Catalan Institute of Oncology experience in IORT breast cancer

Evelyn Martínez Pérez, MD, PhD

Radiation Oncologist

Catalan Institute of Oncology (Barcelona)

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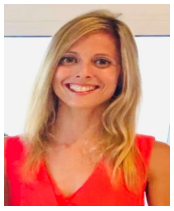
INTRODUCTION

OUR IORT TEAM







E.Martínez H.Pérez MJ.Pla A.García M.Campos P. Saldaña R.Martín

Radiation Oncologists

Gynecologists

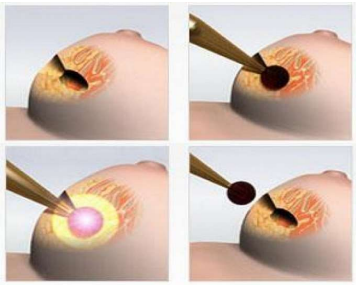
Physicists

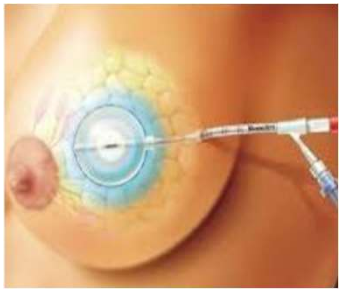

INTRODUCTION

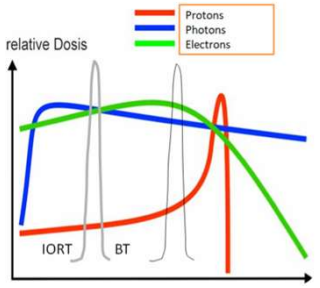
ADVANTAGES OF IORT

Radiation administration can be delivered during the same surgical procedure in a way:

- High dose in a single shot is integrated into the surgical procedure
- Precise targeting to the tumour bed (visual, tactile and ultrasound control)
- Lower doses to healthy tissues
- Less number of travels required for patients
- Quicker return to active life and Impact on quality of life
- High radiobiological effectiveness and the potential for a possible abscopal effect







Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial

Jayant S Vaidya, Frederik Wenz, Max Bulsara, Jeffrey S Tobias, David J Joseph, Mohammed Keshtgar, Henrik L Flyger, Samuele Massarut, Michael Alvarado, Christobel Saunders, Wolfgang Eiermann, Marinos Metaxas, Elena Sperk, Marc Sütterlin, Douglas Brown, Laura Esserman, Mario Roncadin, Alastair Thompson, John A Dewar, Helle M R Holtveg, Steffi Pigorsch, Mary Falzon, Eleanor Harris, April Matthews, Chris Brew-Graves, Ingrid Potyka, Tammy Corica, Norman R Williams, Michael Baum, on behalf of the TARGIT trialists' group

RESULTS 5 years

Randomly assigned in a 1:1 ratio to receive TARGIT (IORT) or whole-breast EBRT

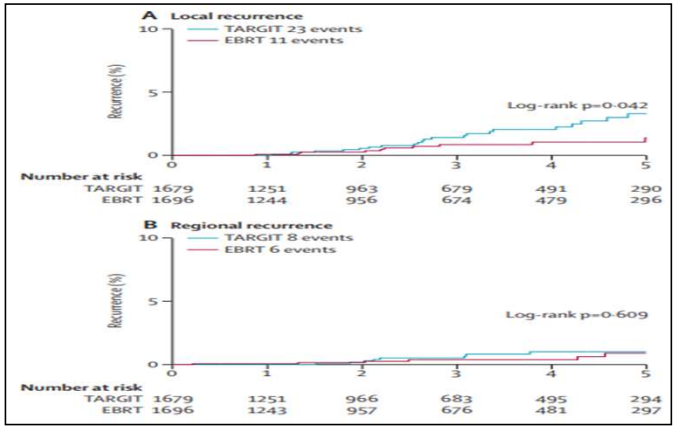
2000-2012
n=3.451 patients
median F/U: 2,5 years
Median age was 63 years
33 centers, 11 countries
X-ray low energy: 50 kV
Spherical applicator: 1.5-5 cm

Treatment was given using a risk adapted approach

1730 patients assigned to EBRT	1721 patients assigned to TARGIT
Standard fractionated EBRT in 15-25 fractions +/- Boost	TARGIT single dose (20 Gy) with INTRABEAM® (in ~85 % of the patients) +/- Post-operative EBRT if unexpected risk factors appeared following the operation

Having a grade 3 cancer, involved nodes or higher risk receptor status, did not exclude the patient from participati).

