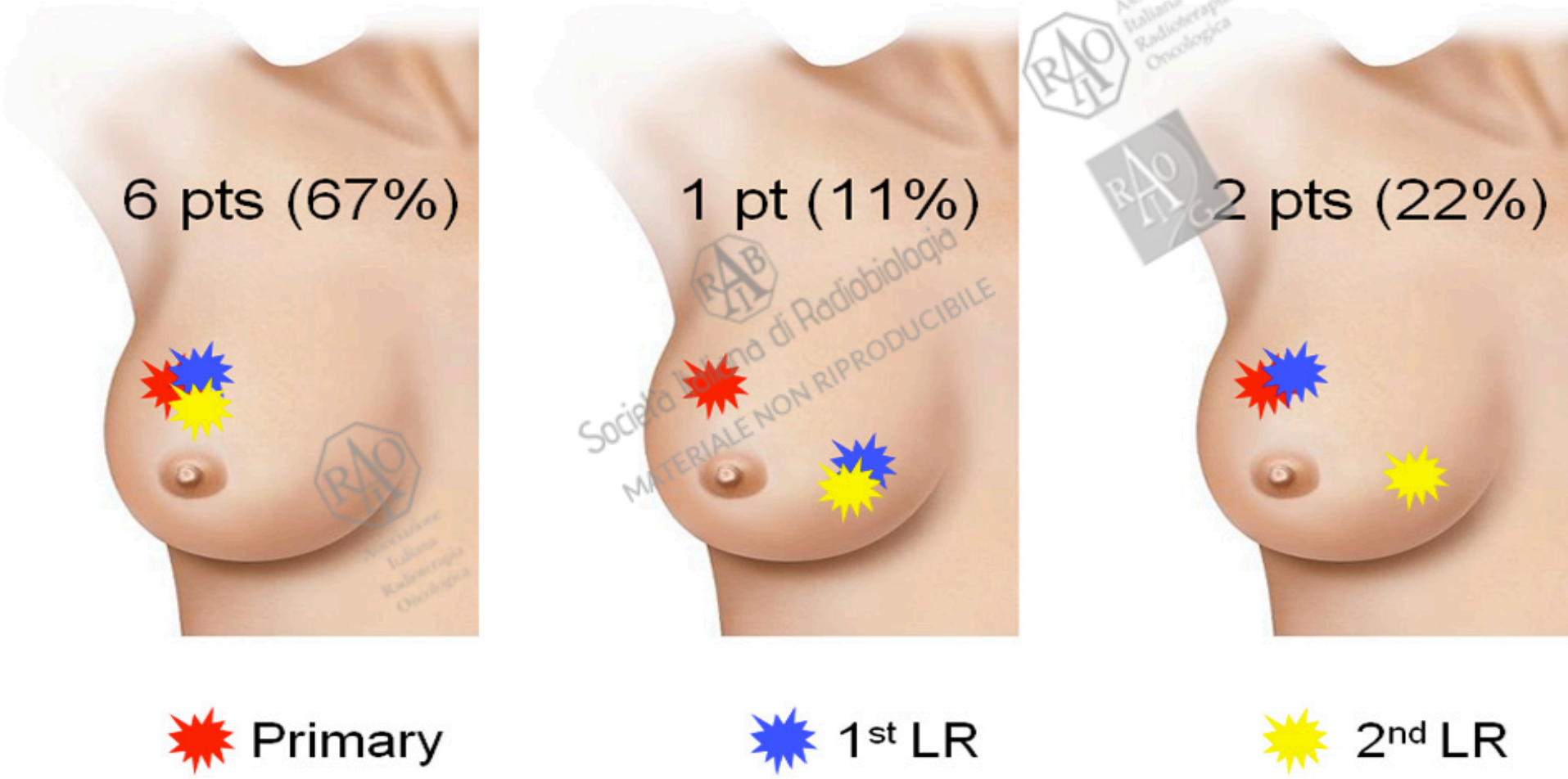


Site of 2nd LR with primary T in red, 1st LR in blue and 2nd LR in yellow

Radiotherapy and Oncology 108 (2013) 226–231

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

Univariate analysis prognostic factor for LR

- age at the time of IBTR (≤55 vs >55 years;p = 0.035),
- histological grade (I–II vs III; p = 0.0003)
- Hormonal receptor status (positive vs negative i.e. ER/PR; p = 0.001)

