Intraoperative Radiotherapy

ROBERTO ORECCHIA

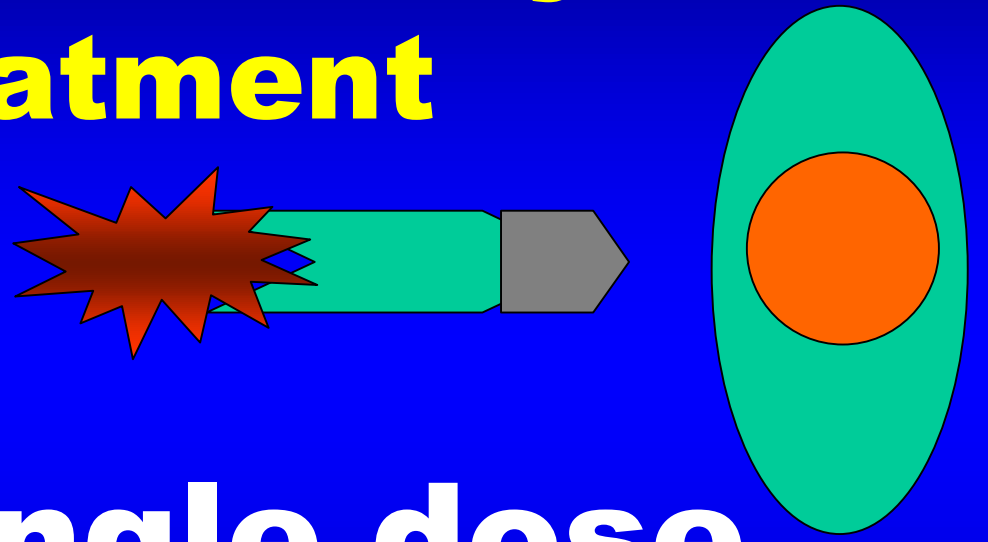
UNIVERSITY of MILAN
& EUROPEAN INSTITUTE of ONCOLOGY
& CNAO FOUNDATION

Breast Cancer

Brescia, 30th September 2011

fondazioneCNAO

IORT, very selective technique to intensify the local treatment



High single dose as sole treatment or boost

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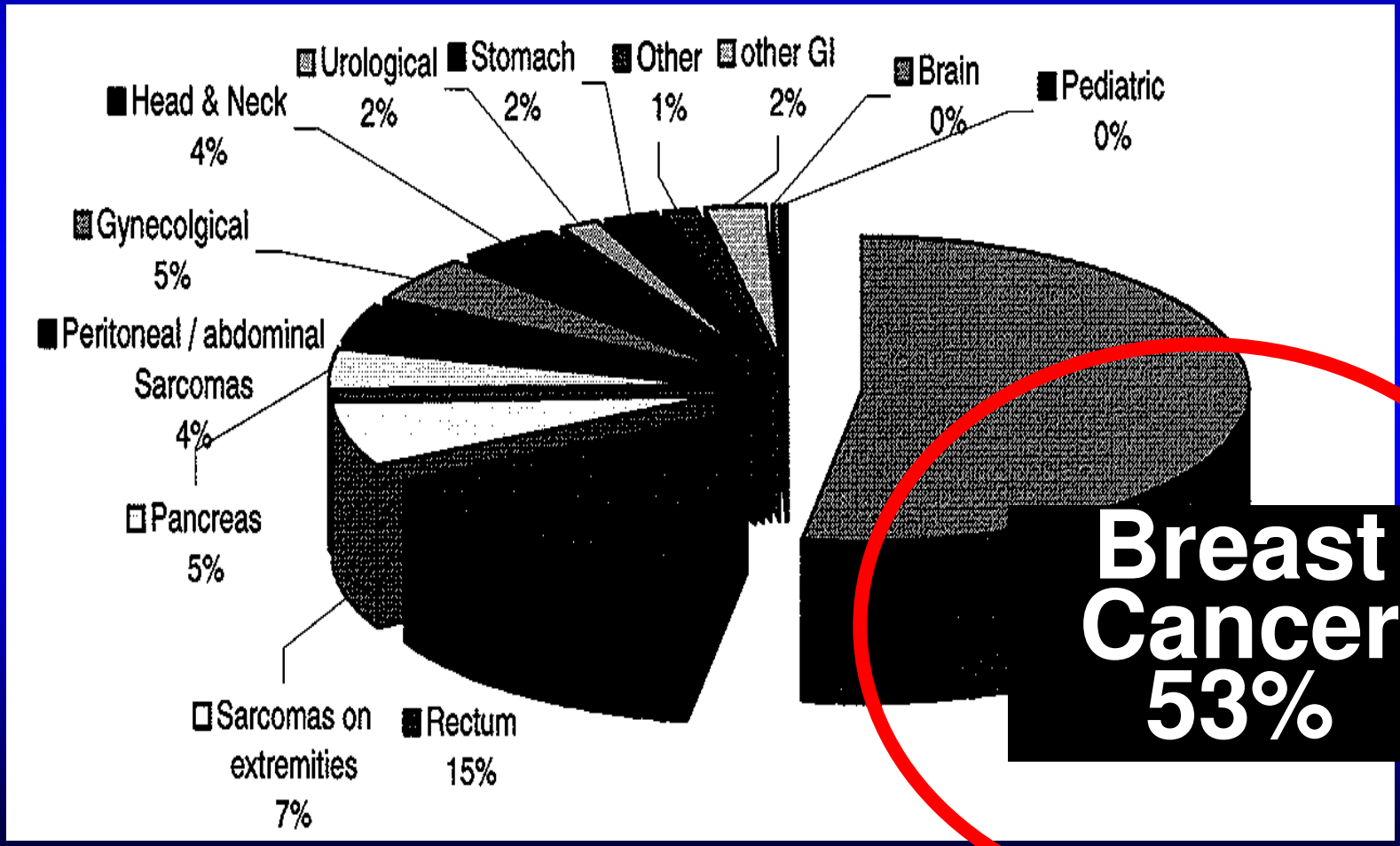
Synergy and team work
Surgery and Radiation Oncology

IORT indications

(average number of yearly patients)

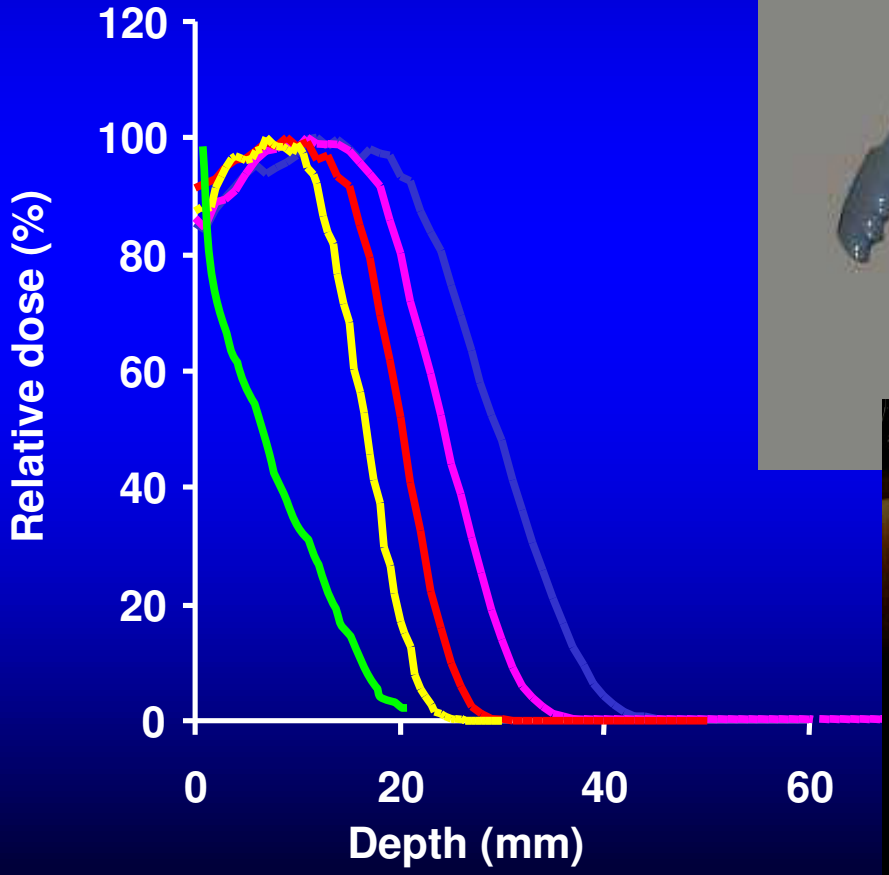


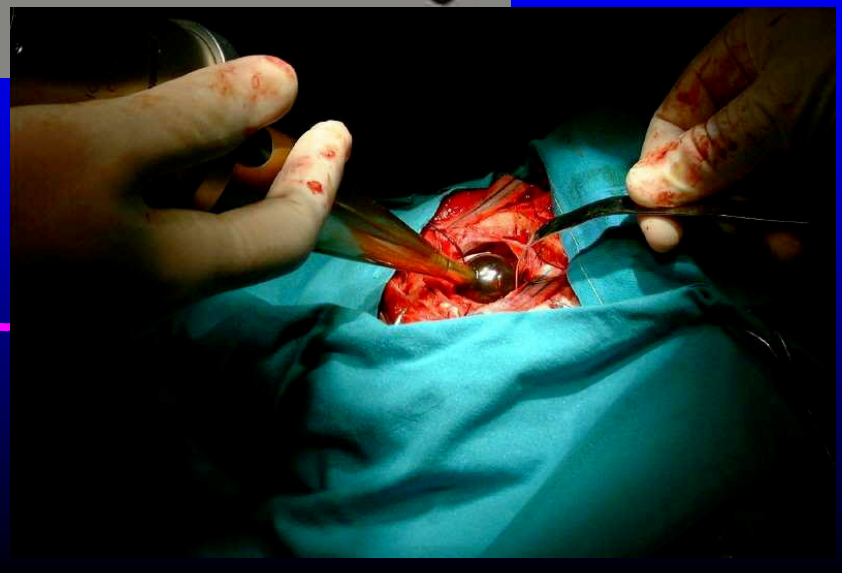
QoL

RT

"FAST"

