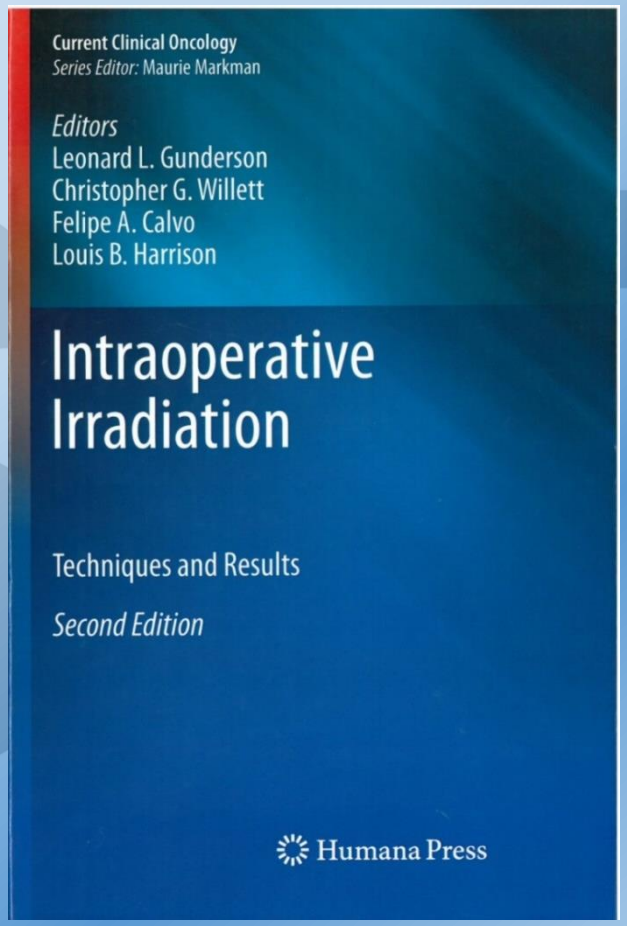
L I A C H W L

mobile IOeRT accelerator

What's IOeRT?

- Intraoperative electron irradiation (IOERT) in its broadest sense refers to the delivery of irradiation at the time of an operation.

- IOERT evolved as an attempt to achieve higher effective doses of irradiation while dose-limiting structures are surgically displaced.



Intraoperative Irradiation: Techniques and Results L. Gunderson, C. Willet, L. Harrison, F. A. Calvo, Humana Press 2007 – ISBN: 0 - 89603 – 523 - 9

IOeRT – Clinical Indications

- Breast cancer
- Primary and recurrent colorectal
- Pancreatic carcinoma
- Liver metastasis
- Sarcomas (retroperitoneal; soft tissue; bone)
- Locally advanced and recurrent gynecologic malignancies
- Bladder cancer
- Prostate cancer
- Lung cancer

Intraoperative Irradiation: Techniques and Results L. Gunderson, C. Willet, L. Harrison, F. A. Calvo, Humana Press 2007 – ISBN: 0 - 89603 – 523 - 9

Last ISIORT Pooled Analysis

IORT for breast cancer

ISIORT pooled analysis 2013 update: clinical and technical characteristics of intraoperative radiotherapy

Marco Krengli[1], Felix Sedlmayer[2], Felipe A. Calvo[3], Elena Sperk[4], Carla Pisani[1], Claudio V. Sole[3], Gerd Fastner[2], Carmen Gonzalez[3], Frederik Wenz[4]

[1]Department of Radiotherapy, University Hospital Maggiore della Carità, Novara, Italy; [2]Department of Radiotherapy and Radio-Oncology, University Hospital of the Paracelsus Medical University (PMU), Salzburg, Austria; [3]Department of Oncology, University Hospital Gregorio Maranon, Madrid, Spain; [4]Department of Radiation Oncology, University Medical Center, Mannheim, Germany

Corresponding to: Marco Krengli, MD, Professor of Radiotherapy, University of Piemonte Orientale; Chief, Department of Radiotherapy. University Hospital Maggiore della Carità, Corso Mazzini 18, 28100 Novara (NO), Italy. Email: krengli@med.unipmn.it.

Table 1 Tumor sites/histologies treated with intraoperative radiation therapy (IORT)

Tumor site	Number of IORT procedures	%
Breast	5,659	78.70
Rectum	643	8.90
Soft tissue sarcoma	262	3.60
Prostate	128	1.80
Pancreas	87	1.20
Stomach	65	0.90
Esophagus	53	0.70
Uterine cervix	46	0.60
Brain	34	0.40
Head and neck	28	0.40
Ovary	16	0.20
Biliary tract	12	0.20
Colon	10	0.10
Lung	10	0.10
Kidney	8	0.10
Bladder	8	0.10
Sacrum	6	0.01
Adrenal glands	5	0.01
Other or undefined sites	116	1.60

ISIORT database has reached **10.675** patients (instead of 7.196 patients reported in the ISIORT pooled analysis 2013 update) during the last ISIORT congress on June 24-25th 2016.

Treatments were applied with:

- **IORT high energy electrons for 6.863 cases (95.4%).**
- **IORT low energy X rays for 333 cases (4.6%).**

ISIORT pooled analysis 2013 update: clinical and technical characteristics of intraoperative radiotherapy, Krengli M., Sedlmayer F., Calvo F. A., Sperk E., Pisani C., Sole C. V., Fastner G., Gonzalez C., Wenz F., Translational Cancer Research, Vol. 3, pp. 48-58, 2014.

IOeRT as SINGLE DOSE & IOeRT as BOOST

IntraOperative electron Radiation Therapy (IOeRT), which uses high energy electrons, is the most powerful and effective available IORT technique.
IOeRT can be performed either as a single treatment (**SINGLE DOSE**), which replaces the entire external radiotherapy cycle, or as a **BOOST**, followed by a reduced external radiotherapy cycle.

THE IOeRT IRRADIATION TIME WITH ELECTRONS TAKES LESS THAN 2 MINUTES.

IOeRT for BREAST Application

There are two well established protocols for breast cancer treatment:

- IOeRT as SINGLE DOSE: the **ELIOT Protocol** (21 Gy prescribed at the 90% isodose **[1]**).
- IOeRT as BOOST: the **HIOB Protocol** (10 Gy at the 90% isodose IOeRT boost followed by hypofractionated external radiotherapy (40,5 Gy in 2,7 Gy) **[2]**).

1. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial, Veronesi U., Orecchia R. et al., Lancet Oncology, 2013.
2. http://www.clinicaltrials.gov/ct2/show/NCT01343459?term=hiob&rank=1

BREAST CARCINOMA IOERT: Patients selection criteria

In 2009 and 2010 ASTRO and ESTRO, respectively, published their recommendations on Accelerated Partial Breast Irradiation (APBI). The breast carcinoma IORT treatment represents an implementation of APBI.

According to ASTRO and ESTRO guidelines, the patients are divided in 3 risk groups according to age, tumor size, lymphnodes status etc.; such risk groups have been defined as: **LOW RISK, MEDIUM RISK, HIGH RISK.**

All low risk group patients can be treated with a single dose (**ELIOT protocol**) and all the others can be treated with boost (**HIOB protocol**).

LIAC has been used to implement **ELIOT study**.

ESTRO RECOMMENDATIONS FOR APBI PATIENT SELECTION

The GEC-ESTRO Breast Cancer Working Group recommends three categories guiding patient selection for APBI:

1. **Good candidates** (a low –risk group) for whom APBI outside the context of a clinical trial is an acceptable treatment option;
2. Possible candidates (an intermediate-risk group), for whom APBI is considered acceptable only in the context of prospective clinical Trials;
3. Contraindication (a high-risk group), for whom APBI is considered contraindicated.

Characteristic	A/low-risk group – good candidates for APBI
Patient age	>50 years
Histology	IDC, mucinous, tubular, medullary, and colloid cc.
ILC	Not allowed
Associated LCIS	Allowed
DCIS	Not allowed
HG	Any
Tumour size	pT1–2 (≤30 mm)
Surgical margins	Negative (≥ 2 mm)
Multicentricity	Unicentric
Multifocality	Unifocal
EIC	Not allowed
LVI	Not allowed
ER, PR status	Any
Nodal status	pN0 (by SLNB or ALND*)
Neoadjuvant chemotherapy	Not allowed

Table: ESTRO statement on good candidates for APBI .

Patient selection for accelerated partial-breast irradiation (APBI) after 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), Polgár C., et al., Radiotherapy and Oncology 94, pp. 264–273, 2010.

ASTRO RECOMMENDATIONS FOR APBI PATIENT SELECTION

The Task Force proposed three patient groups:

1. **“suitable” group**, for whom APBI outside of a clinical trial is acceptable;
2. “cautionary” group, for whom caution and concern should be applied when considering APBI outside of a clinical trial;
3. “unsuitable” group, for whom APBI outside of a clinical trial is not generally considered warranted.

Table 2. Patients “suitable” for APBI if all criteria are present

Factor	Criterion
Patient factors	
Age	≥60 y
BRCA1/2 mutation	Not present
Pathologic factors	
Tumor size	≤2 cm*
T stage	T1
Margins	Negative by at least 2 mm
Grade	Any
LVSI	No†
ER status	Positive
Multicentricity	Unicentric only
Multifocality	Clinically unifocal with total size ≤2.0 cm‡
Histology	Invasive ductal or other favorable subtypes§
Pure DCIS	Not allowed
EIC	Not allowed
Associated LCIS	Allowed
Nodal factors	
N stage	pN0 (i^-, i^+)
Nodal surgery	SN Bx or ALND‖
Treatment factors	
Neoadjuvant therapy	Not allowed

Table 2: ASTRO statement.

Accelerated Partial Breast Irradiation Consensus Statement From The American Society For Radiation Oncology (ASTRO), Smith D. B, Arthur D.W., Buchholz T. A., et al., Int. J. Radiation Oncology Biol. Phys., Vol. 74, No. 4, pp. 987–1001, 2009.

