IORT linacs and other possible developments

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CERN, November 7-8, 2016

Introduction to IORT

IORT is a radiotherapy treatment given in the operating room, during surgery.

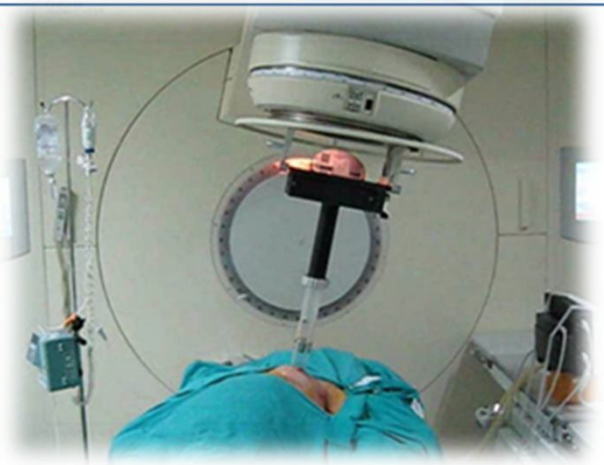
Radiation can be given by

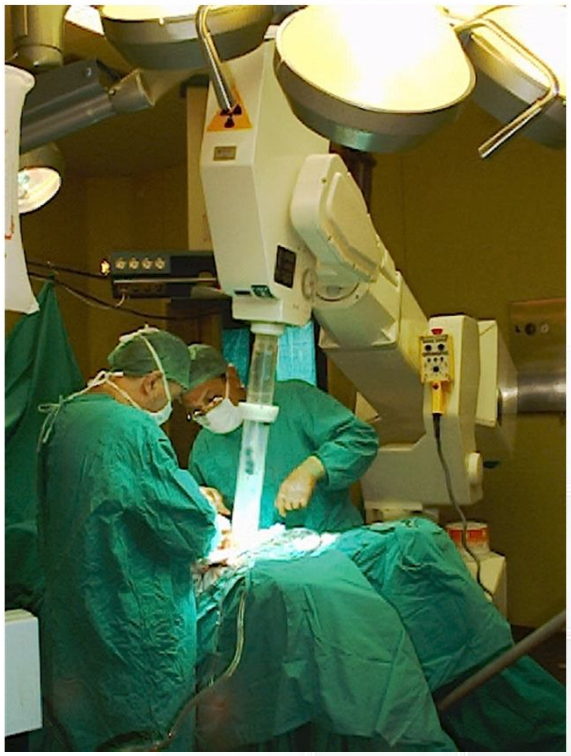
- multimegavolt electrons, and it is called IOERT
- or by multikilovolt x-rays.

Here we describe only IOERT dedicated accelerators.

IOERT can be performed in two ways

- **Carrying the patient in RT room**, a choice that implies a transportation of the patient through the hospital during operation with obvious implications
- Using a dedicated IOERT device able to irradiate in the surgery room, that **has the advantages of** minimizing irradiation time but has the implications of face with some **radioprotection in the surgery room and that the device has to comply sterilizing prescriptions.**





Introduction to IORT dedicated devices

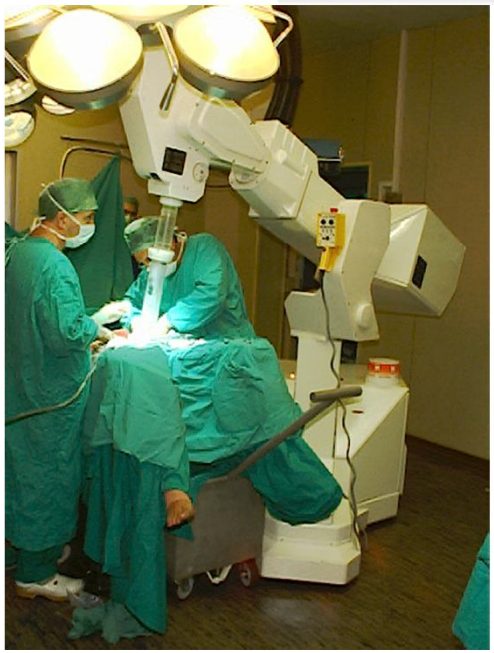
IOeRT dedicated devices are compact devices with very easy installation in the operating room