Univariate analysis prognostic factor for DM

- pathological size of IBTR (≤20 vs >20 mm; p = 0.03)

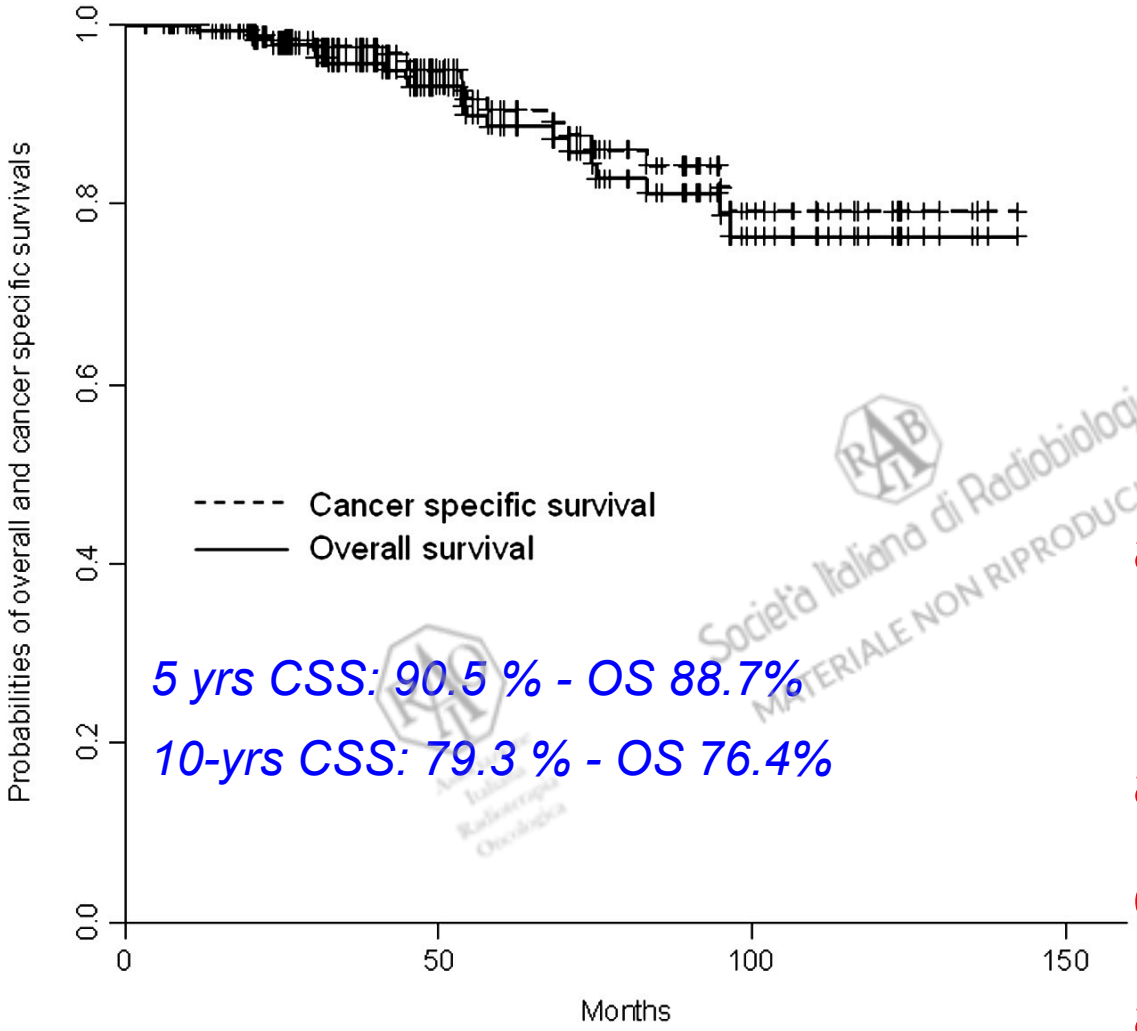
Univariate analysis for OS

- pathological size of IBTR (≤20 vs >20 mm; p = 0.03)
- histological grade (I–II vs III; p = 0.0003)
- Hormonal receptor status (positive vs negative i.e. ER/PR; p = 0.001)

Multivariate analysis

- pathological size of IBTR (≤20 vs >20 mm; p = 0.03) for DM
- Histologic grade (I–II vs III; p = 0.0003) for LR and OS

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



5 yrs CSS: 90.5 % - OS 88.7%

10-yrs CSS: 79.3 % - OS 76.4%

	Time	0	12	24	36	48	60	120
CSS	# pts @ risk	217	196	167	131	98	71	12
	# events	0	1	2	1	3	4	6
OS	# pts @ risk	217	196	167	131	98	71	12
	# events	0	1	3	3	3	4	7

Conclusion

In case of IBTR, BCS plus MCB is feasible and effective in preventing 2nd LR with an OS rate at least equivalent to those achieved with salvage mastectomy.