Intrabeam





X-ray source 50kVp

Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial

Jayant S Vaidya, David J Joseph, Jeffrey S Tobias, Max Bulsara, Frederik Wenz, Christobel Saunders, Michael Alvarado, Henrik L Flyger, Samuele Massarut, Wolfgang Eiermann, Mohammed Keshtgar, John Dewar, Uta Kraus-Tiefenbacher, Marc Sütterlin, Laura Esserman, Helle M R Holtveg, Mario Roncadin, Steffi Pigorsch, Marinos Metaxas, Mary Falzon, April Matthews, Tammy Corica, Norman R Williams, Michael Baum

28 Institutions in 9 Countries

2,232 patients enrolled (started March 2000, closed May 2008)

Age 45 years old or more, with IDC suitable for wide local excision

- **IORT (20 Gy at the surface) vs conventional WBRT (40-56 Gy, w/w-out Boost)**
- **Each center could decide that patients randomized to IORT with certain pathological finding (lobular, EIC+…) receive WBRT in addition**

Vaidya JS et al, Lancet, July 2010

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Median age 63 years,

Tumor size < 1 cm in 36%,

50% b/n 1-2 cm

G3 tumors in 15%,

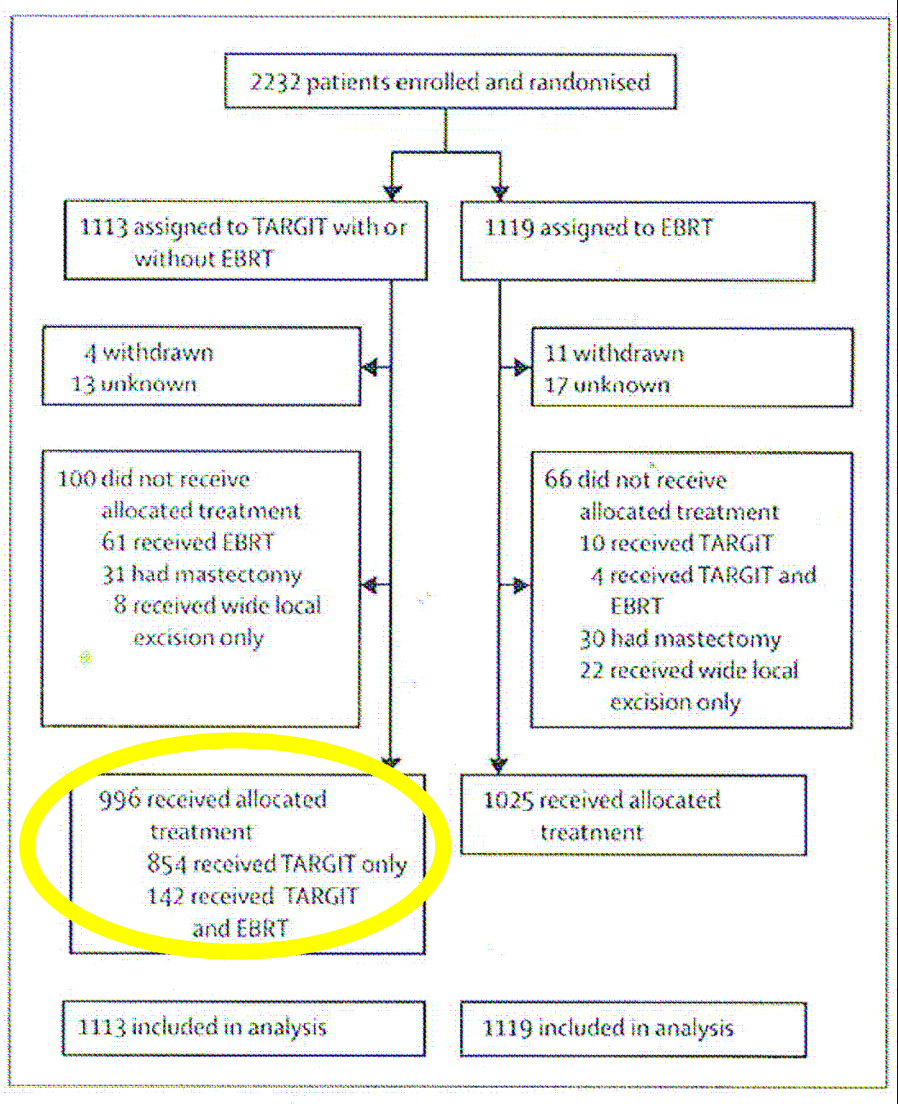
N+ in 17%

Margin free 90.2-90.5%

Re-excision 7.1-9.2%

66% hormone therapy

12% chemotherapy



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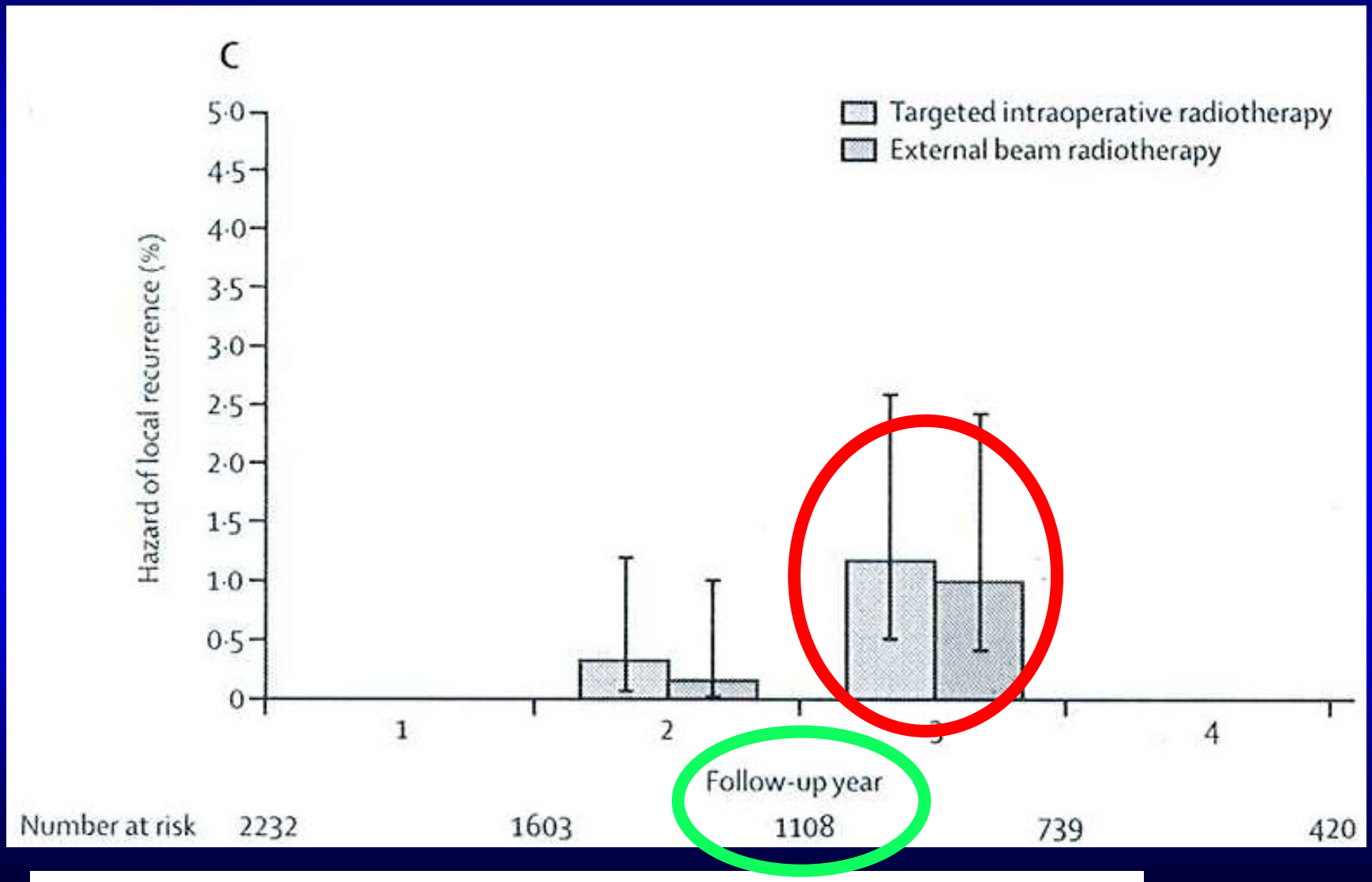