- a small electron linac, with its e-gun, which delivers up to 12 MeV electron beam (about 5 cm of penetration in normal tissue) with a selection of different lower energies
- magnetron and its modulator, electronics, vacuum and ancillary systems
- A robotic arm with several degrees of freedom, remotely controlled, in which the linac is housed, that directs the output beam, toward the irradiation zone
- A delivery system composed by dose monitoring systems and plastic collimators that flatten the dose
- A shielding system that prevents personnel irradiation during tratment
- A control system that assist the linac operation and the treatment and a dedicated software for dose evaluation according to international protocols

By courtesy of SIT company

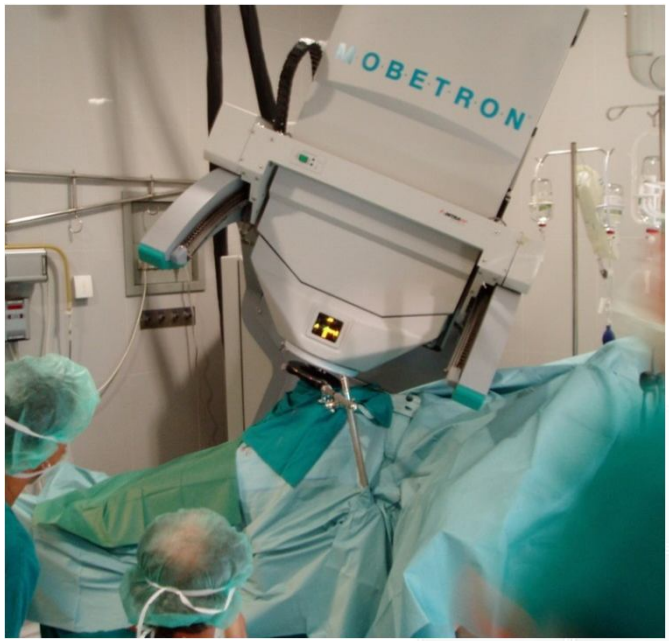
IOERT Accelerators

Three IORT Electron Accelerators are present on the IOERT market: the NOVAC and LIAC accelerators , which are produced now by SIT company (Italy) and the MOBETRON produced by the IntraOp Company (USA)



NOVAC
(ex NRT)

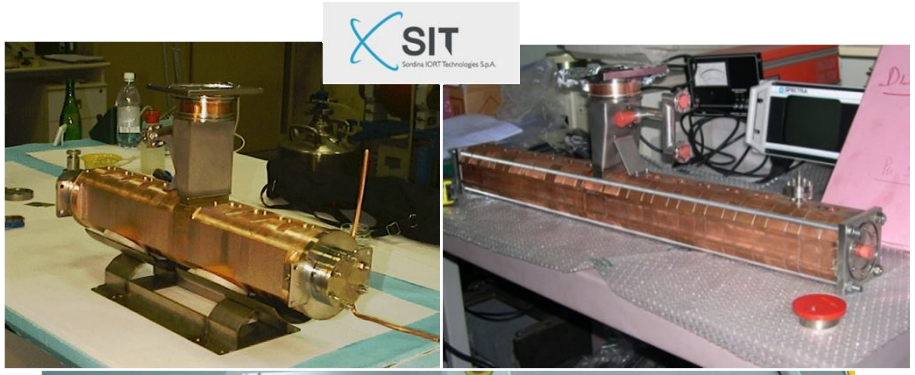
LIAC
(ex Sordina)