- **PRIMARY END POINT:** Local recurrence (LR)
- **SECONDARY END POINT:** Complications and mortality



The 5-year risk for local recurrence (LR)
3.3% for TARGIT versus **1.3% for EBRT (p=0.042)**

- **LR in TARGIT concurrently** (prepathology n=2298)
  - 2.1% TARGIT vs 1.1% EBRT (p=0.31)
- **LR in Delayed TARGIT** (postpathology n=1153)
  - 5,4 TARGIT *vs* EBRT 1.7% (p=0.069)

The between-group difference was larger than 2.5%

Vaidya JS. et al. Lancet 2014

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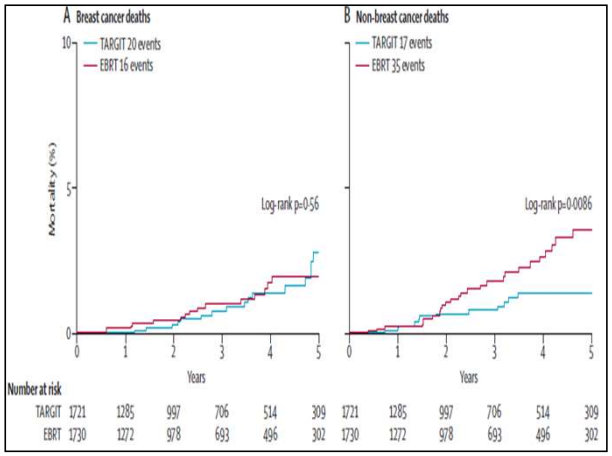
RESULTS 5 years



	TARGIT	EBRT
Other cancers	8	16
Cardiovascular causes		
Cardiac*	2	8
Stroke	0	2
Ischaemic bowel	0	1
Other†	7	8
Total	17	35

5-year risk 1·4% for TARGIT versus 3·5% for EBRT; log-rank p=0·0086. TARGIT=targeted intraoperative radiotherapy. EBRT=external beam radiotherapy. *Included one "sudden death at home" in EBRT group. †TARGIT: two diabetes, one renal failure, one liver failure, one sepsis, one Alzheimer's disease, one unknown; EBRT: one myelopathy, one perforated bowel, one pneumonia, one old age, four unknown.

Table 2: **Causes of death other than breast cancer in all patients**

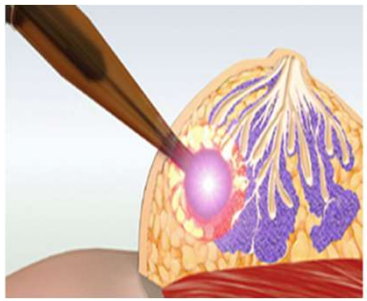
- There were significantly fewer **non-breast-cancer deaths** with TARGIT 1.4% *vs* 3.5% EBRT (p=0.0086)
    - attributable to fewer deaths from cardiovascular causes and other cancers.
- **Overall mortality** was 3.9% for TARGIT versus 5.3% for EBRT (p=0.099)
- **Breast cancer mortality** was much the same between groups 2.6% for TARGIT *vs* 1.9% for EBRT (p=0.56)

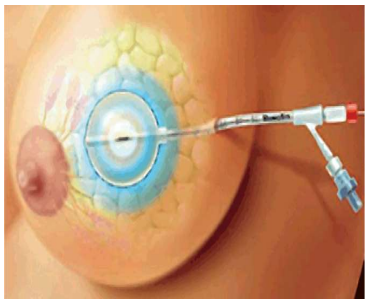
Vaidya JS. et al. Lancet 2014

INTRODUCTION

THERAPY OPTIONS WITH IORT (50 kV)

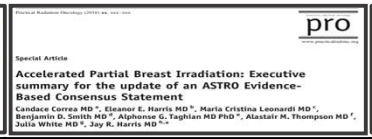
- IORT as APBI (TARGIT-A Trial)
- IORT as a BOOST (TARGIT-B or TARGIT H trial)
- IORT for patients where EBRT it isn‘t an option