6 LR in the TARGIT group (1.2%), 5 in the EBRT group (0.95%)

Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial

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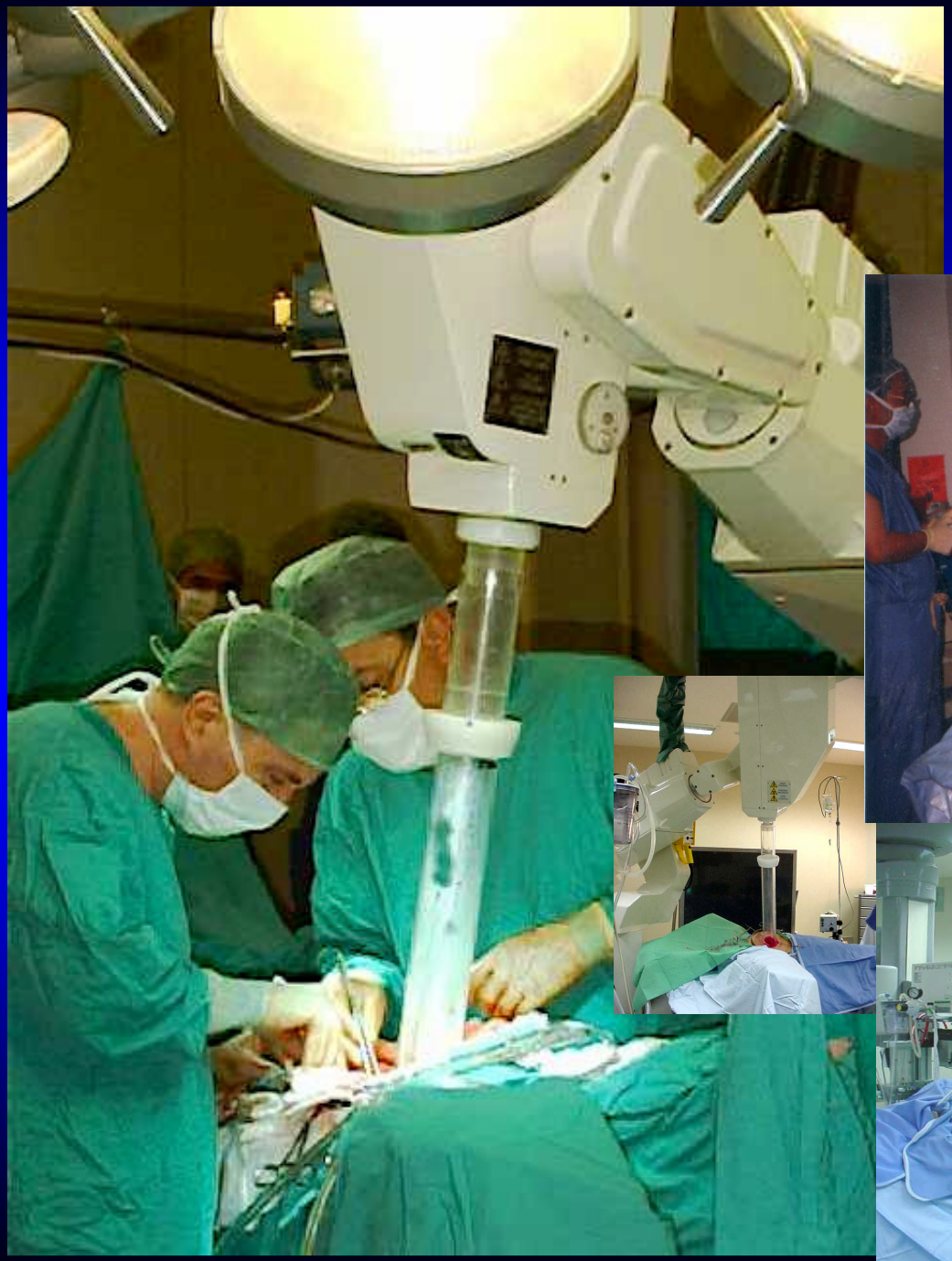
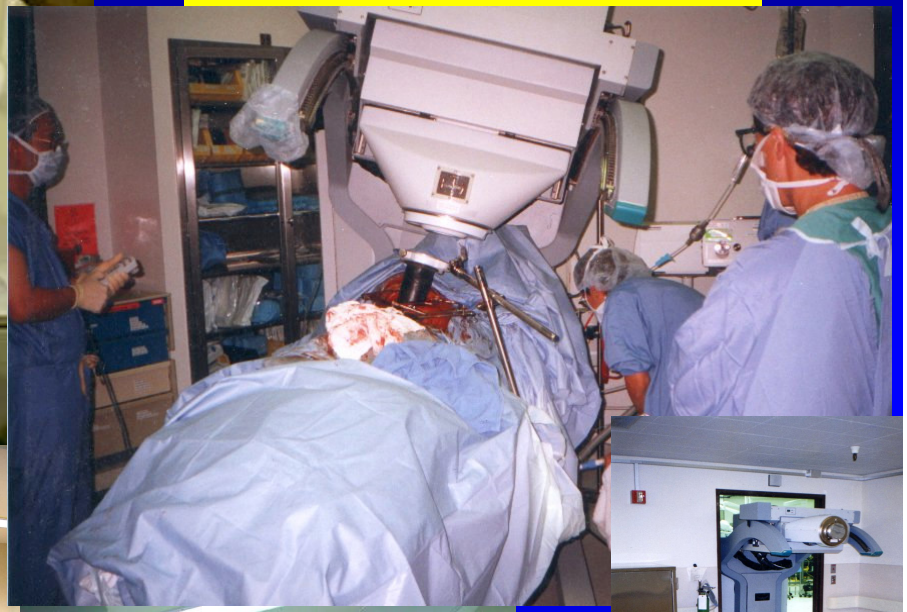
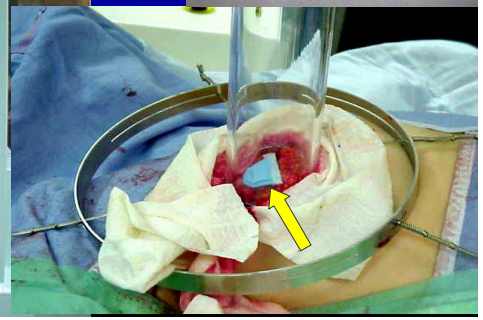
	Targeted intraoperative radiotherapy (n=1113)	External beam radiotherapy (n=1119)	p value
Haematoma needing surgical evacuation	11 (1·0%)	7 (0·6%)	0·338
Seroma needing more than three aspirations	23 (2·1%)	9 (0·8%)	0·012
Infection needing intravenous antibiotics or surgical intervention	20 (1·8%)	14 (1·3%)	0·292
Skin breakdown or delayed wound healing*	31 (2·8%)	21 (1·9%)	0·155
RTOG toxicity grade of 3 or 4†	6 (0·5%)	23 (2·1%)	0·002
Major toxicity‡	37 (3·3%)	44 (3·9%)	0·443

No statistical difference in complication rate (11.5 in Targit arm vs 10.6% in EBRT arm)

“Mobile” Linacs







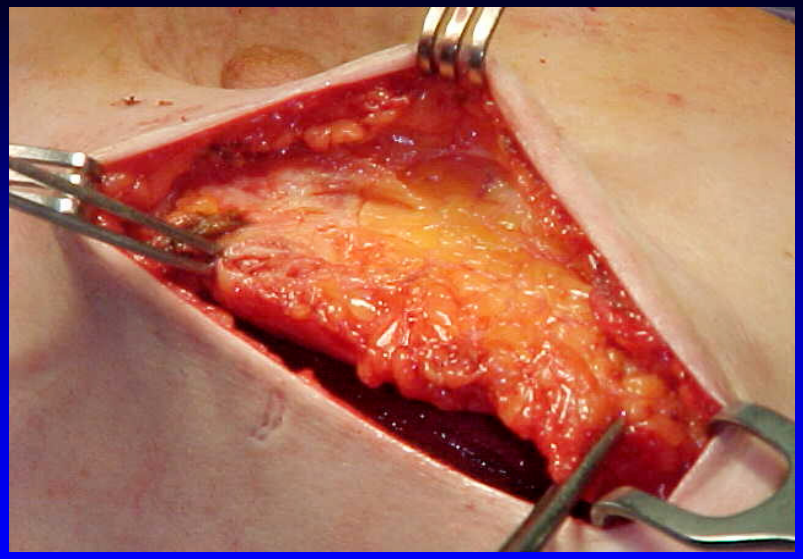
EIO Milan / ELIOT experience

- **Dose-escalation study** (7/1999-4/2000)
- **Pha**
- **Rar** now
  closed
- **Nip** tly
  ongoi
- **ELI**
  (6/2004 and currently ongoing)