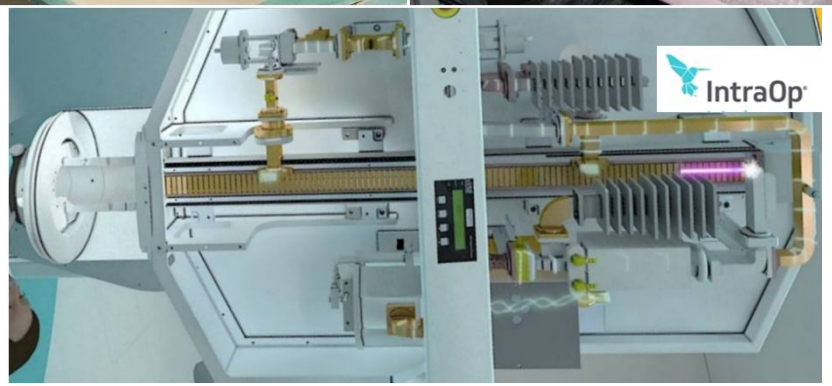
IOERT ACCELERATING STRUCTURES

Electron accelerators (Standing wave side or on-axis coupled):

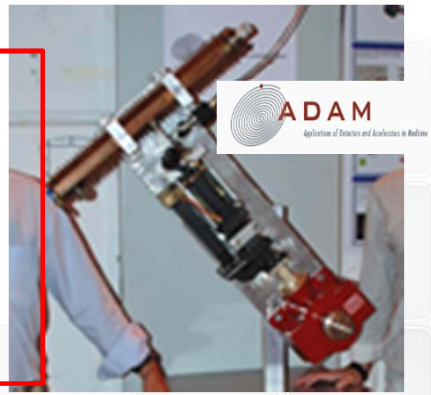
2.998 GHz (S-band) for NOVAC and LIAC, 80 – 100 cm long with Magnetron power 2.6 – 3.1 MW



9.3 GHz for Mobetron.
Although the increase of the RF frequency to X-band, Mobetron linac is still 1 m long, despite the higher shunt impedance, because the magnetron power is low (~1.5 MW)

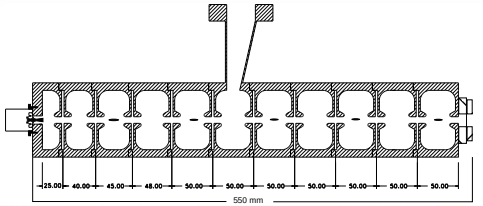


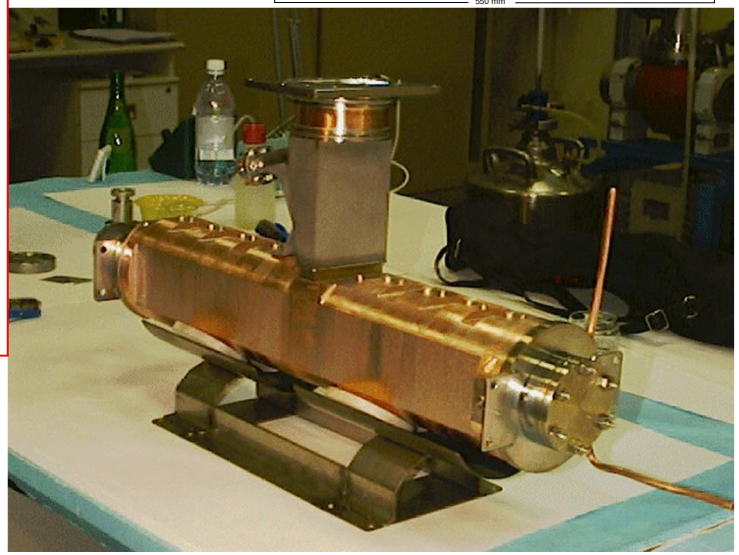
A temporary collaboration between ADAM S.A. company NRT, and ENEA, allowed in 2011 the successful tests of a C-band (5.712 GHz) IORT 10 MeV electron linac. Magnetron power was 2.5 MW and linac length was reduced to 55 cm. However this did not produce a commercial device