INTRODUCTION

APBI GUIDELINES



RISK FACTORS	ASTRO update	GEC-ESTRO update	ABS update
Age (years)	≥50	>50	≥45
Tumour Size	**≤3 cm IDC** and ≤2.5 cm DCIS	**≤3 cm**	**≤3 cm**
Margins	**Negative** (≥2 mm) for IDC and DCIS (≥3 mm)	**Negative**: ≥2 mm	**Negative** (IDC no ink margin and DCIS ≥2 mm)
Grade	Any	Any	-
Linfovascular invasion	**No**	**No**	No
Multicentricity	**Unicentric**	**Unicentric**	-
Multifocality	**Unifocal**	**Unifocal**	-
Histology	All invasive subtypes and DCIS	IDC (and other favorable invasive subtypes)	All invasive subtypes and CDIS
CDIS pure	Only: G1-G2, ≤ 2.5 cm, negative margins (≥ 3 mm).	Not allowed	Allowed
EIC (>25%)	**No**	**No**	**No**
Nodal status	**Negative**	**Negative**	**Negative**
ER status	ER + or ER -	ER + or ER -	ER + or ER -
Axillary evaluation	**SNB or AD**	**SNB or AD**	**SNB or AD**
Neoadjuvant chemotherapy	**Not allowed**	**Not allowed**	-

Correa C et al. Pract Radiat Oncol 2017
Kirby AM et al. Br J Radiol 2018

Polgár C et al. Radiother Oncol (2009)
Strnad V et al. Lancet 2016

Shah C et al. Brachytherapy 2018

INTRODUCTION

SELECTION CRITERIA FOR EXCLUSIVE IORT

- ≥ 60 years
- Conservative surgery or oncoplastic surgery
- Unifocal and unicentric
- Tumor ≤25 mm
- IDC or favourable histologies (not IDCS)
- Histologic grade 1 or 2
- No extensive intraductal component
- Positive hormonal receptors
- No BRCA 1-2 mutation
- No vascular invasion
- Negative margins (≥2 mm)
- No lymph node involvement
- No neoadyuvant therapy
- Tumor at ≥1 cm from skin

INTRODUCTION

17th Desember 2014 – 23th October 2024

284 Patients (285 Treatments)

- **INTRABEAM® Since 17th Desember 2014 (n=237 patients/ 238 treatments)**

Clinical Trials (95 pts)

- IORT Breast cancer or Targit H (Phase II trial)
- Targit B (Phase III trial)

- **XOFT/ELEKTA® Since 20th November 2019 (n=47 patients/treatments)**

All our patients are been treated using 50 Kv photon energy.

CLINICAL TRIALS

- **Targit H or IORT Breast Cancer (Phase II trial)** (Since August 2016) **50 patients**
  - Last recruitment 16-9-2024

Cosmetic outcomes following conservative surgery (with or without oncoplastic surgery) for breast cancer with intraoperative radiotherapy (INTRABEAM) followed with hypofractionated external beam radiotherapy: a phase II trial.

S.EP: Quality of life; Toxicity (acute and late); Local control AND Overall and cancer-specific survival.

- **Targit B (Phase III trial)** since June 2019

45 patients: 2 screening failure
43 patients: **22p Targit & 21 EBRT**

TARGIT BOOST

  - Last recruitment 1/8/2022.
  - A posterior recruitment 16th Sept 2022 but not randomized for global problems of the study (screening failure)

TARGeted Intraoperative radioTherapy Boost vs Postoperative External Beam Radiotherapy boost

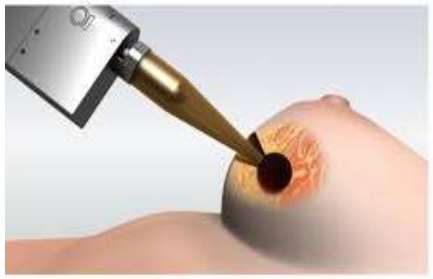
P.EP: Ipsilateral breast recurrence rate

S.EP: Relapse-free survival; Site of recurrence; Overall survival (breast-cancer specific and non-breast cancer death); Quality of life: TOI score (physical and functional well-being) and fact-b+4 (global quality of life and social-emotional-functional and physical well-being); Cost-effectiveness

MATERIAL AND METHODS

- From Desember 2014 to September 2023
- Women with invasive carcinoma
- Conservative surgery
- IORT delivered immediately after lumpectomy
- All patients were suitable to receive at the surgical act a single fraction of 20 Gy (50 KV)