UPDATED ASTRO RECOMMENDATIONS FOR APBI PATIENT SELECTION: BROADER SELECTION CRITERIA

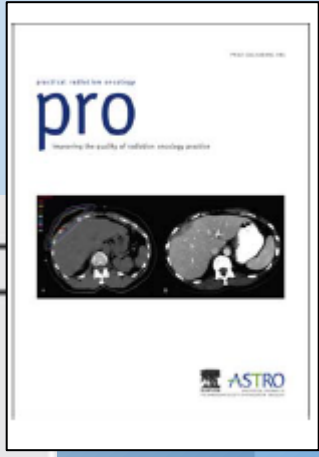


Table 1 Comparison of patient groups in original and updated consensus statements

Patient group	Risk factor	Original	Update
Suitability	Age	≥60 y	≥50 y
	Margins	Negative by at least 2 mm	No change
	T stage	T1	Tis or T1
	DCIS	Not allowed	If all of the below: • Screen-detected • Low to intermediate nuclear grade • Size ≤2.5 cm • Resected with margins negative at ≥3 mm
Cautionary	Age	50-59 y	• 40-49 y if all other criteria for "suitable" are met • ≥50 y if patient has at least 1 of the pathologic factors below and does not have any "unsuitable" factors *Pathologic factors:* • Size 2.1-3.0 cm [a] • T2 • Close margins (<2 mm) • Limited/focal LVSI • ER(-) • Clinically unifocal with total size 2.1-3.0 cm [b] • Invasive lobular histology • Pure DCIS ≤3 cm if criteria for "suitable" not fully met • EIC ≤3 cm
	Margins	Close (<2 mm)	No change
	DCIS	≤3 cm	≤3 cm and does not meet criteria for "suitable"
Unsuitable	Age	<50 years	• <40 y • 40-49 y and do not meet the criteria for cautionary
	Margins	Positive	No change
	DCIS	>3 cm	No change

[a] The size of the invasive tumor component.

[b] Microscopic multifocality allowed, provided the lesion is clinically unifocal (a single discrete lesion by physical examination and ultrasonography/mammography) and the total lesion size (including foci of multifocality and intervening normal breast parenchyma) falls between 2.1 and 3.0 cm.

Table 1: Comparison of patient groups in original and updated statements

Accelerated Partial Breast Irradiation: Executive Summary for the Update of an ASTRO Evidence-Based Consensus Statement, Correa C., Harris E.E., Leonardi M.C. et al., Practical Radiation Oncology, 2016, doi: 10.1016/j.prro.2016.09.007.

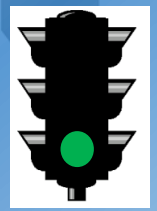
Breast: IOeRT Clinical Results

ASTRO GUIDELINES UPDATE

In September 2016, ASTRO published the Update of the Accelerated Partial breast Irradiation (APBI) Consensus Statement in order to provide a guidance on use of IORT for Partial Breast Irradiation (PBI) in early stage breast cancer [2].

On the basis of the published evidence and the mature results obtained thanks to the **5.8 years follow-up** of the **ELIOT trial**, it has been recognized the efficacy of performing the IORT with electrons compared to the **29 months follow up** of the **TARGIT- A trial** (the reference study of IORT with low energy x-rays).

The ASTRO society stated the following recommendations:



- **IORT with electrons (IOeRT) can be used in the clinical practice outside of a clinical trial for the suitable group of patient;**

- **IORT with low energy x-rays can never be used outside of a clinical trial.**

2. Accelerated Partial Breast Irradiation: Executive Summary for the Update of an ASTRO Evidence-Based Consensus Statement, Correa C., Harris E.E., Leonardi M.C. et al., Practical Radiation Oncology, 2016, doi: 10.1016/j.prro.2016.09.007.

BREAST CANCER IOeRT RATIONALE

ELSEVIER

Seminars in
RADIATION
ONCOLOGY

Is Partial Breast Irradiation A Step Forward or Backward?

Thomas A. Buchholz, MD,* Henry M. Kuerer, MD, PhD,† and Eric A. Strom, MD*

Approximately 80% of the breast tumor recurrences origins at the site of the original disease. These data suggest that the majority of breast tumor recurrences result from residual foci of disease from the original index tumor that approximate the site of the original surgery.

Thus is clear that giving radiation only to a volume of 1-cm radius around the tumor site would also be an ineffective strategy.

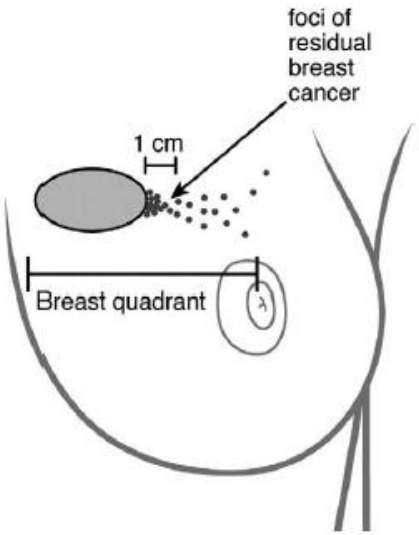
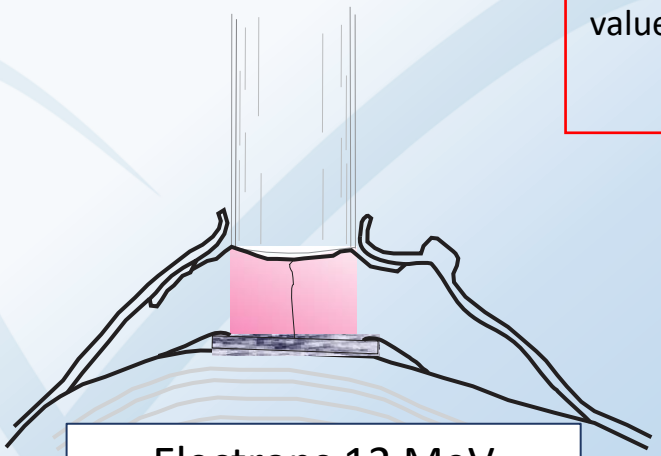


Figure 1 Illustration of a medial tumor bed with residual disease extending from the tumor bed into upper lateral quadrant. If no radiation was given in this situation, it is likely that the tumor would recur first at the tumor bed site. However, it is clear that giving radiation only to a volume of 1-cm radius around the tumor site would also be an ineffective strategy.

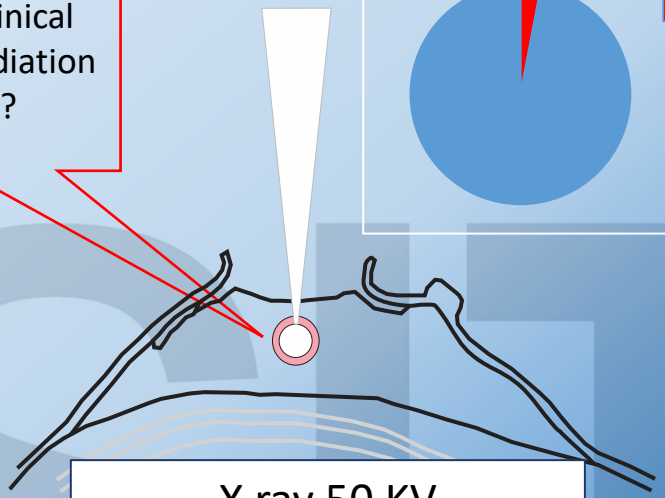
Is Partial Breast Irradiation A Step Forward or Backword?, Buchholz T. A., Kuerer H., Strom E. A., Semin. Radiat. Oncol., pp. 69-75, 2005.

Electrons vs. low energy X rays: a comparison

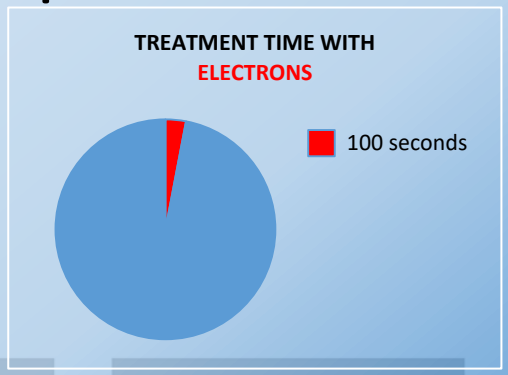


Electrons 12 MeV
applicator ∅ 60 mm

What is the clinical value of this radiation treatment?