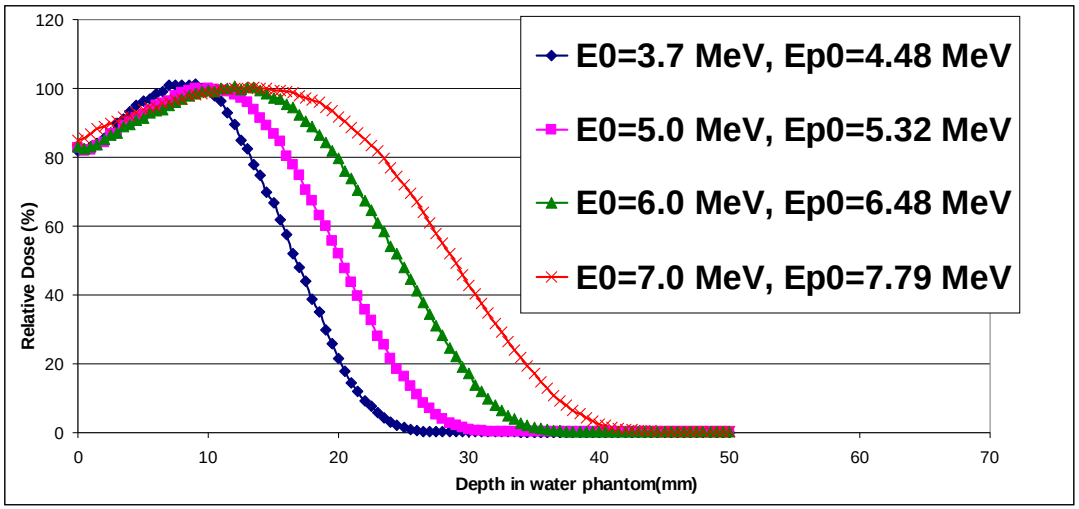
Typical IORT Accelerator characteristics

Output Energies	3 -to-12 MeV in steps
Pulse duration	4 µsec
Peak current	**1.5 mA**
Repetition frequency	1-30 Hz
Accelerating Structure	Standing wave
Magnetic lenses	**none, autofocusing**
Length	**82-92 cm (10-12 MeV)**
Weigth	**25 - 33 Kg**

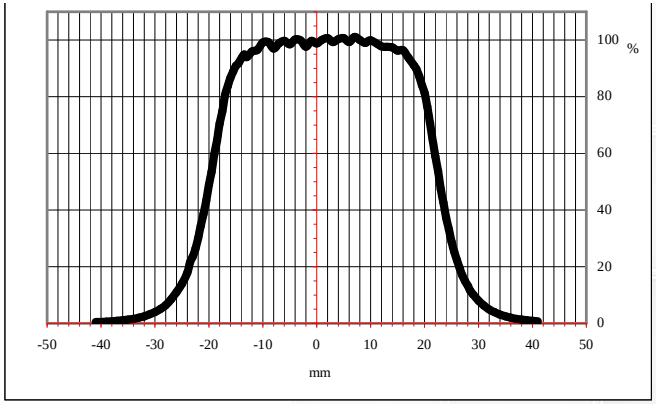




Depth dose curves (NOVAC 7)



Distribution at patient surface



IOeRT – Clinical Indications

ISIORT database has reached **10.675** patients according the last ISIORT congress on June 24-25th 2016.

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

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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.*

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

By courtesy of SIT company

Recommendations for breast IOERT

In 2009 and 2010 ASTRO and ESTRO guidelines has been published for **Accelerated Partial Breast Irradiation (APBI).** Patients are divided in 3 risk groups according to age, tumor size, lymphnodes status etc.

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

ESTRO

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

ASTRO

Patient Group	Risk Factor	Original	Update
Suitable	*Age*	≥ 60 years	≥ 50 years
	Margins	Negative by ≥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 years	• 40-49 years if all other criteria for "suitable" are met • ≥ 50 if patient has at least one of the pathologic factors below and does not have any "unsuitable" factors. *Pathologic factors:* • Size 2.1-3.0 cm* • T2 • Close margins (<2 mm) • Limited focal LVSI • ER Negative • Clinically unifocal with total size 2.1-3.0 cm† • 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 years • 40 – 49 years and do not meet the criteria for cautionary

- All low risk group patients can be treated **with a single dose** (**ELIOT** Protocol), **21 Gy at 90% of isodose**
- All the others can be treated **with boost** (**HIOB protocol, 10-12 Gy IORT + 40.5 Gy hypofractionated EBRT in 15 fractions of 2.7 Gy**)

By courtesy of SIT company

SINGLE DOSE APPROACH: ELIOT STUDY

The rationale of ELIOT

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

When using postoperative EBRT ***"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****."*

EVIDENT ADDITIONAL BENEFITS OF SINGLE DOSE RT:

TIME SAVING:

ONE MINUTE of irradiation inside the operating room avoids FIVE WEEKS of external radiotherapy.