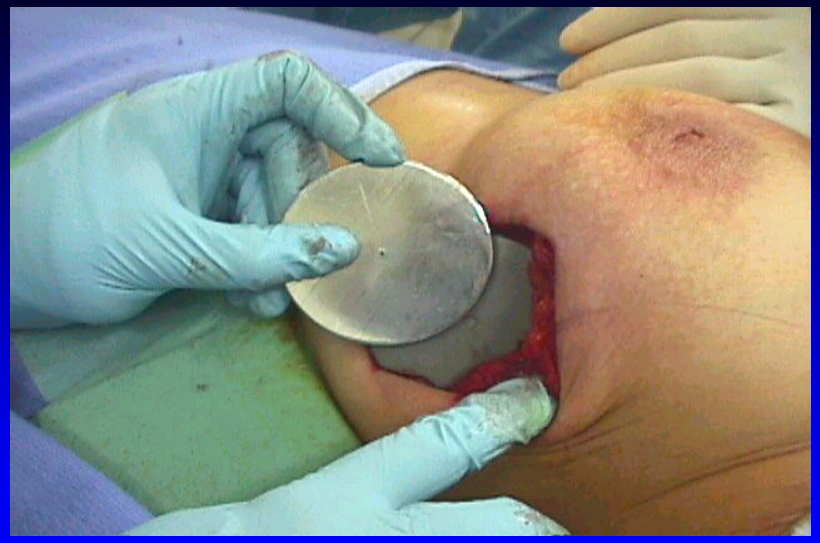
Almost 7,000 cases

Average per year 800 cases

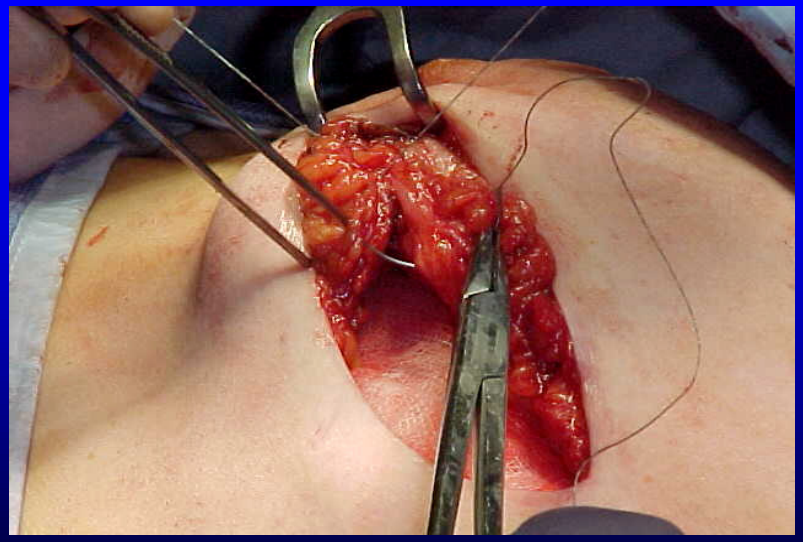
.....1822 Out Trials patients



I Mobilization



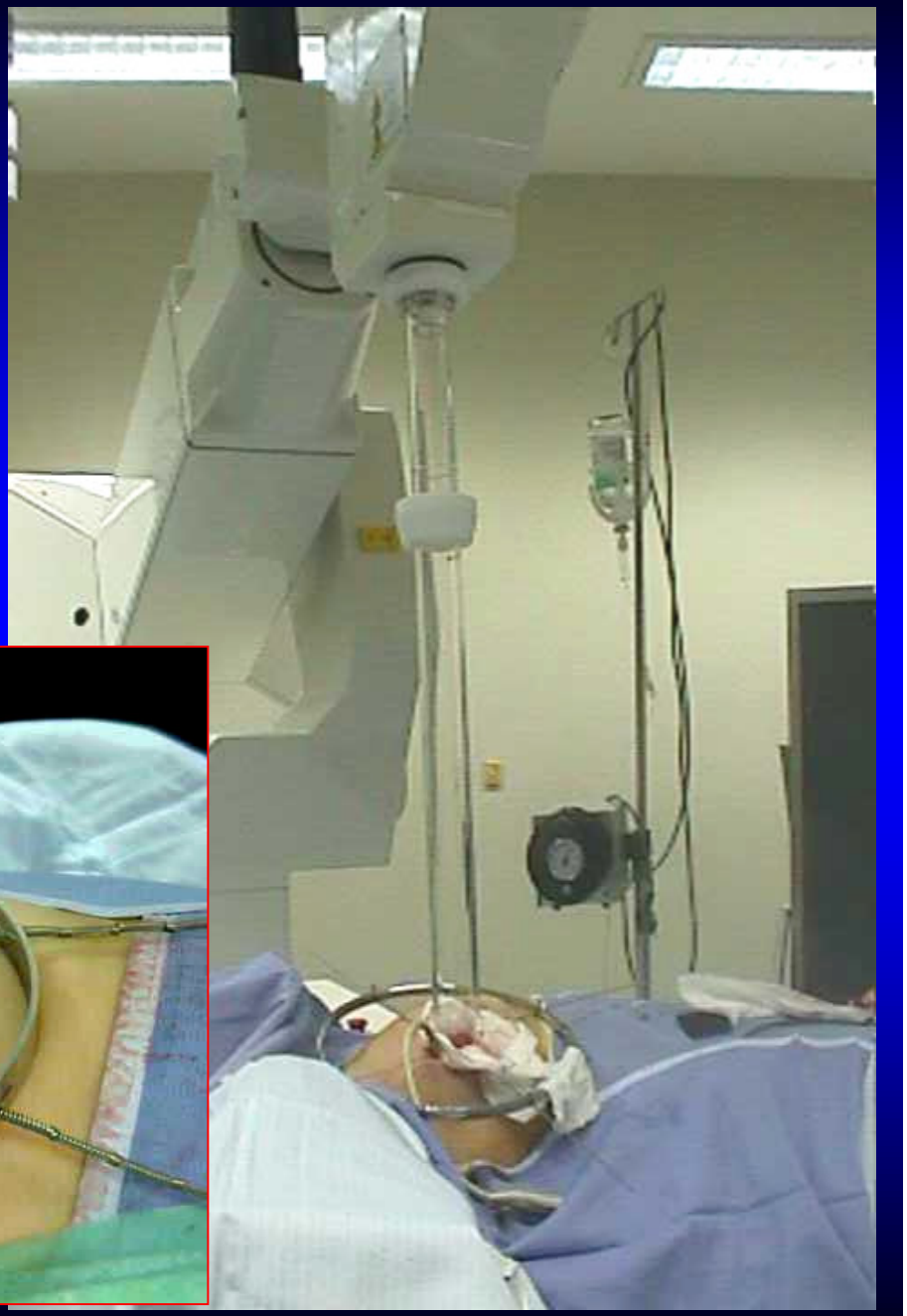
II Chest wall protection

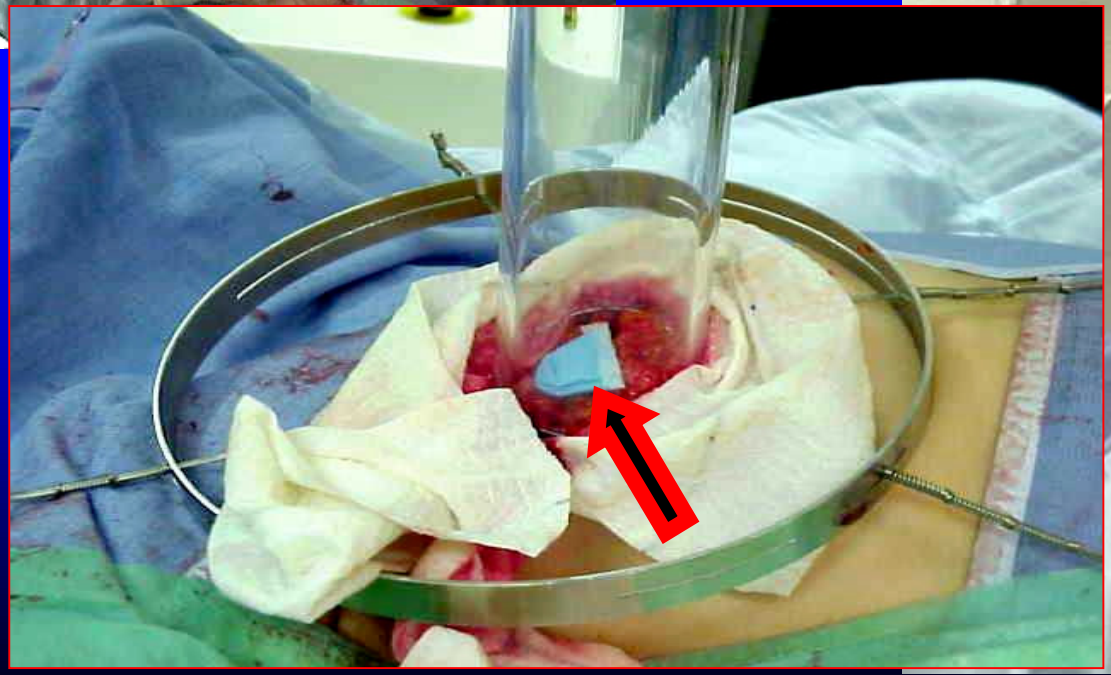


III Reconstruction

IV Skin protection

Set-up and delivery





Involved sub-process	Potential failure mode	Potential causes of failure	Potential effects of failure	O	S	D	RPN
Normal tissue protection	1) Wrong orientation of internal shield (for two-layered shields)	Human error in the placement of the shield	Wrong dose delivery and/or dose distribution	3	5	5	75
Normal tissue protection; applicator placement	2) Misalignment of internal shield	Shield displacement, wrong applicator placement	Unintended normal tissue irradiation	9	3	8	216
Selection of the applicator	3) Inadequate safety margins	Underestimation of CTV extension, inadequate selection of the applicator	CTV underdose	3	8	5	120
Evaluation of target thickness; selection of beam energy	4) Inadequate energy selection	Human error in the measurement of target thickness or consultation of dosimetry atlas, failure in the communication between operators	CTV underdose or viceversa unintended normal tissue irradiation	2	8	7	112
Applicator placement	5) Inadequate preparation of the area to be treated or inaccurate placement of the applicator base	Biologic fluid accumulation, tissue protrusion inside the applicator, air gap presence	Wrong dose delivery and/or dose distribution	3	6	5	90
Applicator placement	6) Geographic miss of the CTV	Inadequate localization of the CTV; applicator displacement due to physiological movements	CTV underdose; unintended normal tissue irradiation	3	3	7	63
Applicator docking to the linac	7) Inaccurate docking (for soft-docking systems)	Malfunctioning or tolerances of the alignment optical system	Wrong dose delivery and/or dose distribution	2	3	7	42
MU calculation	8) Wrong MU calculation	Human error in the calculation, failure in the communication between operators	Wrong dose delivery	2	9	8	144
Data entry at the treatment console	9) Incorrect data entry at the treatment console (beam energy, MU, field size)	Human error in manual data entry, failure in the communication between operators	Wrong dose delivery and/or dose distribution	2	9	8	144
Physical delivery of radiation dose	10) Undetected failure of the linac	Linac malfunctioning, linac operated in physics rather than clinical mode, linac start-up procedures not correctly followed	Wrong dose delivery and/or dose distribution	2	6	8	96

M. Ciocca, …

& R. Orecchia

Failure Mode and Effect Analysis (EMEA)

A semi-quantitative approach to prevent accidental exposures to the patients

IJROBP 2011,

June *25*

(Epub ahead of print)

Milan ELIOT out-trial on 1822 patients

	N	%	Annual rate (%)
First event			
True local recurrence	42	2.3	
Ipsilateral breast cancer	24	1.3	
Regional metastasis	18	1.0	0.33
Contralateral carcinoma	19	1.0	0.35
Distant metastasis	26	1.4	0.47
Other carcinoma	33	1.8	0.60
Death as first event	11	0.6	0.20
Any first event[a]	171	9.4	3.12
Deaths			
Deaths due to breast cancer	28	1.5	0.46
Deaths due to other causes	12	0.7	0.20
Unspecified cause of death	6	0.3	0.10
Any cause of death	46	2.5	0.76

3.6% at 3-y

Veronesi & Orecchia, Breast Cancer Res Treat, 2010

Milan ELIOT out-trial on 1822 patients

Table 5 True local recurrences and second ipsilateral cancer according to selected patient and tumour characteristics