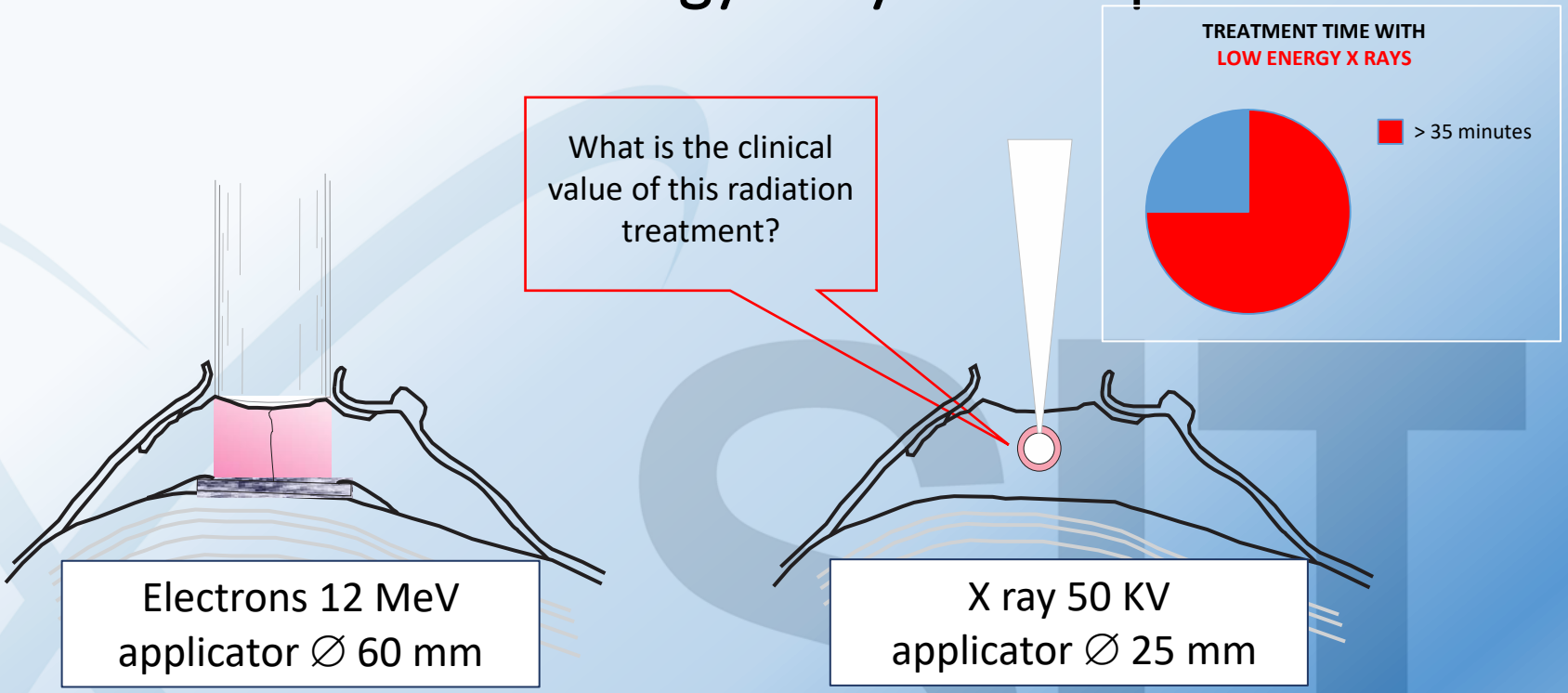
X ray 50 KV
applicator ∅ 25 mm



Consider a patient, who has a 2 cm tumor removed along with a small margin and her incision is sutured in such a way the target to be irradiated is 3 cm thick.
For **LIAC HWL** the recommended settings would be 60 mm diameter applicator, 12 MeV energy and 21 Gy prescribed at 3 cm. The effective irradiated volume inside 90% isodose is a cylinder with a diameter about 50 mm and a depth of 32 mm, for a total volume of about 63 cm^3.

The treatment time with electrons takes 100 seconds.

Electrons vs. low energy X rays: a comparison



Consider a patient, who has a 2 cm tumor removed along with a small margin and her incision is sutured in such a way the target to be irradiated is 3 cm thick.
Intrabeam using a 25 mm applicator and 20 Gy at the surface of the applicator.
The volume treated within the 90% isodose is less about 2,1 cm^3.
The volume treated within the 50% isodose is less than 7,1 cm^3.

The low energy X rays treatment takes between 35 and 50 minutes.

EIO TECHNIQUE: ELIOT PROTOCOL

ELSEVIER

Seminars in RADIATION ONCOLOGY

Intraoperative Electrons

Roberto Orecchia, MD* and Umberto Veronesi, MD†

Intraoperative radiotherapy (IORT) has been used for many years for treating patients with various locally-advanced malignancies, usually combined with external-beam radiation therapy (EBRT). Long-term results confirm that IORT improves local control, which is generally associated with increased survival. Recently, electron-beam IORT has been used as the sole treatment for patients with earlier-stage cancers, especially for breast tumors, with extremely promising results. Most of this work has been done at the European Institute of Oncology in Milan. We report the rationale and techniques of the use of electron intraoperative treatment (ELIOT) and the results of our different clinical studies. In our opinion, ELIOT may be an excellent alternative to EBRT for the treatment of patients with early-stage breast cancer. However, intensive long-term follow-up is needed to fully evaluate local control and possible side effects.

Semin Radiat Oncol 15:76-83

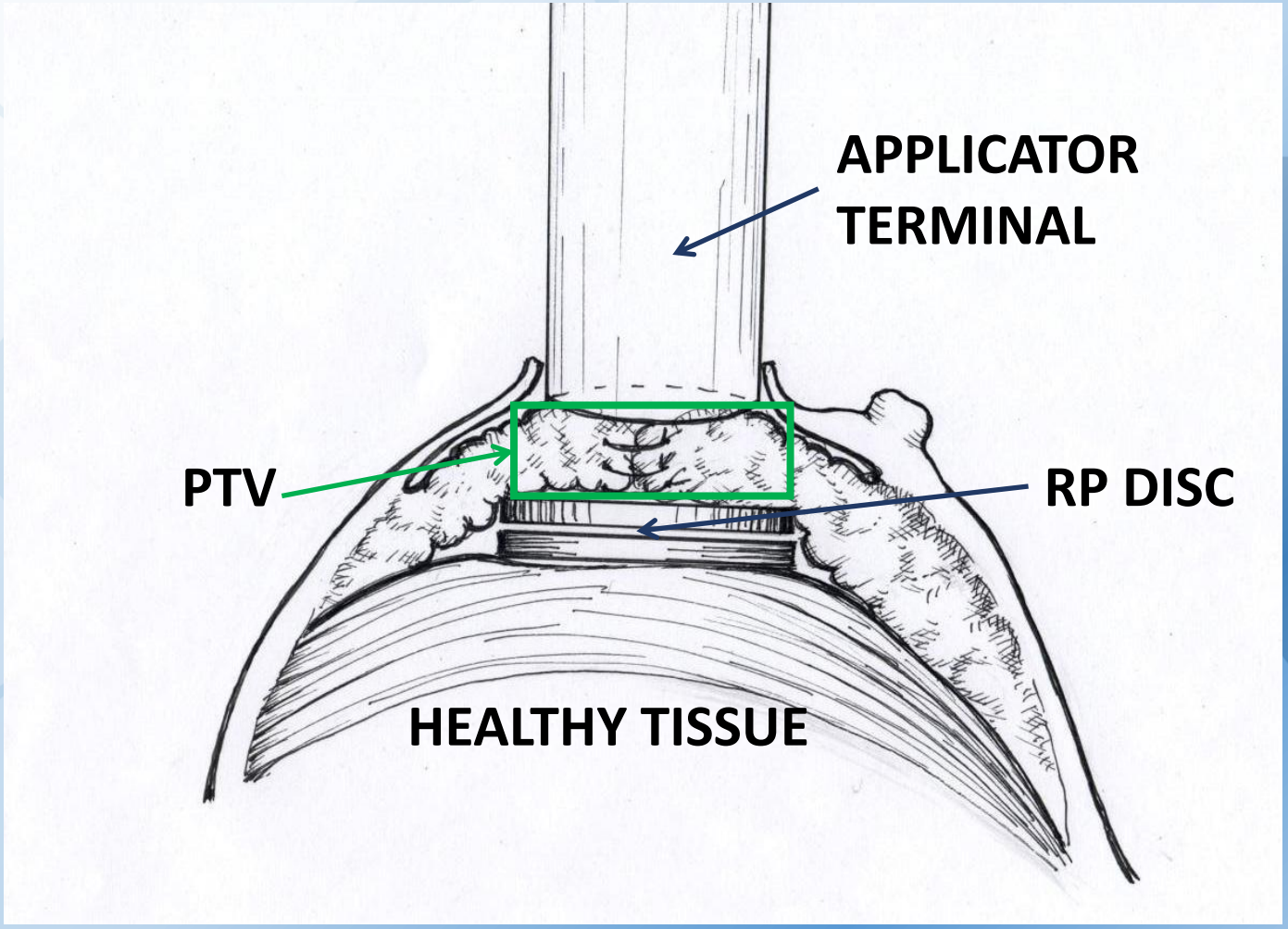
The rationale of ELIOT

"Intra-Operative Electron Radiation Therapy (IOERT) offers an important theoretical advantage in comparison to conventional postoperative EBRT. In the latter case, the time between surgical removal of the tumor and the start of radiotherapy allows repopulation from the neoplastic clones present in microscopic residual disease. Indeed, after surgery, there can be "accelerated repopulation," during which the first phases of neoplastic cellular growth follow an exponential course. Thus, giving IOERT immediately after surgery (either as a boost or as the sole treatment) may avoid this problem."

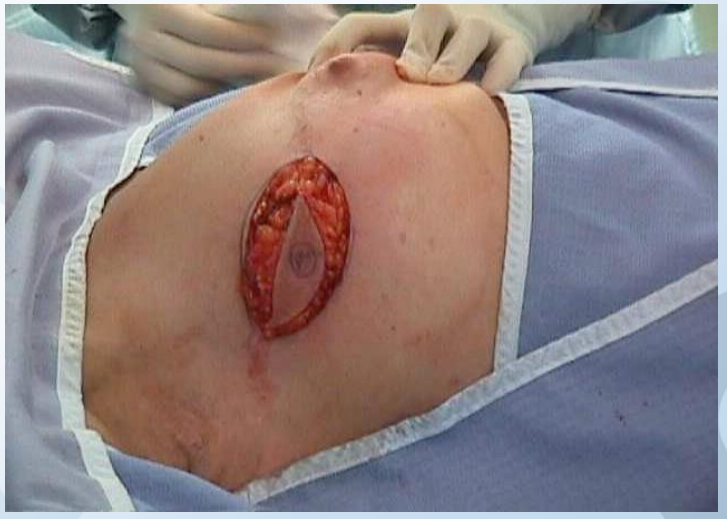
ELIOT study started before the ESTRO and ASTRO guidelines.

Intraoperative electrons, Orecchia R., Veronesi U., Semin. Radiat. Oncol., Vol. 83, pp. 76-83, 2005.