PATIENT QUALITY OF LIFE:

Drastic reduction of waiting list in radiotherapy.

By courtesy of SIT company

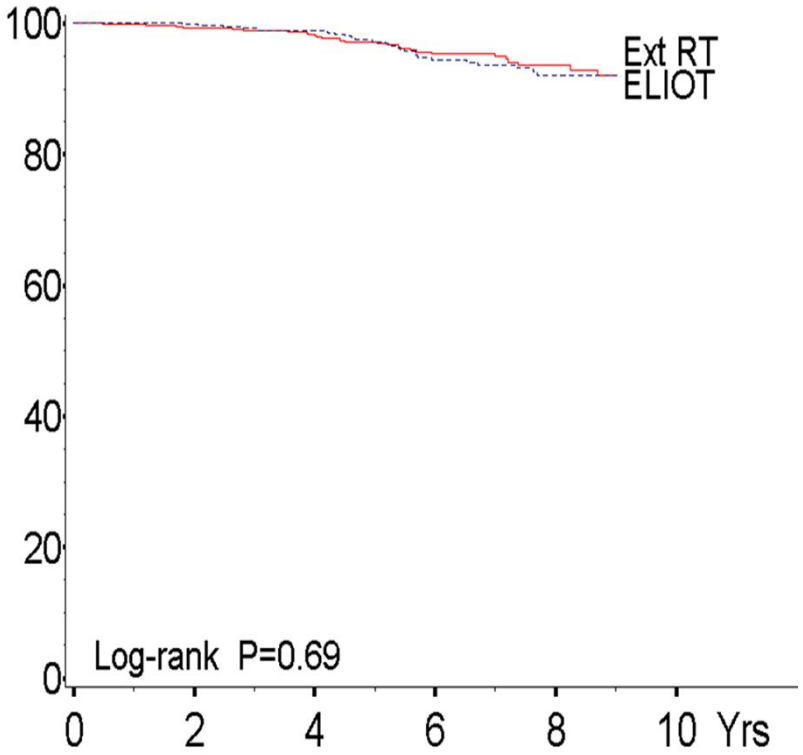
IOeRT as SINGLE DOSE: summary of ELIOT studies

Several studies compared in last years the effect of single dose IORT to the External Beam Radiotherapy for patients in Group 1

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 slightly better in ELIOT arm than EBRT arm: 96.9% vs. 96.8%.



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).

However IOERT seemed to show slightly higher percentages of recurrences than EBRT (1.5% vs 0.4%), although still 1.5% is considered an acceptable number

Courtesy of SIT

IORT BOOST RESULTS: BREAST CANCER

The second Patients Group can be treated according to **HIOB IOeRT** Boost which decreases significantly the EBRT fractions [**33 to 15**] and provide both excellent Overall Survival and Local Recurrences at 5 years

1998-2005, 1.131 patients, IOeRT boost of 9,7Gy at 90% isodose with perspex tube (5-8cm) and electron energies of mainly 6 and 8 MeV followed by WBI 50-54 Gy in single fractions of 1.7 -2 Gy.