	All patients	True local recurrences			Second ipsilateral cancer			Deaths		
	N	*N*	%	Annual rate (%)	*N*	%	Annual rate (%)	*N*	%	Annual rate (%)
Total	1822	42	2.31	0.77	24	1.32	0.44	46	2.52	0.76
Age										
<50	368	16	4.35	1.40	10	2.72	0.88			
51–59	665	13	1.95	0.62	9	1.35	0.43			
>60	789	13	1.65	0.58	5	0.63	0.22	23	2.92	0.94
Tumour size[a]										
<1 cm	611	7	1.15	0.38	3	0.49	0.16			
1.1–2 cm	938	23	2.45	0.81	13	1.39	0.46			
>2 cm	264	12	4.55	1.56	7	2.65	0.91	16	6.06	1.81
Positive nodes[a]										
0	1301	27	2.08	0.70	9	0.69	0.23			
1–2	371	8	2.16	0.69	8	2.16	0.69			
3+	146	7	4.79	1.57	6	4.11	1.35	15	10.27	2.97
Grading										
G1	467	2	0.43	0.14	2	0.43	0.14			
G2	853	14	1.64	0.54	12	1.41	0.46			
G3	459	26	5.66	1.91	7	1.53	0.52			
Peritumoral vascular invasion										
Absent	1528	30	1.96	0.65	15	0.98	0.33			
Present	294	12	4.08	1.37	9	3.06	1.03			
Molecular subtype[a]										
Luminal A	648	3	0.46	0.15	4	0.62	0.20			
Luminal B	977	28	2.87	0.96	16	1.64	0.55			
Cerb+++	53	6	11.32	3.88	0	–	–			
Basal	137	5	3.65	1.19	4	2.92	0.95	12	8.76	2.59

Age

T size

Nodes

Grading

PVI

Molecular Subtype

Veronesi & Orecchia, Breast Cancer Res Treat, 2010

Multivariate Analysis

Characteristics	Patients (n = 1822)					P value
Age						
<50	368	26	2.21 (1.25–3.90)	0.006	2.10 (1.18–3.74)	0.01
50–59	665	22	1.00		1.00	
>60	[illegible]	[illegible]	[illegible].49)	0.48	0.79 (0.42–1.49)	0.47
Histology						
Ductal carci[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	1.00	
Lobular carcinoma	[illegible]	[illegible]	[illegible].77)	0.39	1.89 (0.90–3.95)	0.09
[illegible]	194	7	0.86 (0.39–1.89)	0.70	0.98 (0.44–2.18)	0.96
Tumour size						
<1 cm					1.00	
1.1–2 cm				0.03	1.46 (0.73–2.92)	[illegible]
>2 cm				0.0001	2.29 (1.02–5.15)	0.04
[illegible]itive nod[illegible]						
0	1301	36	1.00		1.00	
1–2	371	16	1.44 (0.80–2.59)	0.23	1.02 (0.54–1.93)	0.95
3+	146	13	3.05 (1.62–5.76)	0.0006	1.32 (0.64–2.72)	0.45
Grading						
G1	467	4	1.00		Excluded from multivariate model due to colinearity with molecular subtype	
G2	853	26	3.55 (1.24–10.2)	0.02		
G3	459	33	8.71 (3.08–24.6)	<0.0001		
Peritumoral vascular invasion						
Absent	1528	45	1.00		1.00	
Present	294	21	2.45 (1.46–4.11)	0.0007	1.63 (0.90–2.96)	0.10
Ki-67						
<14%	664	7	1.00		Ki-67, ER receptor, PgR receptor and Her2/Neu overexpression are part of the molecular subtype	
≥14%	1152	58	4.81 (2.20–10.5)	<0.0001		
Estrogen receptor						
Negative	194	15	1.00			
Positive	1625	51	0.42 (0.23–0.74)	0.003		
Progesterone receptor						
Negative	398	24	1.00			
Positive	1420	42	0.59 (0.36–0.97)	0.04		
Her2/Neu						
Not overexpressed	1639	51	1.00			
[illegible]verexpressed	173	15	3.19 (1.79–5.67)	<0.0001		
Molecular subtype						
Luminal A	64				1.00	
Luminal B	97			[illegible]04	3.46 (1.52–7.90)	0.003
Cerb+++	53	6	10.6 (3.56–31.6)	<0.0001	5.68 (1.72–18.8)	0.004
Basal	137	9	5.95 (2.22–16.0)	0.0004	5.26 (1.84–15.0)	0.002

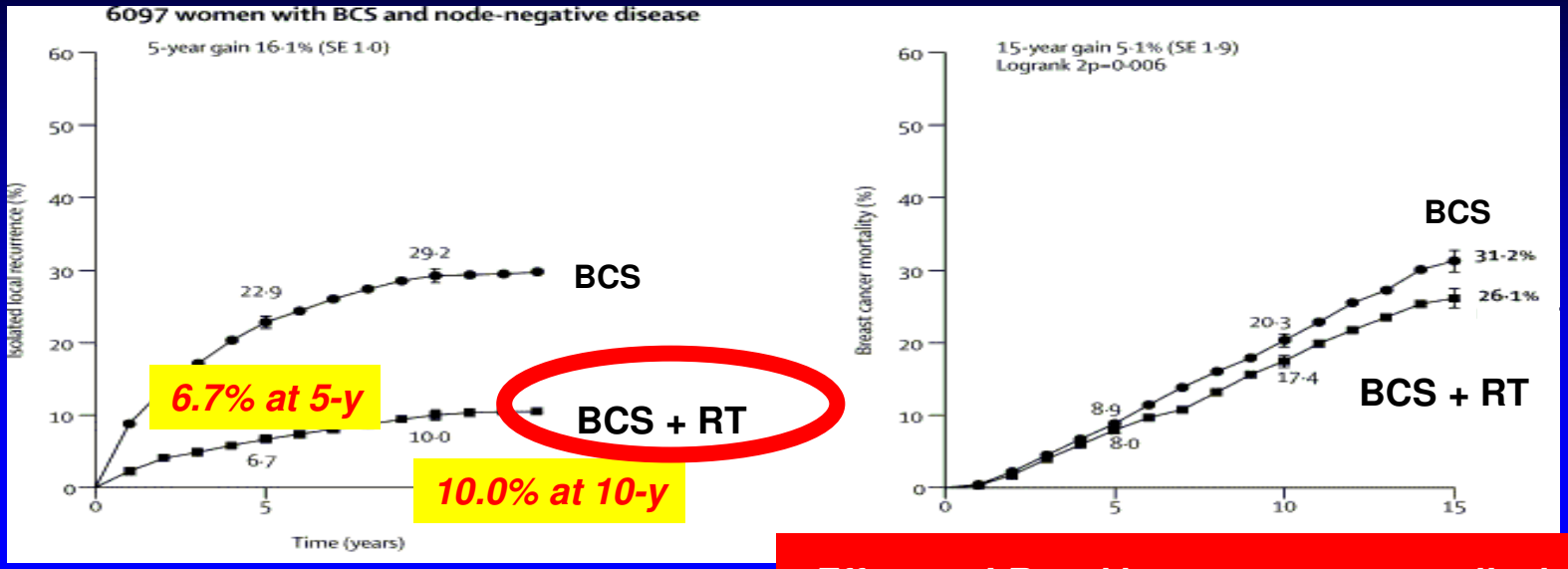
Age

T - size

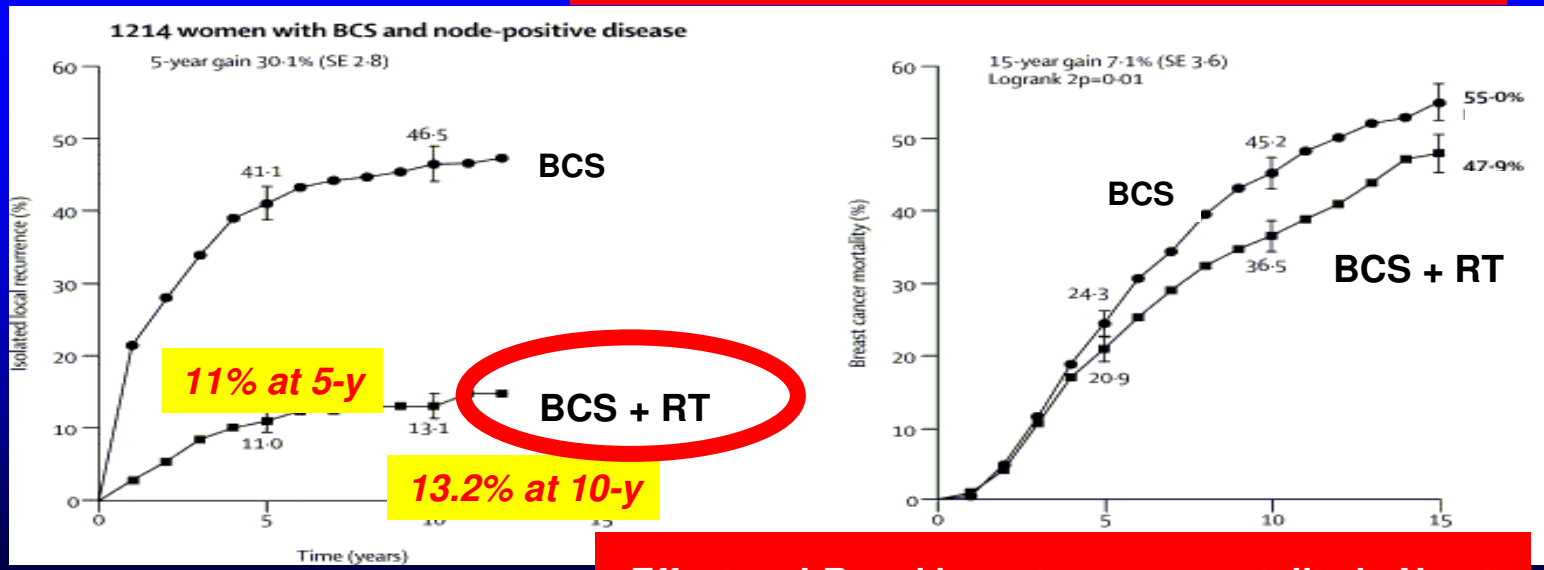
Molecular Subtype

Veronesi & Orecchia, Breast Cancer Res Treat, August 2010

Early Breast Cancer Trialists' Collaborative Group (EBCTCG)