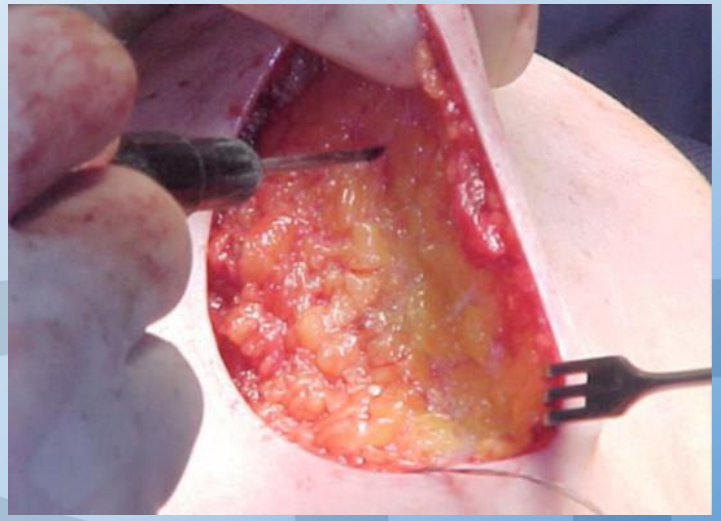
IOeRT BREAST CANCER
One specific approach: European Institute of Oncology (EIO)