6 Centres of ISIORT-Europe such as Salzburg (Austria), Gemelli (Rome), San Filippo Neri (Rome), IEO (Milan), Münster (Germany).
At median follow up period of 52,3 months, only 5 in breast recurrences were observed, yielding a **local tumor control rate of 99,4%.**
At 7 years the **OVERALL SURVIVAL (OS) RATE WAS 90,9%.**

In a 2008 study, the analisys of 211 premenopausal pts (46% adjuvant CT) who were given **12Gy boost + hypofractionated RT (2,85Gy x 13f)** reported Maximal acute toxicity skin toxicity 67% G1, 28% G2, 4% G3 and **0% in-breast recurrence**

Strahlentherapie und Onkologie — Supplement Article

IORT with Electrons as Boost Strategy during Breast Conserving Therapy in Limited Stage Breast Cancer: Results of an ISIORT Pooled Analysis

Felix Sedlmayer[1], Gerd Fastner[1], Florian Merz[1], Heinz Deutschmann[1], Roland Reitsamer[2], Christian Menzel[2], Antonella Ciabattoni[3], Assunta Petrucci[3], Eva Hager[4], Norman Willich[5], Roberto Orecchia[6], Vincenzo Valentini[7] on behalf of the ISIORT Europe

ELSEVIER

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0360-3016/08/$–see front matter

doi:10.1016/j.ijrobp.2007.12.038

CLINICAL INVESTIGATION — Breast

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.†

By courtesy of SIT company

Extension of the Use of ELIOT protocol

In the case of middle or low-income countries in conditions of very few RT facilities it seems obvious to think to an extension of the single dose (ELIOT) protocol to the 2nd group or even to the 3rd group

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%

The 5-year Overall Survival (OS) is in any case close to 97%

ELIOT with single dose of 21 Gy

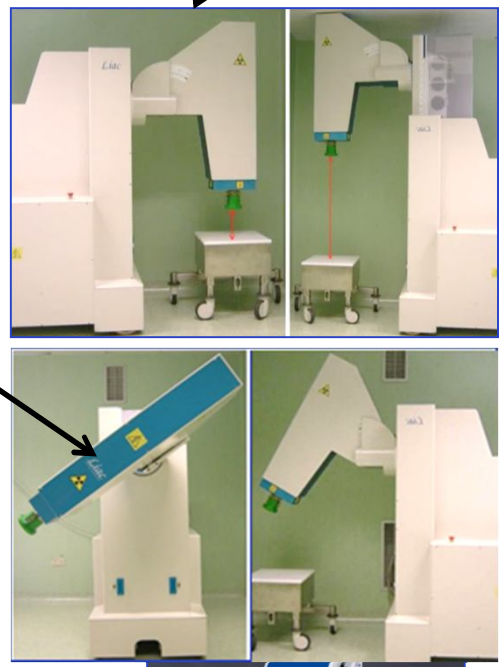
HIOB IOeRT Boost if EBRT easily available
or
Single dose 21 Gy when EBRT is unavailable or too delayed

Tolerating the increase of Local recurrencies

By courtesy of SIT company

A dedicated IOERT accelerator must fulfill simplicity criteria in order to run in surgery room

- **Maximum mobility, able to move inside standard hospital space (elevators, doors…):** LIAC mobile unit dimensions 210 x 76 x 180 cm.
- **As small and light as possible;** LIAC unit weights 400 Kg
- **Plug and play accelerator.** The impact on the OR is minimum and the total installation and training time is less than 5 days
- **Radiation head with 5 degrees of freedom** each other independent in order to perform an easy, fast and safe docking
- **Different energies up to 12 MeV**: a PTV with thickness up to 3.2 cm can be irradiated inside the 90% isodose (up to 3.8 cm inside the 80% isodose)
- **Biocompatible, sterilized and transparent applicators**, for a better treatment documentation. Applicator terminal bevel angles: 0°, 15°, 30° and 45°diameter.



Such IORT devices allow radiation therapy solutions for any Oncologic Surgical Center without requiring any specific facility, e.g. bunkers or any shielded Operating Room.