INTRABEAM®



XOFT/ELEKTA®

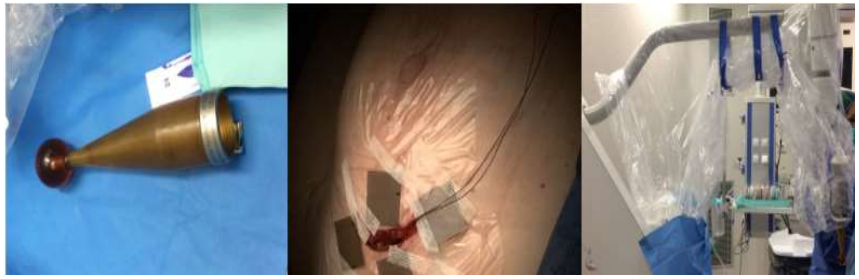
266 Patients (267 Treatments) :

- Exclusive IORT 100 patients (38%)
- IORT + EBRT: 166 patients (167 treatments) (62%) –> 56% in a clinical trial

MATERIAL AND METHODS

TREATMENT CHARACTERISTICS (IORT)

A single dose 20 Gy (50 Kv) was delivered to the surphace of the applicator using the INTRABEAM® or XOFT/ELEKTA® system



Intrabeam Floor Stand

MATERIAL AND METHODS

TREATMENT CHARACTERISTICS (EBRT)

- Post-surgically, if the definitive pathological report shows us some unfavorable characteristics that require the whole breast irradiation (WBI) it will be administered:
  - **50 Gy/ 40,05 Gy delivered in 25/15 frac of 2 or 2,67 Gy/day**
- Patients suitable to participate in the Phase II trial IORT BREAST CANCER (**Targit H**) or in the Phase III trial **Targit B** received EBRT.
  - **40.05 Gy delivered in 15 fractions of 2.67 Gy/day**
- Adjuvant systemic therapy, if deemed necessary, was administered in accordance with the protocols established at the treating center.

MATERIAL AND METHODS

EXCLUSIVE IORT

- From 21th Jan 2015 to 13th Sept 2023
- **100 patients**
- Single dose: 20 Gy (50 Kv)
- **100% tumors stage I**
- Median follow up: 52 months; Mean follow up: 46 months
- Median age: 69 years; Mean age: 69 years (range: 50 – 91 years)

N= 76 pts

N= 24 pts

MATERIAL AND METHODS

IORT + EBRT

- From 17th Des 2014 to 27th Sept 2023
- **166 patients (167 treatments)**
- IORT (20Gy/50Kv) followed by EBRT
- **Early stage tumors and tumors with high risk factors (Targit B/Targit H)**
- Median follow up: 60 months; Mean follow up: 55 months
- Median age: 62 years; Mean age: 60 years (range: 39-86 years)

N= 149 pts (150 tts)

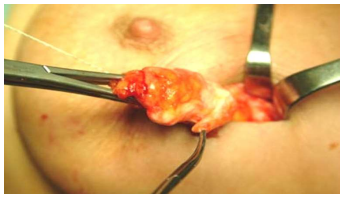
N= 16 pts

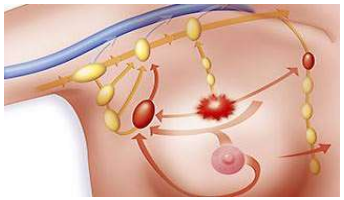
RESULTS

TREATMENT CHARACTERISTICS

EXCLUSIVE IORT

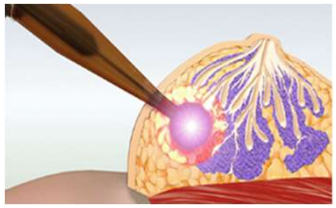
100 patients

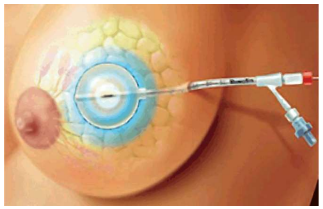




SURGERY CHARACTERISTICS	N (%)
Breast surgery	
Conservative surgery	100 (100%)
Axillary surgery	
SLNB	84 (84%)
No axillary approach	16 (16%)

RADIOTHERAPY	N (%)
Exclusive IORT (20Gy;50 Kv)	100 (100%)
Adjuvant EBRT	0 (0%)