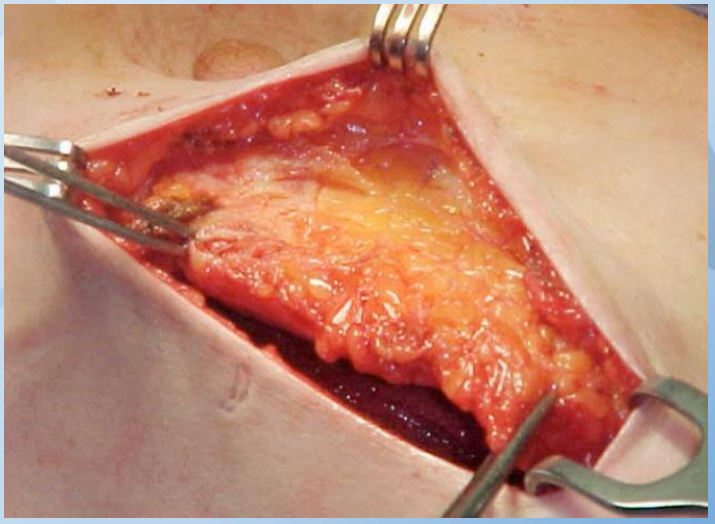
ELIOT PROTOCOL



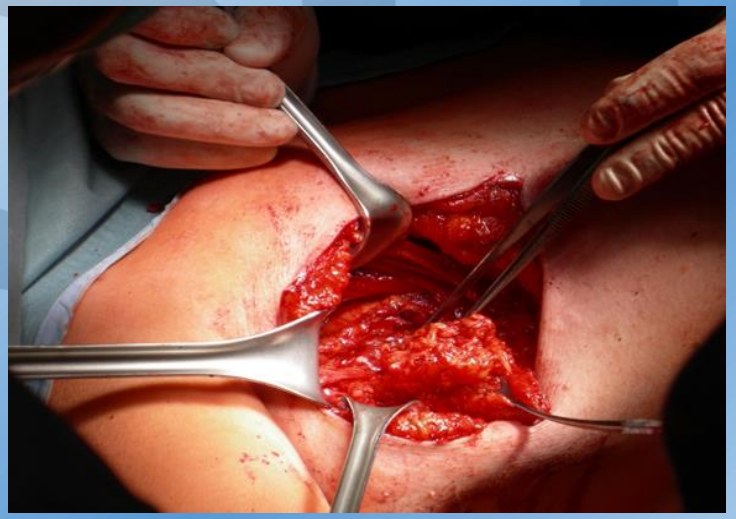
Tumor removal



Mammary gland mobilization

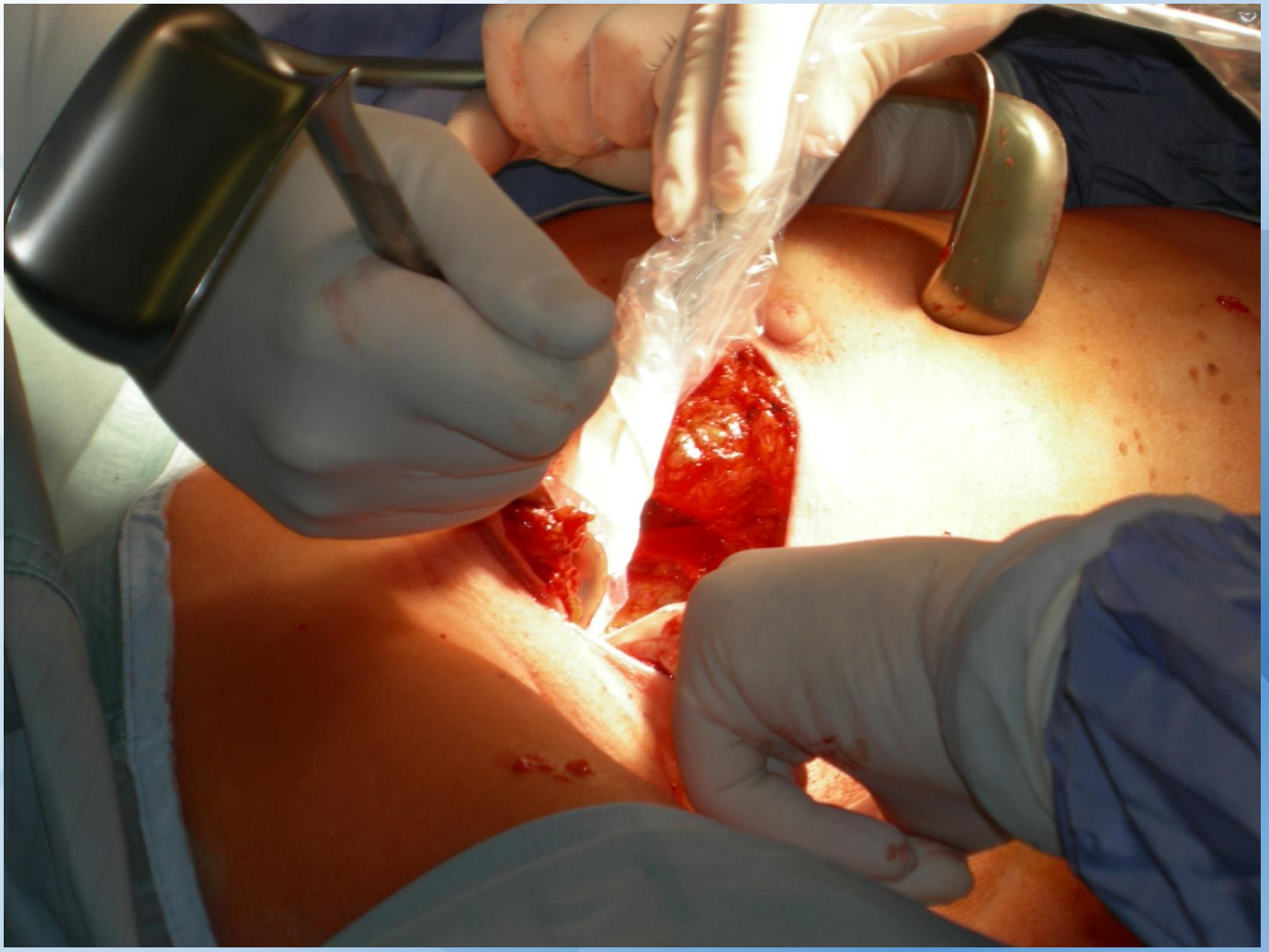


Mammary gland mobilization



Surgical breach after lumpectomy

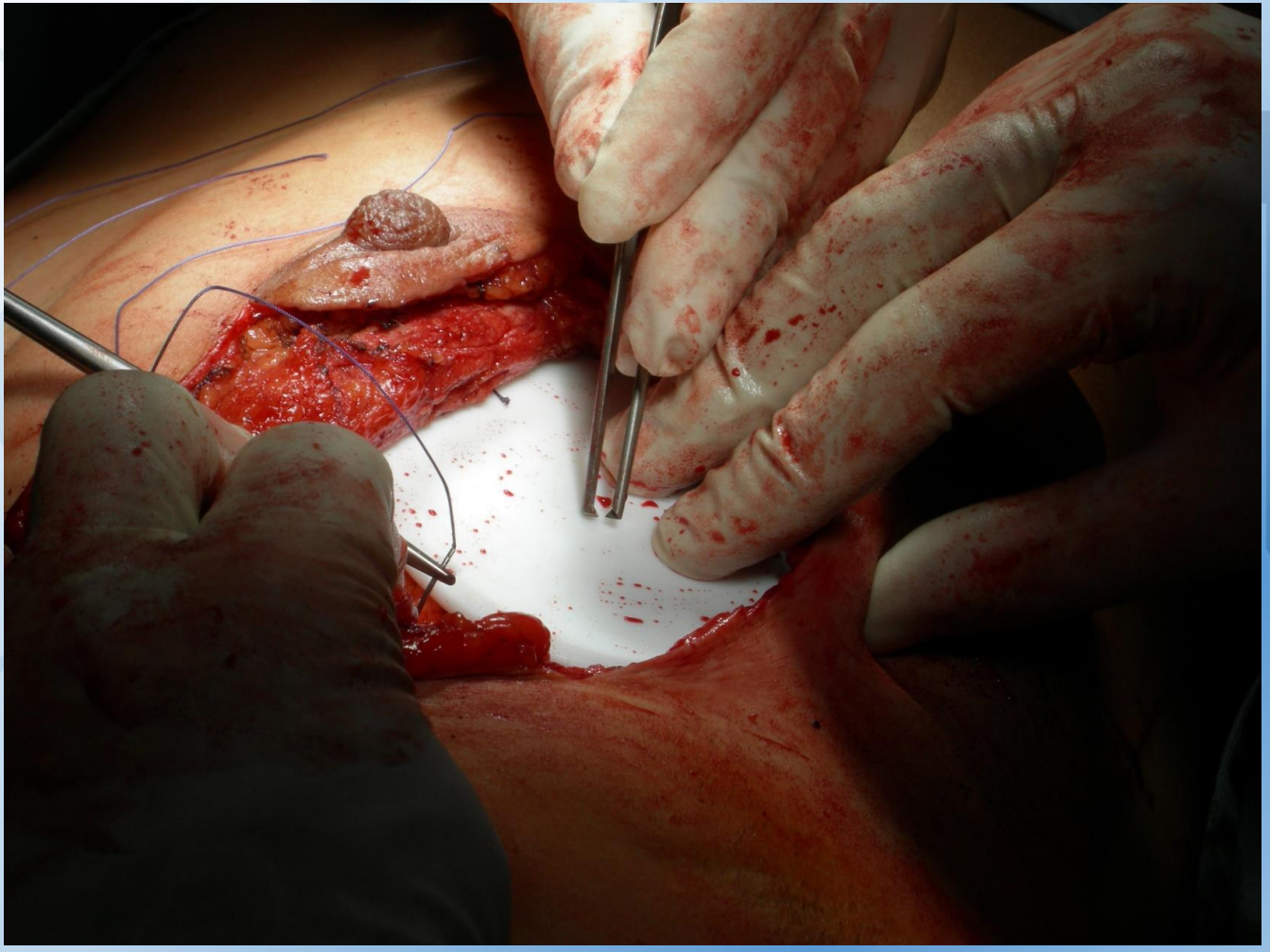
ELIOT PROTOCOL : Sentinel Lymph Node



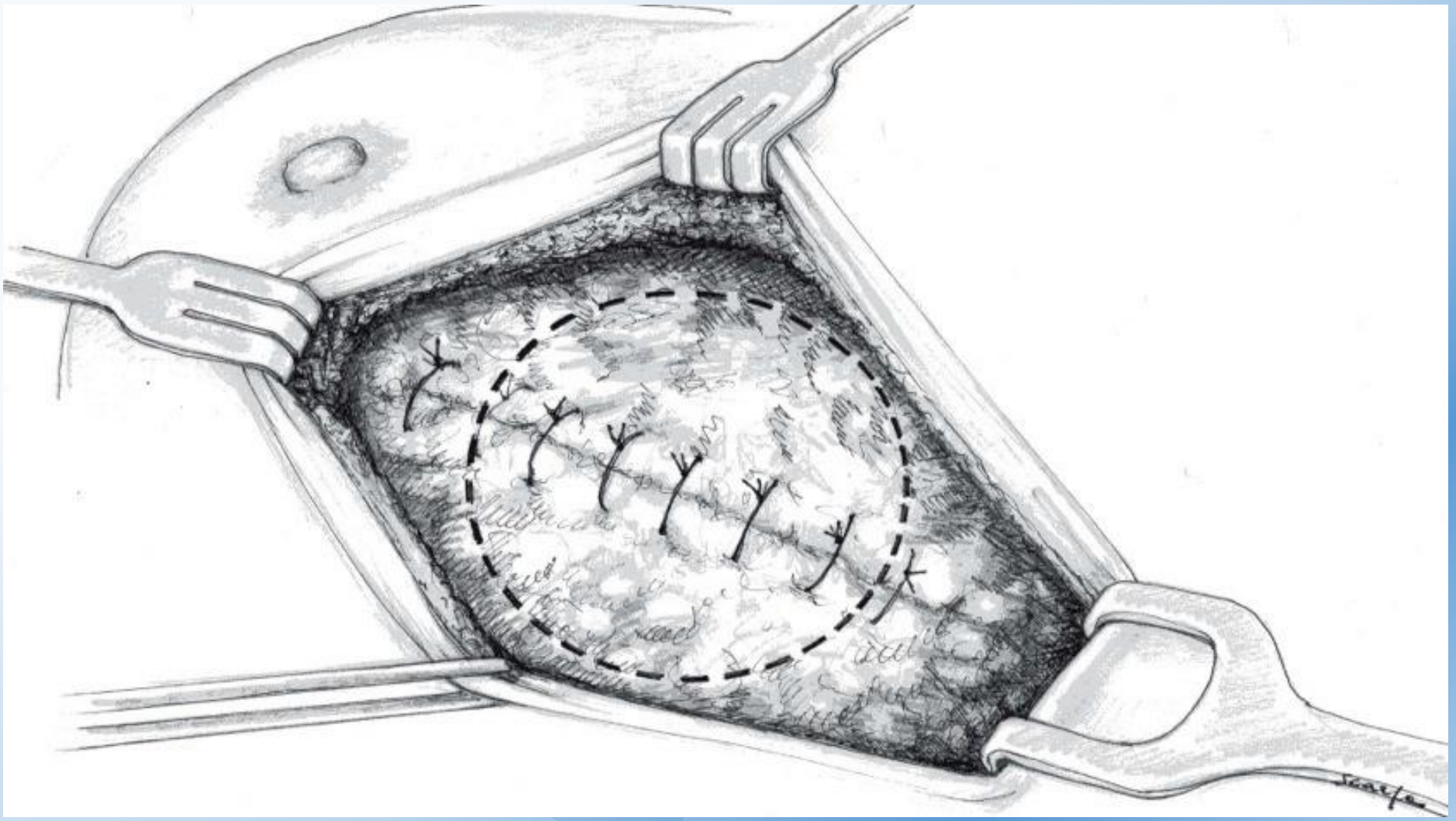
Extemporaneous examination of the sentinel lymph node for the confirmation of delivery IOeRT as single dose.

ELIOT PROTOCOL

RP disc insertion and positioning



ELIOT PROTOCOL



IOeRT as SINGLE DOSE: ELIOT study

Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial

Umberto Veronesi, Roberto Orecchia, Patrick Maisonneuve, Giuseppe Viale, Nicole Rotmensz, Claudia Sangalli, Alberto Luini, Paolo Veronesi, Viviana Galimberti, Stefano Zurrida, Maria Cristina Leonardi, Roberta Lazzari, Federica Cattani, Oreste Gentilini, Mattia Intra, Pietro Caldarella, Bettina Ballardini

1305 randomized patients
(November 2000 – December 2007)

2 CRITERIA SELECTION ONLY:

- women aged 48 – 75 years with early breast cancer;
- tumor size up to 25 mm.

ELIOT TRIAL

654 PATIENTS

BREAST CONSERVING SURGERY +

EBRT (50 Gy in 25 fractions) followed by EXTERNAL BOOST (10 Gy in 5 fractions)

651 PATIENTS

BREAST CONSERVING SURGERY +

ONLY ONE FRACTION OF IOeRT: 21 Gy at 90% isodose

IOeRT as SINGLE DOSE: ELIOT study

Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial

Umberto Veronesi, Roberto Orecchia, Patrick Maisonneuve, Giuseppe Viale, Nicole Rotmensz, Claudia Sangalli, Alberto Luini, Paolo Veronesi, Viviana Galimberti, Stefano Zurrida, Maria Cristina Leonardi, Roberta Lazzari, Federica Cattani, Oreste Gentilini, Mattia Intra, Pietro Caldarella, Bettina Ballardini

What EIO expected

Equivalence expected rate at 5 years

(Not inferiority study):

- EBRT arm: 3-3.5%
- ELIOT arm: 7-7.5%

What EIO observed

Total ipsilateral event rate observed at a median 5 years of follow up (Log-rank p< 0.0001):
- EBRT arm: 0.4%
- ELIOT arm: 4.4%

True recurrence rate observed at median 5 years of follow up (Log-rank p= 0.0002):
- EBRT arm: 0.4%
- ELIOT arm: 2.5%

	External radiotherapy (n=654)		Intraoperative radiotherapy with electrons (n=651)		Log-rank p value
	Number	5-year event rate (95% CI)	Number	5-year event rate (95% CI)	
Ipsilateral breast tumour recurrence	4	0·4% (0·0–1·0)	35	4·4% (2·7–6·1)	<0·0001
Local relapse	4	0·4% (0·0–1·0)	21	2·5% (1·2–3·8)	0·0003
New ipsilateral breast tumour	0	0	14	1·9% (0·8–3·1)	0·0001
Axillary or other regional lymph node metastasis	2	0·3% (0·0–0·8)	9	1·0% (0·2–1·9)	0·03
Locoregional tumour recurrence	6	0·8% (0·0–1·5)	44	5·4% (3·5–7·2)	<0·0001
Contralateral breast tumour	13	1·7% (0·6–2·7)	8	1·1% (0·2–2·1)	0·34
Distant metastasis*	35	4·8% (3·1–6·5)	33	5·1% (3·3–6·9)	0·94
Other primary cancer	22	3·2% (1·8–4·7)	20	2·5% (1·2–3·8)	0·88
Death as first event	7	0·9% (0·1–1·7)	8	1·0% (0·1–2·0)	0·69
Total deaths	31	3·1% (1·7–4·5)	34	3·2% (1·7–4·7)	0·59
Breast cancer	20	2·0% (0·9–3·2)	23	2·1% (0·9–3·3)	0·56
Other cause	11	1·1% (0·2–2·0)	11	1·1% (0·2–2·0)	0·93

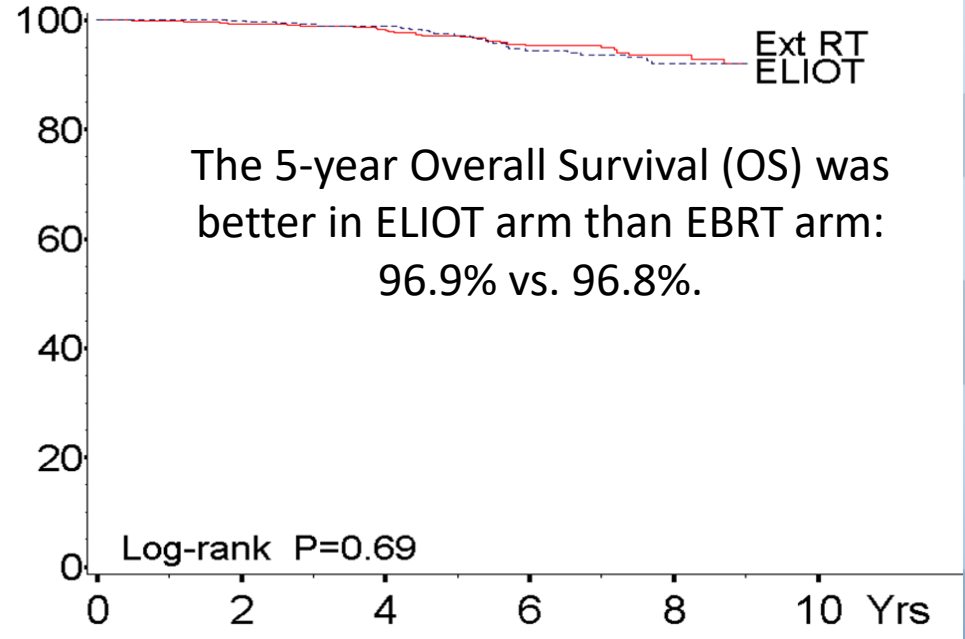
Person-years until last visit 3920 for external radiotherapy, 3716 for intraoperative radiotherapy with electrons. Person years until last contact 4107 for external radiotherapy, 3997 for intraoperative radiotherapy with electrons. *As first or secondary event (including four diagnosed at the time of surgery, all in the intraoperative radiotherapy group).