By courtesy of SIT company

LIAC and NOVAC worldwide Installations

These are the reasons for which IOERT installations are increasing also in middle-low-income countries

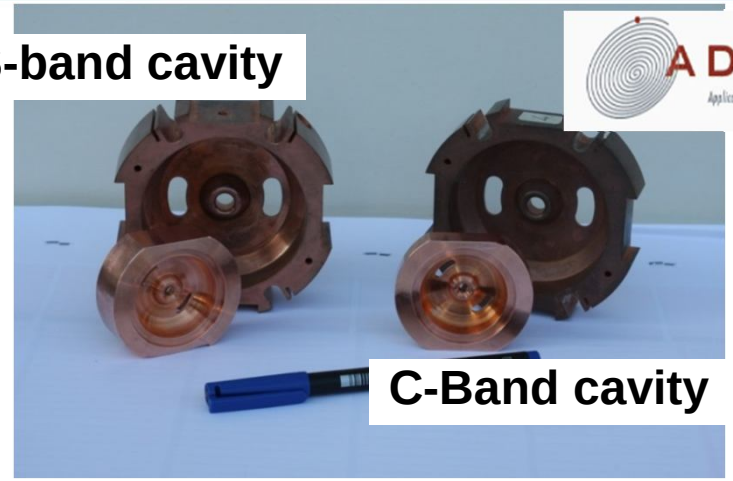
By courtesy of SIT company

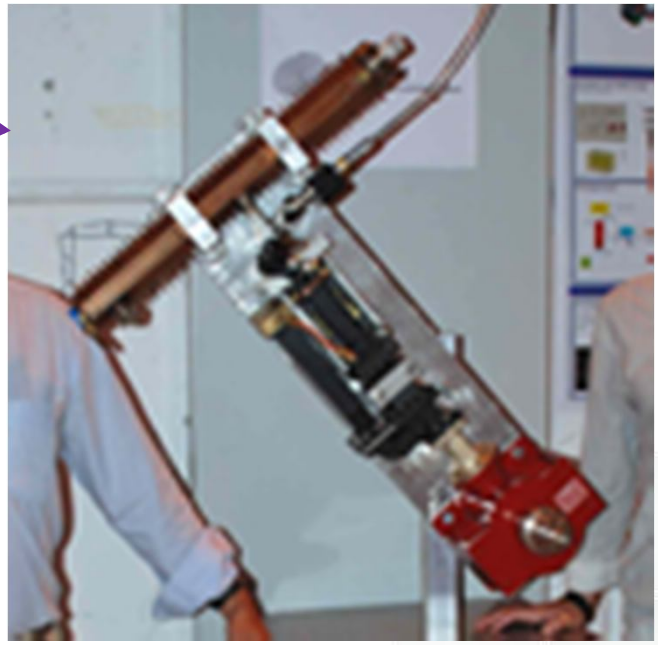
Further developments of compact accelerators

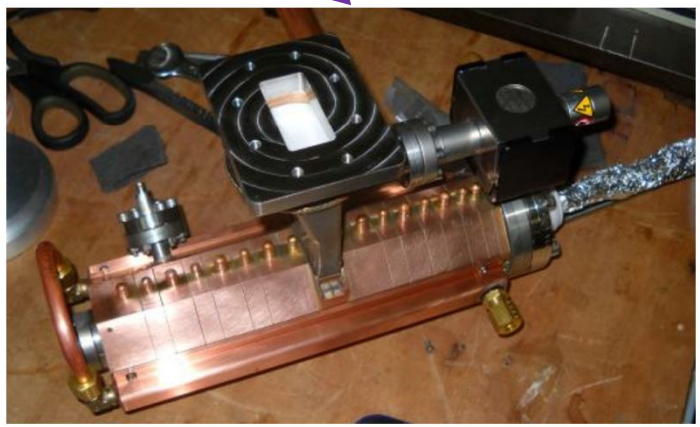
In 2010 -2012 ADAM S.A. company asked ENEA to help in the development of C-band (5712 MHz) Linacs for applications in medicine

2 accelerators were produced and successfully tested at NRT (now SIT) and at ADAM site