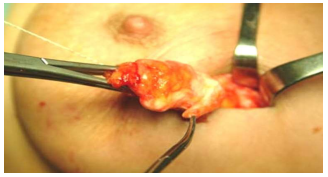
RESULTS

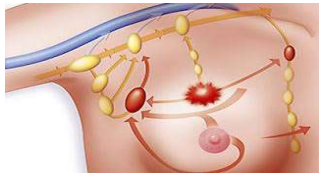
IORT + EBRT

166 patients

TREATMENT CHARACTERISTICS

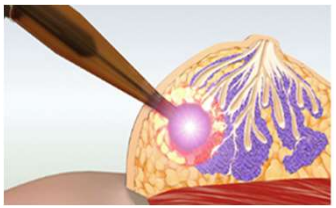
SURGERY:

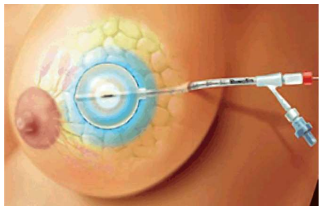




- ALL Conservative /oncoplastic surgery
- +/- SLNB or ALND

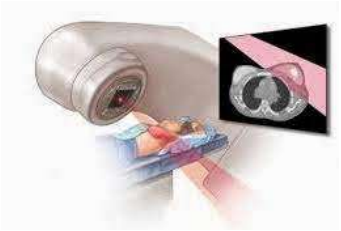
IORT





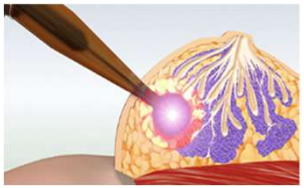
- Single dose 20 Gy (50 Kv): 100%
- Immediately after lumpectomy

EBRT



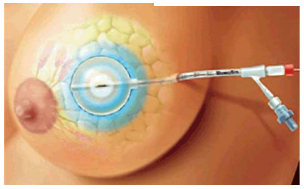
- **Schedules of EBRT:**
  - 50 Gy 2Gy/ses (34,7%) or 40,05Gy a 2,67Gy/ses (63,5%) (164 pts; 98,8%)
    - WBI + RNI in 15/164 patients: 9% (12 pts 50 Gy and 2 pts 40.05)
  - 50,04 1,8Gy (Rheumatoid arthritis; bilateral pneum. sec. CTH;) (1 pt)
  - 31,25 Gy 6,25 Gy/ses (1 pt)
  - 46 Gy 2 Gy/ses (1pt treated in another center with WBI + RNI)

RESULTS



EXCLUSIVE IORT

100 patients



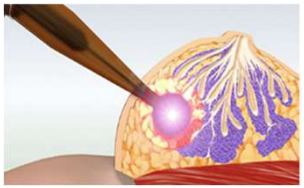
Irradiation time	minutes
Min	11,05
Max	29,59
Mean	22,03

Aplicator (cm)	N (%)
2	1 (1,45%)
2,5	2 (2,90%)
3	17 (24,64%)
3.5	35 (50,72%)
4	14 (20,29%)
Distance (aplicator-skin)	**mm**
Min	8
Max	38
Mean	14,81

Irradiation time	minutes
Min	7,9
Max	15,3
Mean	11,14

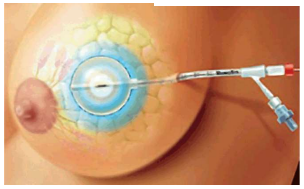
Aplicator (cm)	N (%)
3-4	12 (50%)
4-5	11 (45,83%)
5-6	1(4,17%)
Distance (aplicator-skin)	**mm**
Min	15
Max	20
Mean	12,02
Volume SF	**cc**
Min	30
Max	65
Mean	43,75

RESULTS



IORT + EBRT

167 treatments (166 patients)



Irradiation time	minutes
Min	10,10
Max	39,51
Mean	22,58

Aplicator (cm)	N (%)
2	-
2,5	8 (5%)
3	23 (14,5%)
3.5	86 (54,1%)
4	35 (22%)
4,5	7 (4,40%)
Distance (aplicator-skin)	**mm**
Min	5
Max	40
Mean	15,49

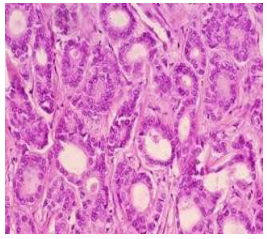
Irradiation time	minutes
Min	8
Max	14
Mean	11

Aplicator (cm)	N (%)
3-4	7 (44%)
4-5	9 (56%)
5-6	-
Distancia (aplicator-skin)	**mm**
Min	10
Max	20
Mean	14,68
Volume SF	**cc**
Min	30
Max	50
Mean	42,5