Pz dopo BCS and RT → recidive trattate con re-BCS e IORT

- 115 PTS
- Median Age: 56 (37-76)
- Median time to 2nd surgery:

  122 mts – (12-324) 10.1 yrs

Characteristics	N	%
Type of surgery		
QU+DA	58	50.4
QU+LS	26	22.6
QU	16	13.9
QU+LS+DA	7	6
QU+ UNKNOWN ALTRO	8	6.9
TOT	**115**	
Histology		
Ductal	65	56.5
Lobular	10	8.6
Other invasive carcinoma	17	14.8
DCIS+ OTHER	12	10.4
Missing data	11	9.5
TOT	**115**	
Tumor diameter (cm)	N	%
IS	7	6
X	0	0
1	1	0.8
≤ 0.5 pT1a	7	6
> 0.5 - ≤ 1 pT1b	18	15.6
> 1 - ≤ 2 p T1c	34	29.5
> 2 - ≤ 5 pT2	11	9.6
Missing data	37	32.1
Vascular Invasion		
Absent	35	30.4
Present	4	3.5
Missing data	76	66.1
Grading		
G1	13	11.4
G2	26	22.6
G3	11	9.5
Missing data	65	56.5
ER and PgR OLNY % NOT + OR -		
ER- PgR-	10	8.7
ER+ PgR-	3	2.6
ER+ PgR+	53	46
ER- PgR+	2	1.8
Missing data	47	40.9
c-erb2		
Not Over-expressed	23	20
Over-expressed (UNKNOWN FISH)	8	7
Missing data	84	73

Ritrattamenti Mammari con IORT

Median age at 2nd surgery: 62 yrs (40-81 yrs)

IBTR diagnosis	N	%
Clinical examination	9	7.8
Clinical/Strument	3	2.6
MX / ECO	89	77.3
RMN	5	4.3
Other	6	5.2
Unknown	3	2.6
TOT	115	

Region of IBTR	N	%
Same quadrant	51	44.3
Other quadrant	59	51.3
Missing data	5	4.4
TOT	115	

Characteristics	N	%
Type of surgery		
QU	62	53.1
QU+LS	30	26
QU+cmi	3	2.6
Qu+LS+cmi	4	3.5
QU+DA	3	2.6
QU+DA+LS	1	0.8
OTHER	12	10.4
TOT	115	
Histology		
Ductal	93	80.9
Lobular	13	11.3
Other invasive carcinoma	4	3.5
Other	4	3.5
Unknown	1	0.8

Tumor diameter (cm)	N	%
IS	3	2.6
X	1	0.9
≤ 0.5	16	13.9
> 0.5 - ≤ 1	41	35.6
> 1 - ≤ 2	50	43.4
> 2 - ≤ 5	2	1.7
Missing data	2	1.7
tot	115	
Vascular Invasion		
Absent	89	77.5
Present	12	10.4
UNKNOWN	14	12.1
Grading		
G1	8	7
G2	58	50.4
G3	26	22.6
Missing data	23	20
ER and PgR 27 ER E PGR 2 SOLO ER 5 MANCANTI		
ER- PgR-	14	12.1
ER+ PgR-	13	11.3
ER+ PgR+	83	72.1
ER- PgR+	1	0.9
unknown	4	3.5
Ki-67 %		
<= 20	53	46
>20	56	48.7
missing	6	5.3
c-erb2		
Not overexpressed	84	73
Overexpressed (UNKNOWN FISH)	14	12.2
Missing data	17	14.8

Ritrattamenti Mammari con IORT

IORT data after 2nd surgery.