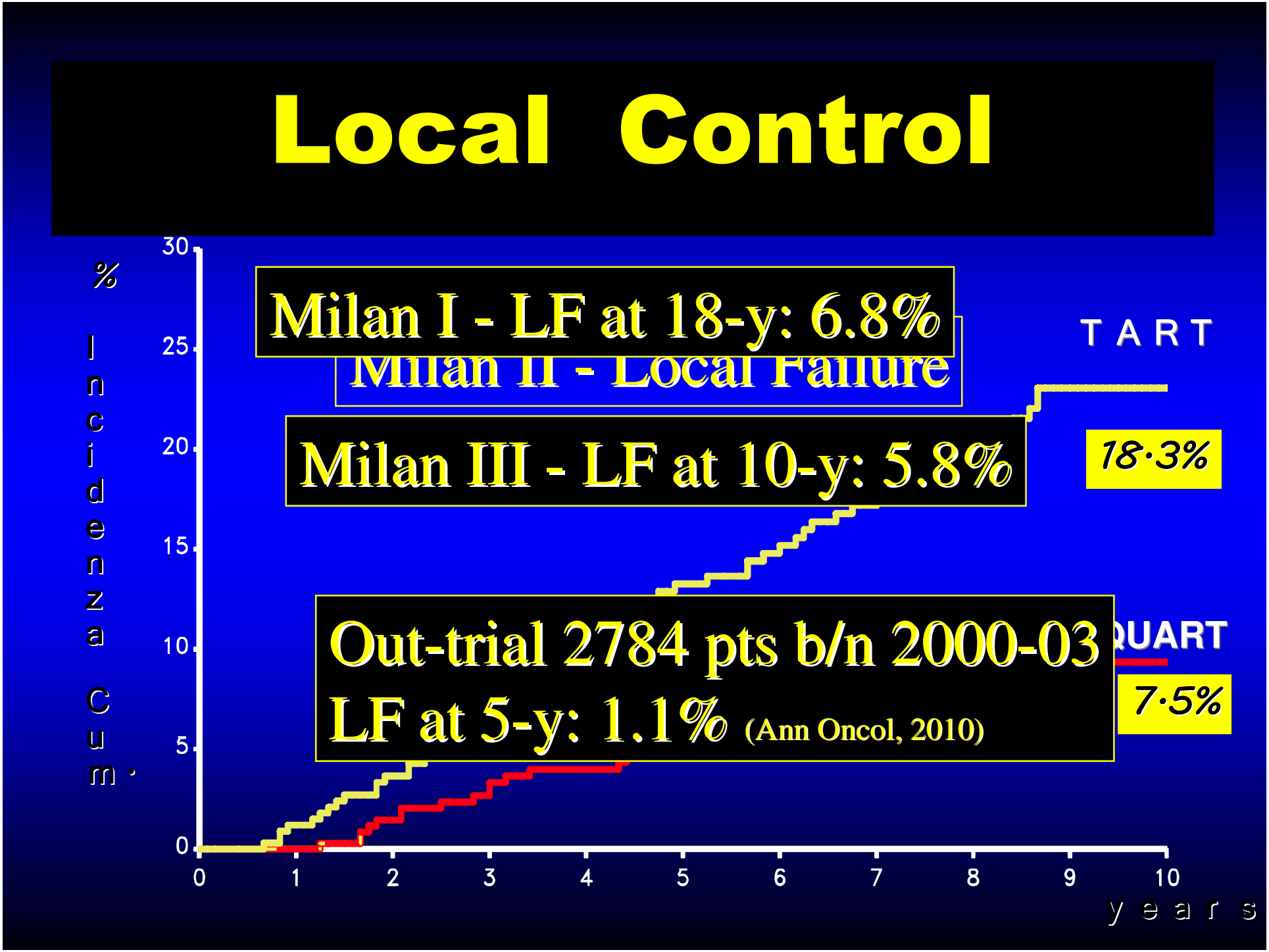
Effect on LR and breast cancer mortality in N- pts



Effect on LR and breast cancer mortality in N+ pts

Lancet 2005;366:2087-2106

Local Control



Patient selection

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0360-3016/09/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2009.02.031

CONSENSUS STATEMENT

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

Benjamin D. S… …z, M.D.,[†]
Bruce G. Ha… …M.D.,[¶]
Thomas B. … …h.D.,[‡]
Frank A. Vicini, M.… …Y. Wo, M.D.,[‖]

Low risk group to be treated ouside clinical trial !!!

ELSEVIER

Radiotherapy & Oncology

Review

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

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

ASTRO Consensus Statement

Factors	"Suitable" group	"Cautionary" group	"Unsuitable" group
Patient factors			
Age, y	≥60	50 to 59	<50
BRCA1/2 mutation	Not present	NA	Present
Pathologic factors			
Tumor size, cm	≤2†	2.1–3.0†	>3†
T stage	T1	T0 or T2	T3 or T4
Margins	Negative by at least 2 mm	Close (<2 mm)	Positive
Grade	Any	NA	NA
LVSI	No‡	Limited/focal	Extensive
ER status	Positive	Negative§	NA
Multicentricity	Unicentric only	NA	If present
Multifocality	Clinically unifocal with total size ≤2 cm‖	Clinically unifocal with total size 2.1 to 3.0 cm‖	If microscopically multifocal >3 cm in total size or if clinically multifocal
Histology	Invasive ductal or other favorable subtypes**	Invasive lobular	NA
Pure DCIS	Not allowed	≤3 cm in size	If >3 cm in size
EIC	Not allowed	≤3 cm in size	If >3 cm in size
Associated LCIS	Allowed	NA	NA
Nodal factors			
N stage	pN0 (i^-, i^+)	NA	pN1, pN2, pN3
Nodal surgery	SN Bx or ALND††	NA	None performed
Treatment factors			
Neoadjuvant therapy	Not allowed	NA	If used

GEC-ESTRO Recommendations

Characteristic	A/ Low-risk group - Good candidates for APBI	B/ Intermediate-risk group - Possible candidates for APBI	C/ High-risk group – Contraindication for APBI
Patient age	>50 years	>40-50 years	=40 years
Histology	IDC, mucinous, tubular, medullary, and colloid cc.	IDC, ILC, mucinous, tubular, medullary, and colloid cc.	-
ILC	Not allowed	Allowed	-
Associated LCIS	Allowed	Allowed	-
DCIS	Not allowed	Allowed	-
HG	Any	Any	-
Tumour size	pT1-2 (=30 mm)	pT1-2 (=30 mm)	pT2 (>30 mm), pT3, pT4
Surgical margins	Negative (=2 mm)	Negative, but close (<2 mm)	Positive
Multicentricity	Unicentric	Unicentric	Multicentric
Multifocality	Unifocal	Multifocal (limited within 2 cm of the index lesion)	Multifocal (>2 cm from the) index lesion)
EIC	Not allowed	Not allowed	Present
LVI	Not allowed	Not allowed	Present
ER, PR status	Any	Any	-
Nodal status	pN0 (by SLNB or ALND*)	pN1mi, pN1a (by ALND*)	pNx; =pN2a
Neoadj. chemoth.	Not allowed	Not allowed	If used

Major differences between:

	ASTRO	GEC/ESTRO
Age:	60 years	50 years
Stage:	T1 (2 cm)	T1-T2 (3 cm)
ER status:	Positive	Any

	Variable DB ELIOT-OUT	ASTRO GUIDELINES			GEC-ESTRO GUIDELINES		
		SUITABLE	CAUTIONARY	UNSUITABLE	GOOD CANDIDATES	POSSIBLE CANDIDATES	CONTRA-INDICATION
Patient factors							
Age	AGE	≥60 y	50-59	<50	>50 y	>40-50	≤40
BRCA1/2 mutation	-	Absent	Absent	Present	-	-	-
Pathologic factors							
Tumor size							>3cm
pT							pT2(>3cm) pT3-pT4
Margins							Positive
Grade							Any
LVI							Present
ER status							-
Multicentricity multifocality							Present Multifocal>2cm
Histology							Any
Pure DCIS							-
EIC (is)							Present
Nodal factors							
N stage							pNx; ≥pN2a (≥4 positive nodes)
Nodal surgery							Not performed
Treatment factors							
Neoadj. CT	NEOADJ	Not allowed	Not allowed	Yes	Not allowed	Not allowed	Yes