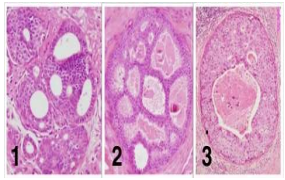
RESULTS

TUMOUR CHARACTERISTICS

Histology	IORT N (%)	IORT +EBRT (N%)
Infiltrating ductal carcinoma	**86 (6%)**	**129 (77,7%)**
Infiltrating lobular carcinoma	0	13 (7,8%)
Infiltrating Ductal and lobular	0	1 (0,6%)
Others	12 (12%)	23 (13,9%)



Pathological tumor size	IORT N (%)	IORT +EBRT (N%)
≤ 1.0 cm	**52 (52%)**	**51 (31%)**
> 1.0 cm – 1.5 cm	**28 (28%)**	**55 (33%)**
> 1.5 cm – 2.0 cm	13 (13%)	34 (20%)
> 2 cm	7 (7%)	26 (16%)

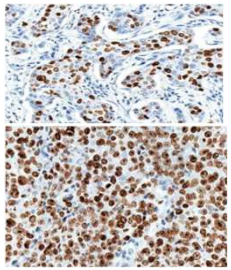


Histologic Grade	IORT N (%)	IORT +EBRT (N%)
1	**52 (52%)**	**47 (28,31%)**
2	**42 (42%)**	**93 (56,02%)**
3	5(5%)	22 (13,25%)
Ungradable	1 (1%)	4 (2,41%)

EIDC	IORT N (%)	IORT +EBRT (N%)
Yes	4 (4%)	**139 (84%)**
No	**96 (96%)**	27 (16%)

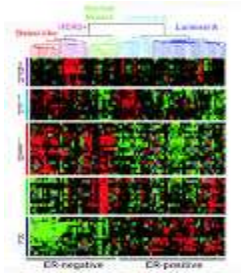
EIDC: extensive intraductal component

TUMOUR CHARACTERISTICS



Proliferative index (Ki 67)	IORT N (%)	IORT +EBRT N (%)
<14%	**58 (58%)**	**62 (37%)**
14-20%	**21 (21%)**	**45 (27%)**
>20%	21 (21%)	59 (36%)

ER	IORT N (%)	IORT +EBRT N (%)	PR	IORT N (%)	IORT +EBRT N (%)
positive	**98 (98%)**	**157 (95%)**	**positive**	**90 (90%)**	**137 (83%)**
negative	2 (2%)	9 (5%)	negative	10 (10%)	29 (17%)

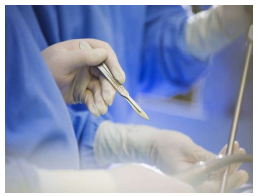


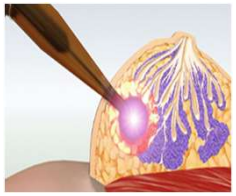
Her 2 status	IORT	IORT +EBRT
negative	**91 (97%)**	**164 (99%)**
positive	3 (3%)	2 (1%)