Table 2: **Events identified during follow-up according to allocated group (intention-to-treat population)**

IOeRT as SINGLE DOSE: ELIOT study

Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial

Umberto Veronesi, Roberto Orecchia, Patrick Maisonneuve, Giuseppe Viale, Nicole Rotmensz, Claudia Sangalli, Alberto Luini, Paolo Veronesi, Viviana Galimberti, Stefano Zurrida, Maria Cristina Leonardi, Roberta Lazzari, Federica Cattani, Oreste Gentilini, Mattia Intra, Pietro Caldarella, Bettina Ballardini



The 5-year Overall Survival (OS) was better in ELIOT arm than EBRT arm: 96.9% vs. 96.8%.

	External radiotherapy	intraoperative radiotherapy with electrons	p value†
Any skin toxicity			
No	427	401	..
Yes, acute	32	5	..
Yes, chronic	5	6	0·0002
Erythema			
No	7	24	..
Grade 1–2	35	5	..
Grade 3	2	0	..
Grade 4	3	0	..
Grade 5	0	0	<0·0001
Dryness			
No	128	147	..
Grade 1–2	20	10	..
Grade 3–5	0	0	0·04
Hyper-pigmentation			
No	138	146	..
Grade 1–2	36	11	..
Grade 3-5	0	0	0·0004
Pruritus (scale 0–10)			
0	174	153	..
1–2	6	5	..
≥3	11	0	0·006
Overall p value	..	..	
Necrosis (radiological)			
Absent	136	129	..
Present	10	22	0·04

*Information available only for a subset of patients. †Overall p value.

Table 4: **Skin side-effects (per-protocol analysis)***

Compared with the conventional arm, ELIOT reported:
- less skin damage (i.e., erythema, dryness, hyper-pigmentation, or itching),
- no differences for fibrosis, retraction, pain or burning;
- less pulmonary toxicity than the EBRT as diagnosed by follow-up spiral CT (4 in the ELIOT arm and 38 in the EBRT arm).

These differences in skin and pulmonary toxicity are not unexpected given the differences in IOeRT versus EBRT breast irradiation techniques.

IORT: CLINICAL RESULTS

BREAST CANCER SINGLE DOSE

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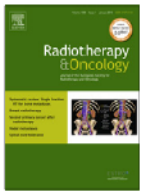

Breast cancer

Accelerated partial breast irradiation with intraoperative electrons: Using GEC–ESTRO recommendations as guidance for patient selection

Maria Cristina Leonardi [a,*], Patrick Maisonneuve [b], Mauro Giuseppe Mastropasqua [c], Anna Morra [a], Roberta Lazzari [a], Veronica Dell'Acqua [a], Annamaria Ferrari [a], Nicole Rotmensz [b], Claudia Sangalli [d], Alberto Luini [d], Umberto Veronesi [e], Roberto Orecchia [a,f]

Last data published in 2013 by Leonardi et al. according to GEC – ESTRO RECOMMENDATIONS .

5 year recurrences rate in Good Candidates (low risk):

- In Breast Tumour Recurrence 1.9 %
- True Local Recurrence 1.6 %

Table 2
Five-year clinical outcomes for breast cancer patients treated with ELIOT categorised according to the GEC–ESTRO recommendations.

	GEC–ESTRO consensus statement						
	Good		Possible		Contraindication		
Patients	573		468		767		
Person-years	1845		1492		2970		
Outcome	Events	Rate* (%)	Events	Rate* (%)	Events	Rate* (%)	Log-rank *p*
In breast tumour recurrence	7	1.9	22	7.4	46	7.7	0.001
True local recurrence	6	1.6	12	4.0	28	4.7	0.052
Ipsilateral breast cancer	1	0.3	10	3.3	18	3.0	0.012
Regional lymph node failure	8	2.2	2	0.7	8	1.3	0.275
Distant metastases	5	1.4	5	1.7	23	3.9	0.016
Breast cancer related event	26	7.0	32	10.7	91	15.3	0.003
Disease free survival	34	90.8	42	85.9	110	81.5	0.004
Cause-specific survival	3	99.2	4	98.7	24	96.0	0.014
Overall survival	5	98.6	9	97.0	33	94.4	0.044

* 5-Year rate (%) assuming constant rate during the first 5 years.

IORT: CLINICAL RESULTS

BREAST CANCER SINGLE DOSE

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Clinical Investigation: Breast Cancer

How Do the ASTRO Consensus Statement Guidelines for the Application of Accelerated Partial Breast Irradiation Fit Intraoperative Radiotherapy? A Retrospective Analysis of Patients Treated at the European Institute of Oncology

Maria Cristina Leonardi, M.D.,* Patrick Maisonneuve, Ing.,† Mauro Giuseppe Mastropasqua, M.D.,‡ Anna Morra, M.D.,* Roberta Lazzari, M.D.,* Nicole Rotmensz, M.Sc.,† Claudia Sangalli, D.M.,§ Alberto Luini, M.D.,§ Umberto Veronesi, M.D.,¶ and Roberto Orecchia, M.D.*,‖

Last data published in 2012 by Leonardi, Orecchia et al. according to ASTRO CONSENSUS STATEMENT.

5 year recurrences rate in Suitable Patients (low risk):

- In Breast Tumour Recurrence 1.5 %
- Regional lymph node failure 1.5 %

Table 3 Five-year clinical outcomes for breast cancer patients treated with full-dose intraoperative radiotherapy with electrons categorized according to the American Society for Radiation Oncology (ASTRO) consensus statement

	ASTRO consensus statement						
	Suitable		Cautionary		Unsuitable		
Patients	294		691		812		
Person-years	1,009		2,416		2,837		
Outcome	Events	Rate* (%)	Events	Rate* (%)	Events	Rate* (%)	Log-rank *p*
Ipsilateral breast tumor recurrence	3	1.5	21	4.4	50	8.8	0.0003
Regional lymph node failure	3	1.5	9	1.9	6	1.1	0.55
Distant metastases	3	1.5	8	1.7	22	3.9	0.047
Breast cancer related event	14	6.9	46	9.5	87	15.3	0.0025
Progression free survival	17	91.6	58	88.0	109	80.8	0.0005
Cause-specific survival	2	99.1	7	98.7	22	96.5	0.026
Overall survival	3	98.6	13	97.5	30	95.2	0.039

ASTRO group was not assessable for 25 patients.
* Five-year rate (%) assuming constant rate during the first 5 years.

ELIOT Out-trial according to ASTRO /ESTRO recommendations

Class of risk according to ASTRO/ESTRO	No. Patients selected according to ASTRO statement	In-breast recurrence according to ASTRO statement	No. Patients selected according to ESTRO reccomendations	In-breast recurrence according to ESTRO reccomendations
#	1822		1822	
Unclassifiable	25		7	
Suitable / good	**294 (16 %)**	**1.5%**	**573 (31 %)**	**1.9%**
Cautionary / possible	691	4.4%	468	7.4%
Unsuitable / contraindication	812	8.8%	767	7.7%

IOeRT as single dose: ELIOT protocol:

Current Guidelines for low risk patients selection at the EIO

TABLE 3 Reported guidelines at the EIO for low-risk IOERT Group

Age	≥60 years
Tumor size	<2 cm
Applicator size	6 cm minimum, 5 cm occasionally
Grade	G1/G2
ER status	ER+
Proliferative index	Ki-67 < 20
Biology	Luminal A
Lobular CA	Only with MRI assessment

As reported at ISIORT 2012, Baveno, Italy, and with permission of Springer Science & Business Media[24]

Patients found with higher risk factors post-IOERT will also receive 8 fractions of 3.6–4.0 Gy of EBRT, excluding the breast volume irradiated by IOERT

More than **7.000** patients treated **from 1999 to 2013** at European Institute of Oncology (IEO) in Milan (Italy).

Intraoperative Radiation Therapy: A Critical Analysis of the ELIOT and TARGIT Trials. Part 1- ELIOT, Silverstein M. J., Fastner G., Maluta S., Reitsamer R., Goer D. A., Vicini F., Wazer D., Ann. Surg. Oncol, 2014.

ELIOT Advantages

TIME SAVING: **100 SECONDS** of irradiation inside the operating room avoids **5-7 WEEKS** of external radiotherapy.

Many women live far away from a Radiotherapy institute:
How many km (and €) saved ?!

PATIENT QUALITY OF LIFE.

DRASTIC REDUCTION OF WAITING LISTS IN RADIOTHERAPY.