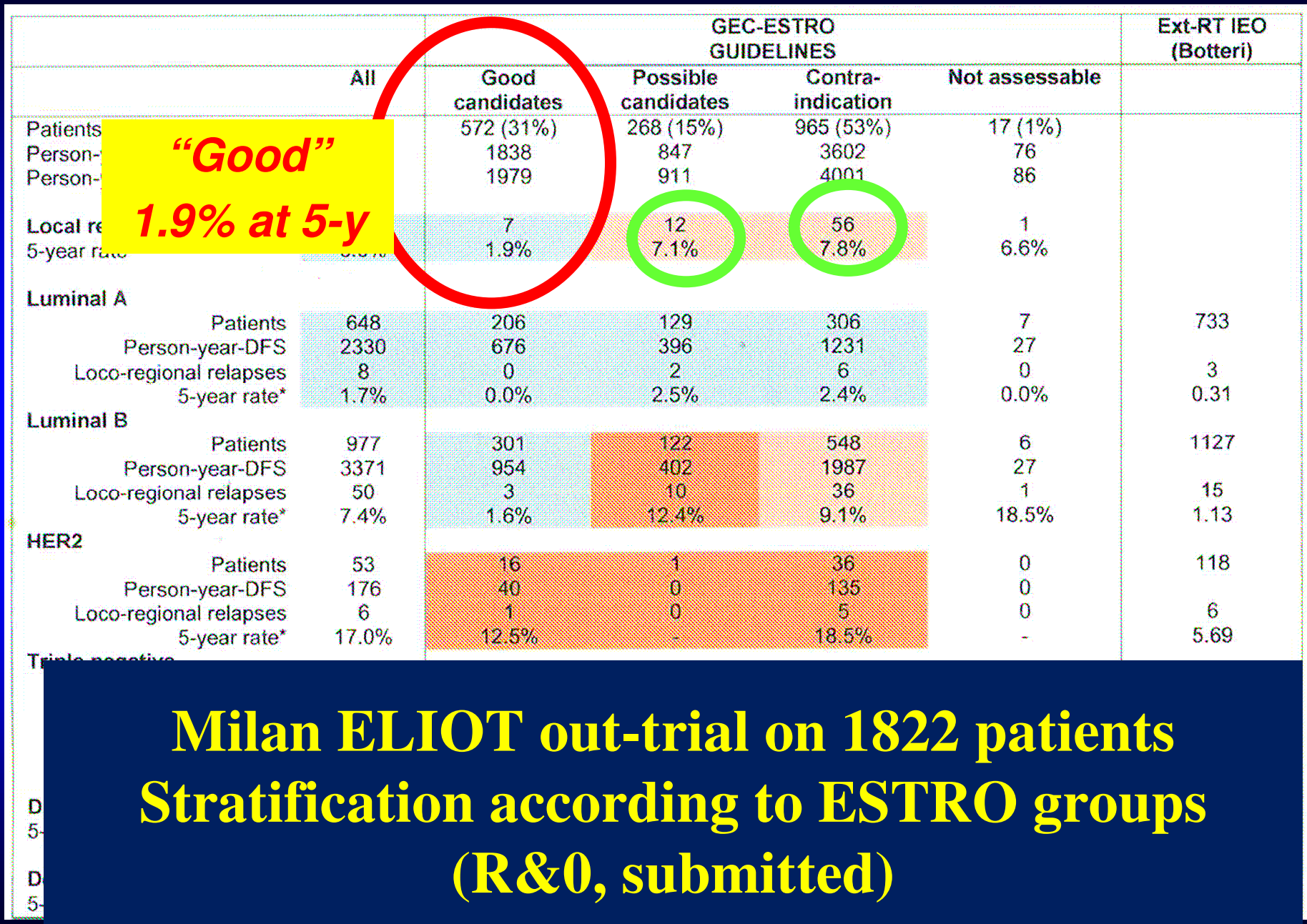
Update at 5-years

Local Failure Rate : 6%

	All	ASTRO GUIDELINES				Ext-RT IEO (Botteri)
		Suitable	Cautionary	Unsuitable	Not assessable	
Patients	1822	295 (16%)	690 (38%)	812 (45%)	25 (1%)	
Person-year-DFS	6364	1016	2409	2837	101	
Person-year-OS	6977	1091	2613	3157	116	
Local relap		3	21	50	2	
5-year rate*		1.5%	4.4%	8.8%	9.9%	
Luminal A						
Patients		118	271	251	8	733
Person-year-DFS	2330	436	948	916	30	
Loco-regional relapses	8	2	3	3	0	3
5-year rate*	1.7%	2.3%	1.6%	1.6%	-	0.31
Luminal B						
Patients	977	176	318	474	9	1127
Person-year-DFS	3371	576	1101	1650	44	
Loco-regional relapses	50	1	10	38	1	15
5-year rate*	7.4	0.9%	4.5%	11.5%	11.4	1.13
HER2						
Patients	53	-	25	28	0	118
Person-year-DFS	176	-	82	94	-	
Loco-regional relapses	6	-	3	3	-	6
5-year rate*	17.0	-	18.3%	16.0%		5.69
Triple negative						
Patients	137	-	74	58	5	208
Person-year-DFS	469	-	276	175	17	
Loco-regional relapses	12	-	5	6	1	7
Distar						
5-year						
Death						
5-year						

"Suitable"
1.5% at 5-y

Milan ELIOT out-trial on 1822 patients
Stratification according to ASTRO groups
(IJROBP, in press)



	All	GEC-ESTRO GUIDELINES: Good candidates	Possible candidates	Contra-indication	Not assessable	Ext-RT IEO (Botteri)
Patients		572 (31%)	268 (15%)	965 (53%)	17 (1%)	
Person-		1838	847	3602	76	
Person-		1979	911	4001	86	
Local re		7	12	56	1	
5-year rate		1.9%	7.1%	7.8%	6.6%	
Luminal A						
Patients	648	206	129	306	7	733
Person-year-DFS	2330	676	396	1231	27	
Loco-regional relapses	8	0	2	6	0	3
5-year rate*	1.7%	0.0%	2.5%	2.4%	0.0%	0.31
Luminal B						
Patients	977	301	122	548	6	1127
Person-year-DFS	3371	954	402	1987	27	
Loco-regional relapses	50	3	10	36	1	15
5-year rate*	7.4%	1.6%	12.4%	9.1%	18.5%	1.13
HER2						
Patients	53	16	1	36	0	118
Person-year-DFS	176	40	0	135	0	
Loco-regional relapses	6	1	0	5	0	6
5-year rate*	17.0%	12.5%	-	18.5%	-	5.69
Triple negative						

Milan ELIOT out-trial on 1822 patients
Stratification according to ESTRO groups
(R&0, submitted)

IEO TRIAL

November 2000 – December 2007

1,305 patients

Equivalence Expected Rates

EBRT arm: 3 - 3.5%

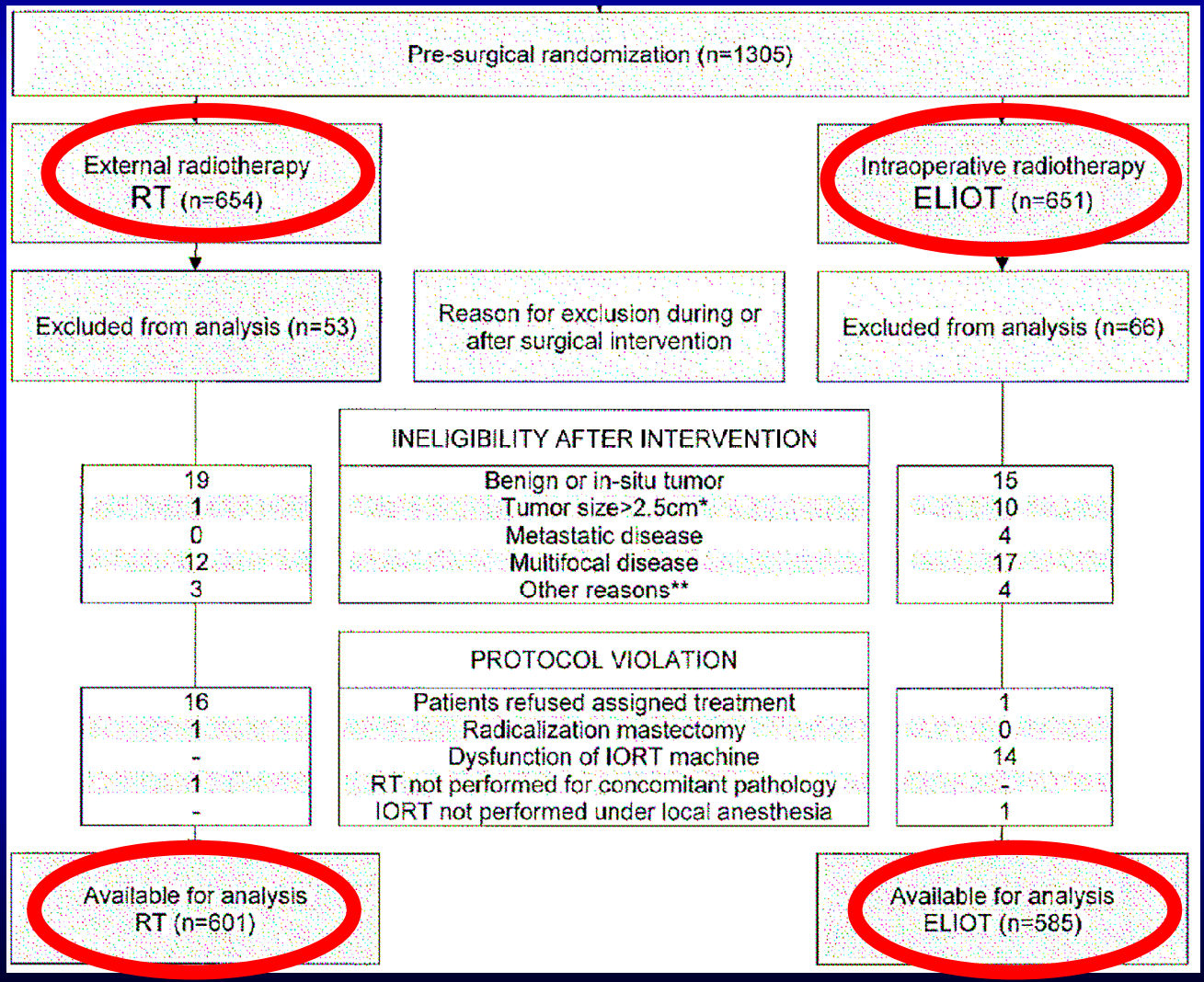
ELIOT arm: 7 - 7.5%

Su
R

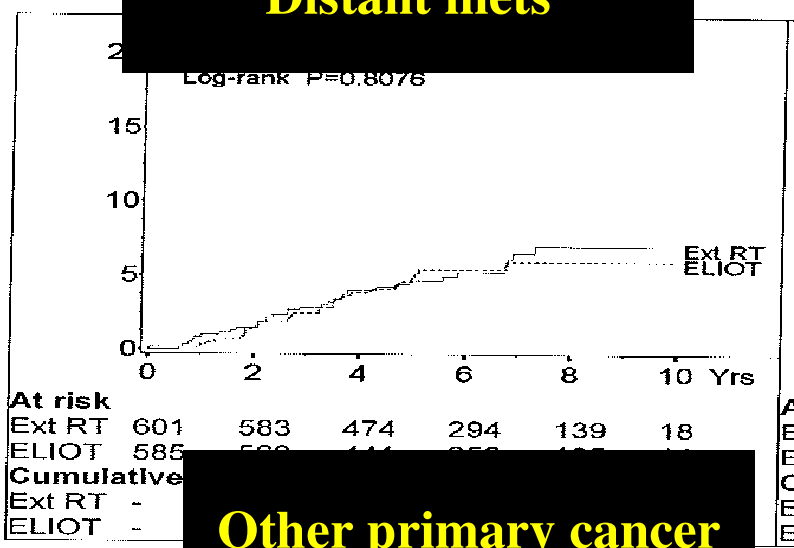
Gy)