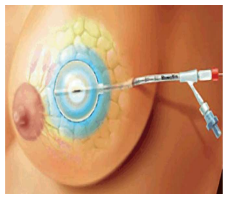
RESULTS

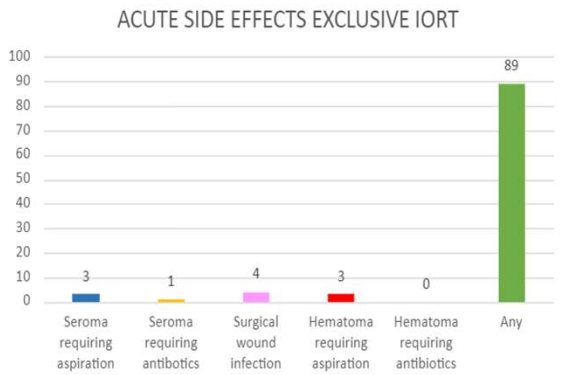
ACUTE SIDE EFFECTS

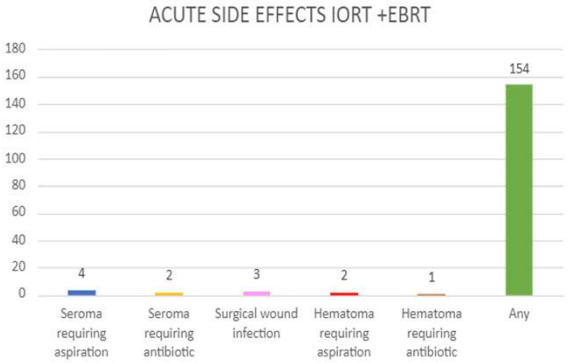
Side effects (AE)	EXCLUSIVE IORT (n=100)	IORT + EBRT (n=166)
Seroma requiring aspiration	3 (3 %)	4 (2,4 %)
Seroma requiring antibotics	1 (1 %)	2 (1,2 %)
Surgical wound infection	4 (4 %)	3 (1,8 %)
Hematoma requiring aspiration	3 (3 %)	2 (1,2 %)
Hematoma requiring antibiotics	0(0 %)	1 (0,6 %)
Any complication	88 (88 %)	154 (93 %)







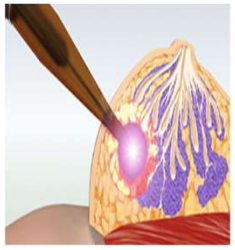


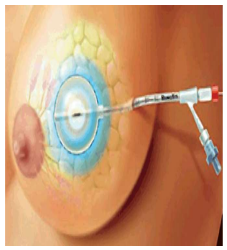


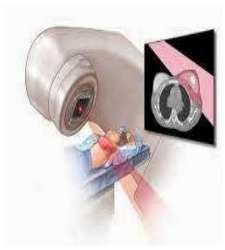
RESULTS

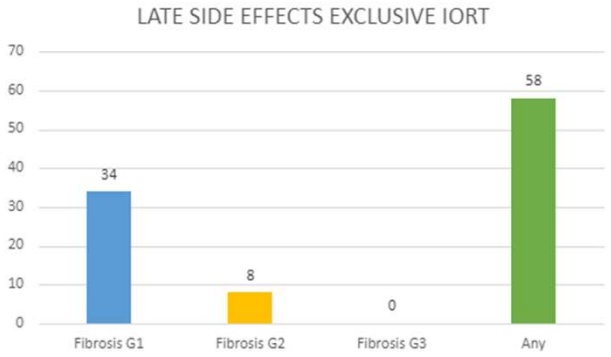
LATE SIDE EFFECTS

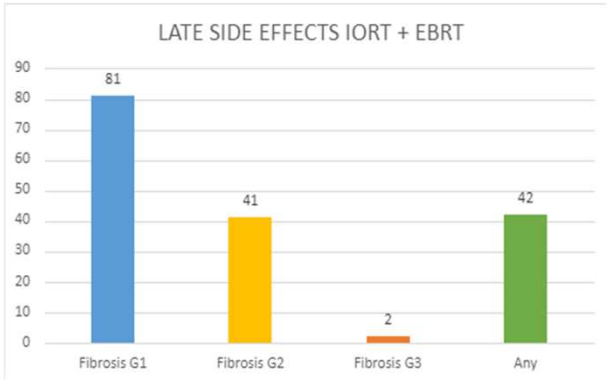
Side effects (AE)	IORT (n=100)	IORT + EBRT (n=166)
Fibrosis G1	34 (34 %)	81 (49 %)
Fibrosis G2	8 (8 %)	41 (24,7 %)
Fibrosis G3	0	2 (1%)
Any	58 (58 %)	42 (25,3 %)











RESULTS

EXCLUSIVE IORT

21 th Jan 2015 - 13th Sept 2023

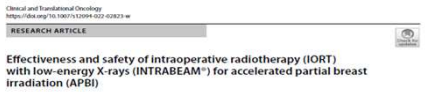
Median follow up: 52 months

Status	Total (n=100)
Local relapse	2 (2%) In the same quadrant
Distant metastasis	2 (2%)
Deaths	2 (2% breast ca.) 13 (13% global)

- 70 months after Surgery + IORT
- 43 months after Surgery + IORT (died 3 years later)

- Femoral met (Thyroid carcinoma)
- Femoral met at 44m and Hepatic met (Breast) died at 83m

- *2 patients died due to Breast cancer*
- 3 patients died due to other tumors
- 8 patients died due to non-oncological causes