Gy	N	%
8	1	0.9
12	9	7.8
14	1	0.9
15	4	3.4
16	4	3.4
18	48	41.7
21	47	40.9
unknown	1	0.9

Side effects after 2nd surgery and IO

Characteristics	N	%
Lyponecrosis Agocentesis confimed	5	4.3
Hematoma	8	6.9
Sieroma	10	8.7
Oedema	8	6.9
Pain	5	4.3
Wound infection	3	2.6
fibrosi	12	10.4
discomie	1	0.9
epiteliosi	1	0.9
other	5	4.3

	Median	Range	Median IEO	Range IEO
Applicator diameter (cm)	5	4,5 - 6	4	3-6
Energy (MeV)	7	6-10	7	4-10
Tissue depth (cm)	1.5	1-2.5	1.4	0.5-2.7

Ritrattamenti Mammari con IORT

115 pts - Median follow-up post IORT: 56 mts (13-124 mts) 4.6 yrs

Events	N	%
Tot event	23	20
Local recurrence	13	11.3
Contralateral tumor	3	2.6
Distant metastases	3	2.6
Other neopl	1	0.9
Dead	3	2.6
NED	92	73.6

AIRO IORT VS GEC ESTRO

Median FU post IORT: 14.8 yrs (3.5-27)

Characteristics	N	%
Lyponecrosis Agocentesis confimed	5	4.3
Hematoma	8	6.9
Sieroma	10	8.7
Oedema	8	6.9
Pain	5	4.3
Wound infection	3	2.6
fibrosi	12	10.4
discomie	1	0.9
epiteliosi	1	0.9
other	5	4.3
TOT	58	50

Median FU post BRT: 14.5 yrs (3.5-38.2)

Characteristics	N	%
Telangectasia		16
Ulceration		1
Sieroma		
Oedema		
Pain		
Wound infection		
fibrosi		67
discomie		16
epiteliosi		
other		
TOT	141	65

Toxicity of PBI after 2° event

AIRO IORT VS GEC ESTRO

Median FU 115 pts: 14.8 yrs

Events	N	%
Tot event	23	20
Local recurrence	13	11.3
Contralateral tumor	3	2.6
Distant metastases	3	2.6
Other neopl	1	0.9
Dead	3	2.6
NED	92	73.6

• **Median FU 217 pts: 14.5 years (3.5-38.2)**

Events	N	%
Tot event	60	27.6
Local recurrence	9	4.1
Contralateral tumor		
Distant metastases	23	10.5
Axillary recurr	1	0.5
Dead	27	12.5
NED	157	72.3

2° event after PBI

E LE RECIDIVE DOPO IORT COME SONO STATE TRATTATE?

Original Article

Cancer September 1, 2012

Outcome After Ipsilateral Breast Tumor Recurrence in Patients Who Receive Accelerated Partial Breast Irradiation

Chirag Shah, MD[1]; Frank Vicini, MD[1]; Martin Keisch, MD[2]; Henry Kuerer, MD[3]; Peter Beitsch, MD[4]; Bruce Haffty, MD[5]; and Maureen Lyden, MS[6]

Table 1. Ipsilateral Breast Tumor Recurrences

	All Patients, N = 1449		Patients With Invasive Disease, N = 1255		Patients With DCIS, N = 194	
Type of Recurrence	No. (%)	5-Year Actuarial Rate, %	No. (%)	5-Year Actuarial Rate, %	No. (%)	5-Year Actuarial Rate, %
All breast failures	50 (3.5)	3.6	42 (3.3)	3.7	8 (4.1)	3.4
True recurrence/marginal miss	14 (1)	1.1	11 (0.9)	1.1	3 (1.5)	1.2
Failure elsewhere	36 (2.5)	2.6	31 (2.5)	2.6	5 (2.6)	2.1
P		.41		.66		.27

Supports the use of repeat BCT, because 75% of recurrences were categorized as new primaries and, thus, amenable to repeat breast-conserving surgery with repeat APBI.

Elsewere failure seems to have improved DFS and CSS after IBTR compared with true failure/MM.