IORT with electrons as single dose: A (SLIGHTLY) DIFFERENT APPROACH

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Clinical Investigation

Accelerated Partial Breast Irradiation Using Only Intraoperative Electron Radiation Therapy in Early Stage Breast Cancer

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July 2006 to December 2009, 226 patients suitable for BCT in a Phase II study in which IOeRT was delivered as a radical treatment after surgical resection.
21 Gy was delivered to Dmax, the prescribed dose to whole target was 18.9 Gy at the 90% isodose. The median follow-up was 46 months.
The energy of 6 MeV was selected for 150 of 226 patients, 4 MeV for 66 patients and 9 MeV for 10 patients. Median applicator was 6 cm, 87% were > 5cm and 31% were >6cm; ensuring good coverage of the tumor bed [1].

On the basis of the ELIOT study and the ASTRO and ESTRO guidelines, it was simple to define the IOeRT present study criteria and thus the eligible patients as reported in Table 1.
Infact only 1 case of local recurrence was reported.

APBI using IOeRT as single dose can be delivered safely in woman with early low risk breast cancer in carefully selected patients.

Table 1 ASTRO and GEC-ESTRO-suitable patient recommendations for APBI outside of clinical trials, compared to the inclusion criteria of our study

Factor	APBI low-risk group by GEC-ESTRO criteria	APBI suitable group by ASTRO criteria	IOERT present study criteria
Age	>50	>60	≥50
BRCA 1, 2 mutation	Not present	NA	NA
Tumor size	<3 cm	<2 cm	≤3 cm
T stage	T1-2	T1	T1-2
Grade	Any	Any	Any
LVI	Not allowed	Not allowed	NA
ER status	Any	Positive	Any
Multicentricity	Unicentric	Unicentric	Unicentric
Multifocality	Unifocal	Unifocal with total size of <2 cm	Unifocal
Histology	IDC, mucinous, medullary, colloid	IDC, mucinous, tubular, colloid	IDC, mucinous, medullary, tubular, colloid
DCIS	Not allowed	Not allowed	Not allowed
EIC	Not allowed	Not allowed	Not allowed
Associated LCIS	Allowed	Allowed	Allowed
Nodal status	pN0 (by SNB or AND)	pN0 (by SNB or AND)	NA
Neoadjuvant therapy	Not allowed	Not allowed	Not allowed

Abbreviations: AND = axillary node dissection; APBI = accelerated partial breast irradiation; ASTRO = American Society for Radiation Oncology; DCIS = ductal carcinoma in situ; EIC = extensive intraductal component; ER = estrogen receptor; GEC-ESTRO = Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; IOERT = intraoperative electron radiation therapy; LCIS = lobular carcinoma in situ; LVI = lymphovascular invasion; NA = not applicable; SNB = sentinel node biopsy.

[1] Intraoperative Radiation Therapy: A Critical Analysis of the ELIOT and TARGIT Trials. Part 1- ELIOT, Silverstein M. J., Fastner G., Maluta S., Reitsamer R., Goer D. A., Vicini F., Wazer D., Ann. Surg. Oncol, 2014.

Milan study vs. Verona study

MAIN DIFFERENCES	ELIOT study (651 pts)	VERONA study (226 pts)
Median Applicator Diameter	4 cm	6 cm (87% > 5cm and 31% > 6cm)
ILC, ILC/IDC	8.1 %, 3% (5 of 35)	0%
Dose [Gy]	21 Gy at the 90% isodose	21 Gy at the Dmax, 16.8 Gy at the 80% isodose
Total positives nodes 1-3+, ≥ 4	21%, 5% (10 of 35)	0%
Age (years) ≤ 40	7%	0%
NUMBER OF RECURRENCES	35	1

Intraoperative Radiation Therapy: A Critical Analysis of the ELIOT and TARGIT Trials. Part 1- ELIOT, Silverstein M. J., Fastner G., Maluta S., Reitsamer R., Goer D. A., Vicini F., Wazer D., Ann. Surg. Oncol, 2014.

Breast Cancer Res Treat
DOI 10.1007/s10549-017-4321-6

REVIEW

Breast cancer electron intraoperative radiotherapy: assessment of preoperative selection factors from a retrospective analysis of 758 patients and review of literature

S. Takanen[1] · A. Gambirasio[1] · G. Gritti[1] · M. Källi[1] · S. Andreoli[2] · M. Fortunato[2] · L. Feltre[1] · F. R. Filippone[1] · E. Iannacone[1] · L. Maffioletti[1] · R. Muni[1] · F. Piccoli[1] · E. M. P. Mauri[3] · A. Paludetti[3] · M. Giovanelli[3] · L. Burgoa[3] · C. Valerii[3] · F. Palamara[3] · M. Ferro[3] · P. Fenaroli[3] · C. A. Tondini[4] · L. F. Cazzaniga[1]

Received: 17 November 2016 / Accepted: 29 May 2017

Bergamo study: retrospective analysis of 758 patients

From February 2006 to January 2016, **758 patients underwent an IOeRT breast cancer treatment as full dose** (21 Gy at 90% isodose) at Papa Giovanni XXIII Hospital, Bergamo (Italy).
Such patients were retrospective analyzed and stratified according to GEC-ESTRO and ASTRO recommendations. **The median follow-up was 5.2 years.**
The energy was 9 MeV, the applicator diameters used were between 4 and 6 cm with a radioprotection disk diameters 2 cm larger than the correspondent applicator .

According to **ASTRO stratification** , the 5 year results for suitable (low risk) group were: 1.2% in breast tumor recurrence as **0% true local recurrence** and **1.2% new ipsilateral recurrence**.

According to **Bergamo Hospital stratification** , the 5 year results for low risk group group were: 1.8% in breast tumor recurrence as **0.6% true local recurrence** and **1.1% new ipsilateral recurrence.**

IOeRT as BOOST – HIOB protocol: for any risk group

LOW RISK **MEDIUM RISK** **HIGH RISK**

Any risk group can be treated according to **HIOB protocol as IOeRT Boost** followed by a reduced cycle of the External Beam Radiation Therapy (EBRT) (**33 to 15 fractions**) providing both excellent LR and OS at 5 years.

first study published about IOERT as BOOST + HYPOFRACTIONATED RT

ARTICLE IN PRESS

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ELSEVIER

doi:10.1016/j.ijrobp.2007.12.038

CLINICAL INVESTIGATION

PRELIMINARY RESULTS OF ELECTRON INTRAOPERATIVE THERAPY BOOST AND HYPOFRACTIONATED EXTERNAL BEAM RADIOTHERAPY AFTER BREAST-CONSERVING SURGERY IN PREMENOPAUSAL WOMEN

Giovanni Battista Ivaldi, M.D.,* Maria Cristina Leonardi, M.D.,* Roberto Orecchia, M.D.,*§ Dario Zerini, M.D.,* Anna Morra, M.D.,* Viviana Galimberti, M.D.,† Giovanna Gatti, M.D.,† Alberto Luini, M.D.,† Paolo Veronesi, M.D.,†§ Mario Ciocca, M.Sc.,‡ Claudia Sangalli, D.M.,† Cristiana Fodor, D.M.,* and Umberto Veronesi, M.D.†

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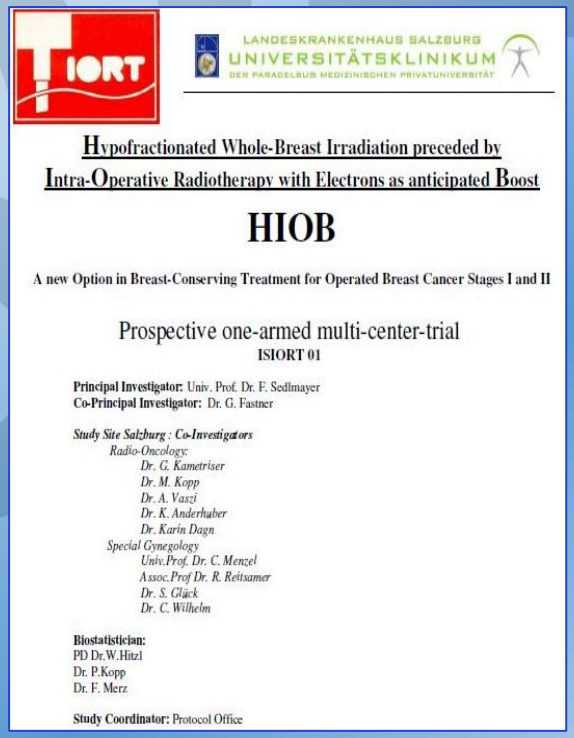
2004-2007, 211 premenopausal pts (46% adjuvant CT)
12Gy IOeRT boost + hypofractionated RT (2,85Gy x 13f)
0% in-breast recurrence.

HIOB PROTOCOL: the international ongoing trial



IORT

LANDESKRANKENHAUS SALZBURG
UNIVERSITÄTSKLINIKUM
DER PARACELSUS MEDIZINISCHEN PRIVATUNIVERSITÄT

Hypofractionated Whole-Breast Irradiation preceded by Intra-Operative Radiotherapy with Electrons as anticipated Boost

HIOB

A new Option in Breast-Conserving Treatment for Operated Breast Cancer Stages I and II

Prospective one-armed multi-center-trial
ISIORT 01

Principal Investigator: Univ. Prof. Dr. F. Sedlmayer
Co-Principal Investigator: Dr. G. Fastner

Study Site Salzburg : Co-Investigators
Radio-Oncology:
Dr. G. Kametriser
Dr. M. Kopp
Dr. A. Vaszi
Dr. K. Anderhuber
Dr. Karin Dagn
Special Gynegology
Univ.Prof. Dr. C. Menzel
Assoc.Prof Dr. R. Reitsamer
Dr. S. Glück
Dr. C. Wilhelm

Biostatistician:
PD Dr.W.Hitzl
Dr. P.Kopp
Dr. F. Merz

Study Coordinator: Protocol Office

From 2011 1.100 patients treated
0% in-breast recurrence.
https://clinicaltrials.gov/ct2/show/NCT01343459