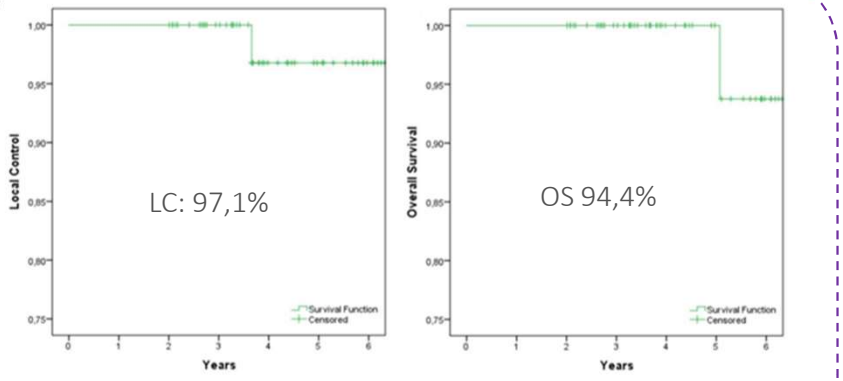

RESEARCH ARTICLE

Effectiveness and safety of intraoperative radiotherapy (IORT) with low-energy X-rays (INTRABEAM®) for accelerated partial breast irradiation (APBI)

59 patients (21th Jan 2015- 16th Sept 2021)

Status	Total (n=59)
Local relapse	2 (3,3%)
Distant metastasis	2 (3,3%)
Deaths	6 (10,16%)

- 5 patients died due to non breast cancer
- 1 patient died due to breast cancer



Kaplan-Meier survival curve depicting 5 year

RESULTS

EXCLUSIVE IORT

21 th Jan 2015 - 13th Sept 2023

Median follow up: 52 months

Status	Total (n=100)
Local relapse	**2 (2%)** In the same quadrant
Distant metastasis	**2 (2%)**
Deaths	**2 (2% breast ca.)** 13 (13% global)

- 70 months after Surgery + IORT
- 43 months after Surgery + IORT (death 3 years later)

- Femoral met (Thyroid carcinoma)
- Femoral met at 44m and Hepatic met (Breast) death at 83m

- *2 patients died due to Breast cancer*
- 3 patients died due to other tumors
- 8 patients died due to non-oncological cause

IORT + EBRT

14th Des 2014 – 27th Sep 2023

Median follow up: 60 months

Status	Total (n=166)
Local relapse	**0** 1 pt (0,6%) a 2nd primary tumour in a diff. quadrant
Distant metastasis	**2 (1,2%)**
Deaths	**1 (0,6% breast ca.)** 6 (3,6% global)

- 62 months after Surgery + IORT (a second primary tumour)

- 1 : Pulmonar metastasis (5 years after treatm and death)
- 1 : OligoMet at the diagnosis (bone mets)

- *1 patient died due to breast cancer (pulmonar mets)*
- 4 patients died due to other tumors
- 1 patient died due to non-oncological cause (AVB)

RESULTS

GLOBAL RESULTS

14 th Des 2014 - 23th Sept 2023

Status	Total (n=266 patients)
Local recurrence	**2 (0,75%)** 2 patients : at 43m and 70m (exclusive IORT) 1 patient: at 62m (IORT + EBRT) second primary tumour in a different quadrant)
Distant metastasis	**3 (1,1%) due to breast cancer** 4 (1,5%) breast ca. & other tumors
Deaths	**3 (1,1%) pts died due to breast cancer** 19 (7,1%) breast ca. & others causes

243 patients alive without disease (91% patients)

CONCLUSIONS

- In our serie we have observed:
  - A low rate of acute adverse effects related to treatments with a few rate of surgical wound infections or hematoma/seroma requiring medical intervention.
  - Fibrosis was not observed in 83.3% of the patients (58% IORT vs 25,3% IORT +EBRT).
  - The most common late side effect was:
    - Fibrosis grade 1 in the 83% of patients (34% IORT and 49% IORT+EBRT)
    - Low rate of fibrosis G2 (8% IORT and 24% IORT+EBRT) and fibrosis G3 (0% IORT and 0.6% IORT +EBRT)
  - The Local Recurrence rate was similar with that reported in the literature.
    - Our results (ICO): 2% IORT (2 at the same quadrant) and 1 secondary tumour in a different quadrant IORT + EBRT (0%)
      - Global LR : 0.75%
    - TARGIT-A : 2,11% IORT and 0,95% IORT+ EBRT
  - The 91% of our patients were alive and free of disease at the moment of the analysis.
  - IORT is a feasible and effective option in very well-selected cases and our results are consistent with those reported in the literature.

Evelyn Martínez Pérez
emperez@iconcologia.net