ELIOT Randomized Trial

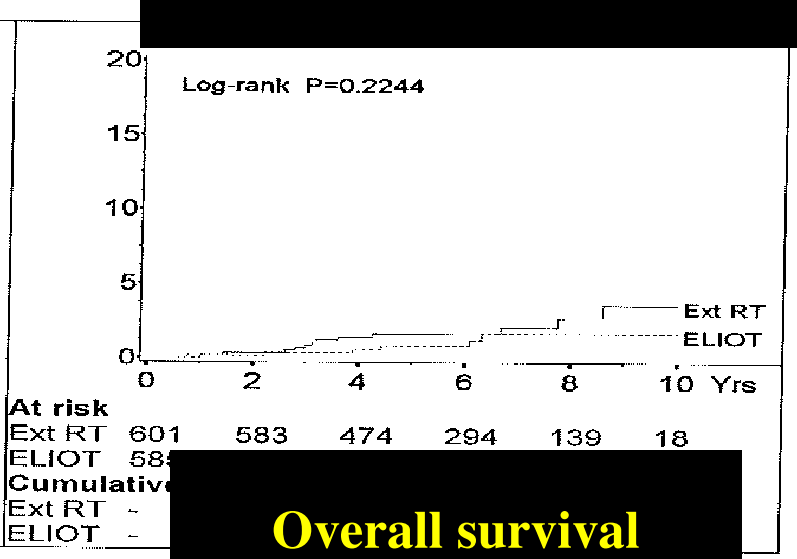
Study Flowchart



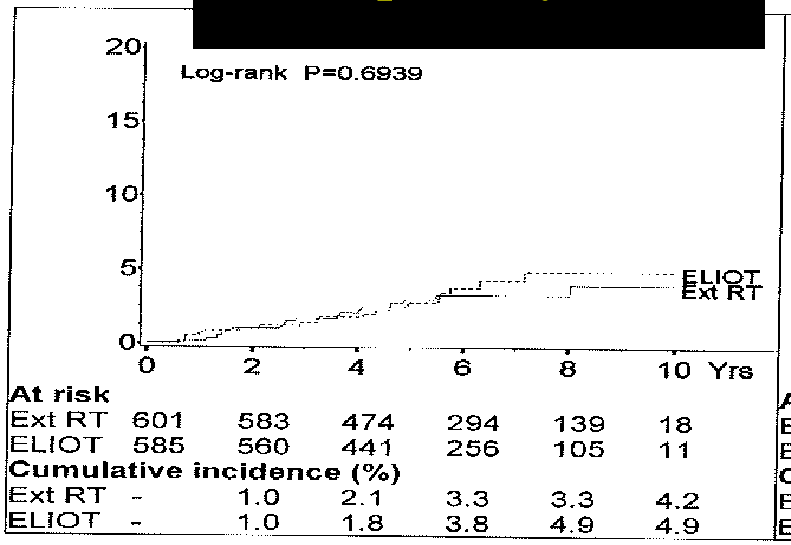
Distant mets



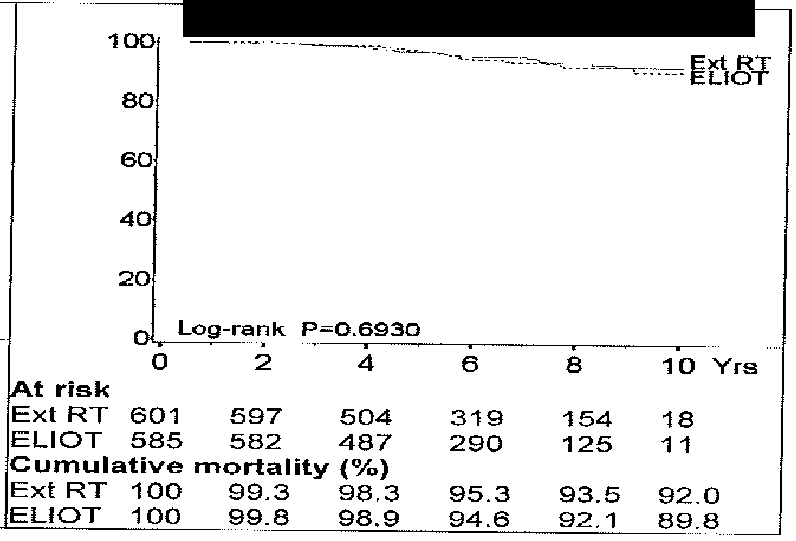
Contralateral breast cancer



Other primary cancer



Overall survival



ELIOT Randomized Trial

ELIOT R/ Toxicities .....

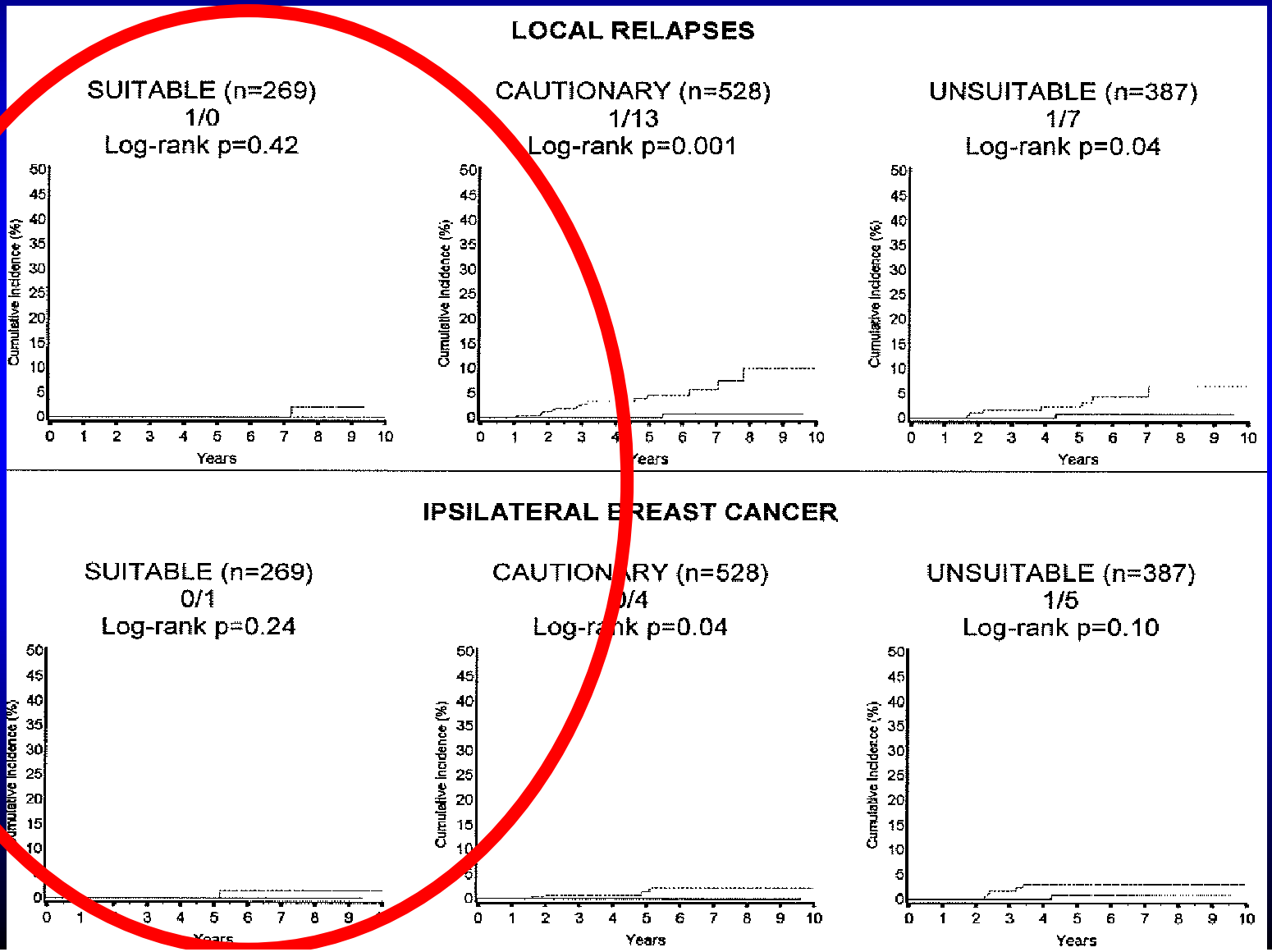
- Pulmonary fibrosis was diagnosed in 42 patients (23.6%): 38 (90%) were in the EBRT arm and 4 (10%) in the ELIOT arm (p?<?0.0001); twenty-six of them were Grade 1 (one ELIOT), fifteen were Grade 2 (three ELIOT) and one was Grade 3. The post-radiotherapy risk in the EBRT arm to develop at least Grade 1 fibrosis was 19 times higher than in the ELIOT one (OR: 19.20; 95%CI: 6.46-57.14) and 6 times higher to develop at least Grade 2 (OR: 5.70; 95%CI: 1.56-20.76).

- Rampinelli C et al, Assessment of Pulmonary Fibrosis after Radiotherapy (RT) in Breast Conserving Surgery: Comparison between Conventional External Beam RT (EBRT) and Intraoperative RT with Electrons (ELIOT), Technol Cancer Res Treat, 2011

ELIOT Random/ASTRO Groups

	Eliot patients	Local Relapse N(rate/100-year)
Suitable	129	5 (0.66)
Cautionary	270	19 (1.26)
Unsuitable	184	13 (1.20)

ELIOT Random/ASTRO Groups



(I)

- **Attention has to be kept on the effect of LR rate on long-term mortality rate (ratio 4:1). Proper selection of patients is the current issue**

- **All the studies have short follow-up, and this period doesn't cover the increased risk for recurrences (o second tumours) in the same breast (it begins at 5 years and more…..)**

(II)

- **ASTRO & GEC-ESTRO have indicated subgroups of patients to be submitted to PBI (and IORT), also outside of clinical trials**
- **ELIOT out trial data suggest that the criteria proposed by ASTRO/GEC-ESTRO guidelines are appropriate to select "suitable patients" for current clinical practice**

(III)

PBI (and IORT) alone could be proposed as standard treatment, in alternative to WBI, in patients with "good characteristics" of age, tumour size, and important, proper biological profile

Preliminary results coming from ELIOT randomized trial seem to confirm, even with some slight difference

Milan, 22-24 June 2012


Thank you very
much for your
attention !!!