IOeRT as BOOST – HIOB protocol: for any risk group

LOW RISK **MEDIUM RISK** **HIGH RISK**

STUDY	TREATMENT	LOCAL CONTROL
SEQUENTIAL INTERVENTION STUDY	EXTERNAL STANDARD RT of 51-56.1 Gy (1.7 Gy per fraction) + **IOeRT BOOST (9 Gy at 90% isodose)**	**100%** (1) 4.3 years follow up
	EXTERNAL STANDARD RT of 51-56.1 Gy (1.7 Gy per fraction) + external BOOST of 12 Gy	95.7% (1) 6.9 years follow up
FIRST IOERT BOOST EXPERIENCE	**IOeRT BOOST (12 Gy at 90% isodose)** + HYPOFRACTIONATED EXTERNAL RT 37.05 Gy (13 fractions of 2.85 Gy per fraction)	**100%** (2) 1 year follow up
ISIORT POOLED ANALYSIS	**IOeRT BOOST (10 Gy at 90% isodose)** + external STANDARD RT of 50-54 Gy (1.7 Gy per fraction)	**99.2%**(3) 6 years follow up
HIOB PROTOCOL: FIRST RESULTS	**IOeRT BOOST (10 Gy at 90% isodose)** + HYPOFRACTIONATED EXTERNAL RT 40.5 Gy (15 fractions, 2.7 Gy per fraction)	**100%** (4) 1 year follow up
CASE SERIES RESULTS OF A Locally Advanced Breast Cancer (LABC) post induction chemotherapy	**IOeRT BOOST (9 Gy at 90% isodose)** + external STANDARD RT of 51-57 Gy (1.7-1.8 Gy per fraction)	**98.5%** (5) 5 years follow up
	EXTERNAL STANDARD RT of 51-57 Gy (1.7-1.8 Gy per fraction) + external BOOST (12 Gy, 2 Gy per fraction)	88.1% (5) 5.7 years follow up
TRIPLE-NEGATIVE BREAST CANCER EXPERIENCE	**IOeRT BOOST (9.6 Gy median Dmax)** + EXTERNAL STANDARD RT (median total dose of 54 Gy)	**93%** (6) 8.1 years of follow up

IOeRT as BOOST – HIOB protocol: for any risk group

LOW RISK **MEDIUM RISK** **HIGH RISK**

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ADVANTAGES OF THE IOeRT TECHNIQUE

FOR CLINICAL PRACTICE:

- **Improvement of local control**; is a conditio sine qua non for disease free and overall survival.
- **Reduction** (in the case of boost) **and elimination** (in case of single dose) of the external radiotherapy cycle.
- **Time zero between surgery and the delivery of radiotherapy, neoplastic cells growth from microscopic residual disease follows an exponential course immediately after surgery. Giving IOeRT this problem is solved.**
- **Precision**, thanks to direct visualization of the target.
- **Significant reduction of dose to healthy tissues**, the direct access of irradiation to the target allows to displace and mechanically protect numerous dose-sensitive normal tissue uninvolved by cancer.
- **Minimization of side effects, less toxicity, complete skin sparing and better cosmesis outcomes** compared to external beam radiation therapy.
- **Feasibility of the treatment as the only solution when external radiation therapy is critical or even not possible** (treatments of recurrences, patients with a pacemaker or decreased mobility).
- **IOeRT boost is particularly efficacious for the treatment of locally advanced cancers. IOeRT boost combined with external RT and chemotherapy allows to achieve excellent results of local control and overall survival (2016-2017 NCCN guidelines).**

ADVANTAGES FOR THE PATIENT

- Reduction of the entire cycle to a single day!
- Elimination of side effects caused by conventional therapy.
- Decrease in costs to undergo treatment.

ADVANTAGE FOR SOCIETY

- Decrease of social costs associated to the need for care and lack of patient productivity.

ADVANTAGE FOR THE MEDICAL FACILITY

- Substantial reductions in waiting lists for radiotherapy centers.

Multicancer Application: most relevant IOeRT Clinical Results (1 of 3)

DISTRICT	INDICATION Stage/ Locally advanced	INSTITUTION Reference	RESULTS	REMARKS/ IOERT effects
PANCREAS	Unresectable	MGH (1)	2 y 16% OS (survivors > 5y)	≤ 8cm, Charlson comorbidity index, ≤ 3, chemotherapy = OS 21 months
	Bordeline	MCR (2)	84% LC; 3 y 40% vs 0% OS	Median survival: 23 m R0 vs 10 m R2/unresectable
	Resectable	HGUGM (3)	58% 5 y LC	98% local control with IOeRT boost
	unresectable or borderline-resectable	MGH (4)	35.1 months of median OS	IORT with neoadjuvant CT and CRT improve survival. No toxicity incremented by IOeRT
ESOPHAGO-GASTRIC	Resectable	HGUGM (5)	5 y 85% LC	IOeRT significant improvement of local control
	Stage II and III	Meta-analysis First Hospital of China Medical University (6)	IORT improved local control	Favourable effect of IORT in patients with stage II and III
GASTRIC	Resectable	Systematic review (7)	St III IOeRT promoted OS	Any stage IOeRT promoted local control
RECTAL	cT2-4 N+	HGUGM (8)	5 y 96% LC	Prognostic index for risk-adapted treatment.
	Primary and recurrent	Systematic review (9)	IOeRT improved LC and OS	No toxicity increment by IOeRT
	Unresectable T4	MCR and CHE (10)	5 y 19.3 % LR, DFS 55%, OS 56%	IOeRT and Preop CRT improve OS
	Recurrent	MCR and CHE (11)	5 y 45.3% local re-recurrence rate	IOeRT advantage in pts with R1 and R2 resection
	pT4N0/T1-4N+	Multivariate analysis (12)	5-year 89.7% LC and 69.0% DFS	No increase of acute and long-term complications
PROSTATE	Metastatic D1 and D2	Saitama Cancer C(13)	5-10 y 75/52% OS	In D2 IORT significantly cancer-specific survival

Multicancer Application: most relevant IOeRT Clinical Results (2 of 3)

DISTRICT	INDICATION Stage/ Locally advanced	INSTITUTION Reference	RESULTS	REMARKS/ IOERT effects
RENAL	Recurrent/Primary resected	US-Europe Pooled-analysis (14)	5y 37% (p) vs 55% (r) OS	Survival affected by nodal involvement, sarcomatoid features and IORT dose
PEDIATRIC	Ewing/Rhabdomyosarcoma	Pooled-European (15)	5-10 y 74% - 68% OS	R1 and recurrent influence outcome
	Neuroblastoma + sarcoma incomplete resection	Heidelberg Univ (16)	1/18 local recurrences	6 clinical significant late toxicity
	primary extremity soft-tissue	Multicentric Pooled Analysis (17)	10-year 85% LC, 76% DFS and 81% OS	IOeRT boost increased local control with low toxicity rates
SARCOMAS	Retroperitoneal	Heidelberg Univ (18)	5 y 72% LC	preoperative IMRT for external RT escalation
	Retroperitoneal	MCR (19)	5 y 89% LC	89% vs 46% S+RT vs S alone (p=0.003)
	Retroperitoneal	Boston University School of Medicine (20)	5 y 54% OS for liposarcoma	IORT and adjuvant EBRT improved survival for liposarcoma
	Resectable retroperitoneal	Univ Freiburg(21)	5 y 89.5% survival rate	Pts ≤ 55 years and R2 resection are adverse for survival
	Extremity soft tissue	Pooled- European (22)	5 y 82% LC	In-field LC promoted by IOERT dose ≥12.5 Gy
	Osteosarcomas	Pooled-European (23)	10 y 82% LC, 73% OS	R1 adverse for local control
OLIGO-RECURRENCES	Gynaecologic, rectal	HGUGM (24)	5 y 53% LC, 46 % OS	External beam radiotherapy + IOeRT compensate adverse factors fragmentation
	STS, head and neck, uterine, colorectal	Univ of Navarre, (25)	5 y 31% LRC, 57% DMFS, 31% OS	Gross macroscopic resection is significant for LRC and radiation dose for survival

Multicancer Application: most relevant IOeRT Clinical Results (3 of 3)

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LEGEND

MGH = Massachusetts General Hospital; **HCMU** = Hospital of China Medical University; **LC** = Local Control; **LRC** = Local Regional Control; **OS** = Overall Survival; **DMFS** = Disease Metastatic Free Survival; **m** = months; **y** = years; **pts** = patients; **(p)** = primary locally advanced disease; **(r)** = recurrent disease; **St** = stage; **IMRT** = Intensity Modulated RadioTherapy; **IOeRT** = IntraOperative electron RadioTherapy; **R1** = microscopic residual disease; **C** = Centre; **S**= Surgery; **CT** = Chemoradiotherapy; **RT**= Radiation Therapy; **EBRT**= External Beam Radiation Therapy; **SR** = Survival Rate; **STS** = Soft Tissue Sarcoma; **D1**= cancer spread to the lymph nodes only; **D2**= cancer spread to the distant lymph nodes and or to bones or internal organs; **cT2-4 N+** = clinical stage transmural or metastatic nodes; **pT4N0/T1-4N+** = locally advanced stage involving other organs/structures or metastatic pelvic nodes.

NCCN GUIDELINES 2016 – 2017 UPDATE: IOeRT PRACTICE CONSOLIDATION

NCCN GUIDELINES AVAILABLE FOR THE IOERT TREATMENT OF:
SOFT TISSUE SARCOMA OF EXTREMITY/TRUNK/HEAD-NECK AND RETROPERITONEAL/INTRA-ABDOMINAL SARCOMA
RECTAL CANCER RESECTABLE FOR VERY CLOSE OR POSITIVE MARGINS, ESPECIALLY FOR T4 OR RECURRENT CANCERS
COLON CANCER LOCALLY UNRESECTABLE OR MEDICALLY INOPERABLE, ESPECIALLY FOR T4 OR RECURRENT CANCERS
PANCREATIC ADENOCARCINOMA UNRESECTABLE OR LOCALLY RECURRENT CANCERS
CERVICAL CANCER RECURRENT DISEASE
ENDOMETRIAL CANCER RECURRENT DISEASE
UTERINE SARCOMA FOR RADIOLOGICALLY ISOLATED VAGINAL/PELVIC RECURRENCE