- A 10 MeV linac for IORT
- A 6 MeV linac for X-rays

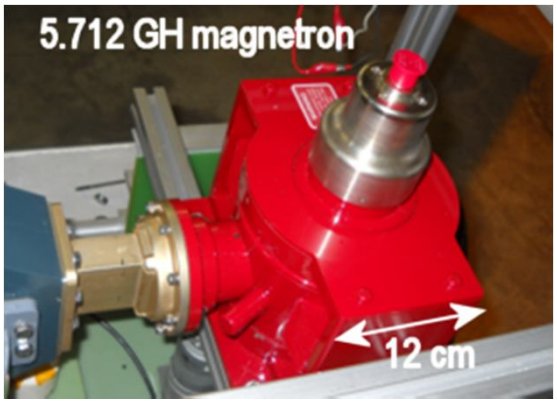






Accelerator development: from S-Band to C-band

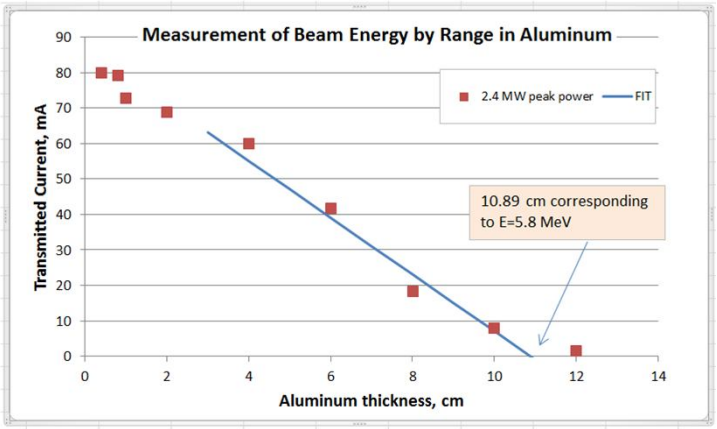
The almost double RF frequency of the accelerating structure by itself does not implies a drastic reduction in size and weight.

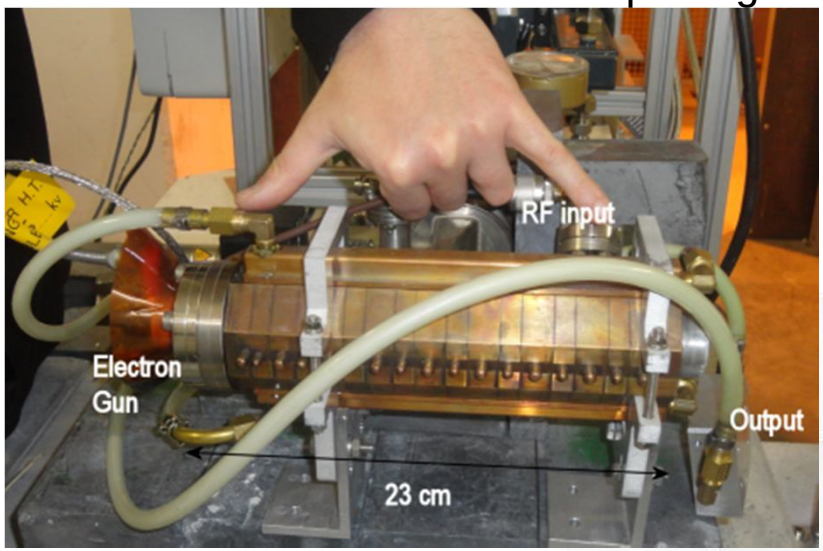


The reduction occurs only if RF power is suitably high, and therefore some companies were asked to produce some 2.5 MW peak power magnetrons

The results were two autofocusing structures

- a 10 MeV short structure for IORT (55 cm long 12 kg weight for IORT)
- a 6 MeV very short structure 23 cm long and a few kg weight for X-rays with the additional feature of inhibition of beam back-bombardment of cathode. This structure can be easily inserted in a conventional RT head sparing space and weight.





Conclusions

We have presented two simple and concrete lines of development that ENEA pursued in the last years in collaboration with small companies, that can be seen as suggestions for the topic of this workshop, in order to diffuse radiotherapy in low-income countries:

- Support and promote the use of IOERT (that is definitely growing) in countries where radiotherapy conventional devices are few or not present. The single dose treatment can carry many benefit to the patients allowing them a radio-treatment that they may even not receive at all.

- The use of C-band in the RT devices allows a strong reduction of weight and dimensions of the therapy head with no additional technical complications, turning in a reduction of the overall costs of the device itself