Cancer September 1, 2012

Outcome After Ipsilateral Breast Tumor Recurrence in Patients Who Receive Accelerated Partial Breast Irradiation

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Table 3. Studies With Repeat Breast-Conservation Therapy Using Accelerated Partial Breast Irradiation

Institution (Reference)	No. of Patients	Technique	Follow-Up After Second BCT, mo	Outcomes
University of Pittsburgh (Deutsch 2002[9])	39	EBRT WBI, 50 Gy + 10 Gy	51.5	LC rate, 80% at 5 y
Beth Israel Medical Center (Chada 2009[10])	15	LDR, 30-45 Gy	36	LC rate, 89% at 3 y
University of Nice (Hannoun-Levi 2010[15])	42	HDR IB	21	LC rate, 97% at 2 y
Drexel University (Trombetta 2011[11])	36	21 Patients, LDR IB PBI; 11 patients, MammoSite; 4 patients, 3D-CRT PBI	37	35 of 36 Patients disease free at 3 y
Barcelona Medical Institute for Radiotherapy and Oncology (Guix 2010[16])	36	HDR IB, 30 Gy × 10	120	LC rate, 89.4% at 10 y
University of Wisconsin (Adkison 2010[17])	11	HDR, 3.4 Gy × 10	53.7	100% disease free at 4 y
University of Paris (Maulard 1995[18])	15	LDR, 30 Gy	40	79% LC at 4 y

Results from this study, along with the previous reports suggest that clinical outcomes after IBTR with APBI are comparable to the outcomes achieved with WBI at 5 years of follow-up.

228 Recidive dopo IORT

- Mean time 1° surg - and 1° rec: 4.4 aa
- Median 3.9 aa - Range 0.4 -15 aa

Sede recidiva	N pazienti 228	%
recidiva locale	128	56.1
Secondo T omolaterale	51	22.3
recidiva locale e distante	6	2.6
recidiva locale +Inn ascellari	20	8.7
recidiva locale e controlaterale	8	3.5
recidiva locale-DIN	1	0.4
recidiva regionale	4	1.7
recidiva pluricentrica	8	3.5
Recidiva a distanza ossee	1	0.4
Manca dato	1	0.4

Terapia della Recidiva

Terapia recidiva	N 228	%
quadrantectomia + dissezione ascellare	21	9.2
mastectomia	112	49.1
solo dissezione ascellare	2	0.8
quadrantectomia + BLS + dissezione ascellare	1	0.4
QUA+PBI	4	1.7
QUA+ 2° IORT	18	7.8
mastectomia +RT	17	7.4
terapia sistemica	6	2.6
RT regionale	1	0.4
RT meta ossee	2	0.8
QUA+RT (WB +/- N regionali)	44	19.2

Eventi successivi e Stato

Eventi successivi	N (228)	%
recidiva locale	3	1.3
mets ascella	2	0.8
ca. Controlat	4	1.7
mets multiple	26	11.4
altro ca primitivo	7	3
secondo T omolaterale	2	0.8
recidiva locale e distante	4	1.7
recidiva locale +regionale	2	0.8
recidiva locale e controlaterale	1	0.4
mets cute mammella	2	0.8
recidiva locale-DIN	1	0.4
ca. Controlat-DIN	3	1.3
recidiva regionale	1	0.4
recidiva pluricentrica	2	0.8
secondo tu omolaterale + recidiva regionale + mets	1	0.4
Altra neoplasia	4	1.7
NED	160	70.1

Follow-up complessivo: Media = 8.3 anni

Mediana = 8.3 anni

Range = 0.6-21.5 anni

Follow-up tra 1°recidiva e data ultimo follow-up: Media = 3.5 anni

Mediana = 3.0 anni

Range = 0 -12.0 anni

Stato ultimo contatto	N (228)	%
NED	160	70.1
AWD	37	16.2
DWD	28	12.2
MISSING	3	1,4

CONCLUSIONS

- **Currently, in terms of evidence based medicine, there is no consistent proof for presenting salvage mastectomy as the treatment of reference for IBTR and to refuse 2nd BCT with adjuvant multicatheter interstitial BT.**

- **To validate and compare these two treatment strategies a randomised trial comparing salvage mastectomy versus 2nd BCT with re-irradiation of the tumour bed would be…..**

- **Some data seems to show that after an IBTR, the patients initially treated with APBI have comparable outcomes with those treated with WBI after salvage therapy.**

- **RTOG 1014 → will help to select local treat strategy for the management of IBTR**

. **Patients selection!!!**

CONCLUSIONS

- Re-irradiation may be proposed for selected patients
- PBI is a option
- Small portion of the patients can be cured with the second course of RTP

- Toxicity of re-irradiation is lower than expected for the high cumulative dose

• In the future, objective standards, including loss-o heterozygosity testing, may be used to better deline new primaries.