Journal of Plastic Surgery

Research Article
Published: 28 Feb, 2022

IOERT in Breast Cancer: Results of Ten-Year Follow-Up in an Italian Experience Confirm High Local Recurrence Rate

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Abstract

Purpose: Accelerated Partial Breast Irradiation (APBI) using Electron-Beam Intraoperative Radiation Therapy (IOERT) in carefully selected breast cancer patients is usually performed as single dose after conserving surgery. IOERT has demonstrated a low incidence of complications without compromising oncological outcomes. In our study we evaluated the rate of LR and progression free survival in a long-term follow-up.

Patients and Methods: We performed IOERT with a 21 Gy single total dose referred to iso dose 90% in 322 selected patients for a total of 332 irradiated tumor lesions at the Breast Center of Pisa between January 2004 and May 2015. A close multidisciplinary follow-up was regularly conducted every 6 months. We evaluated the data at the end of 2020.

Results: At a median follow-up of 10 years, 27 patients had in-field breast recurrence (8.1%) while considering a 5-year follow-up, we observed 16 LR (4.8%). According to our data, although a 5-year follow-up demonstrates an acceptable relapse rate in patients treated with IOERT, the assessed LR rate over a longer follow-up period reveals the occurrence of a significant number of relapses. Our results are consistent with the more important ones revealed by randomized trials.

Conclusion: IOERT remains an acceptable approach to be considered only in carefully selected patients at particularly low risk of relapse (small, well-differentiated, luminal-A tumors, with a low Mib-1) even though the LR rate in a longer follow-up is significantly higher than standard RT.

Keywords: APBI, Intraoperative electron beam; RT; IOERT; Local relapses; Long-term follow-up

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Received Date: *10 Jan 2022*
Accepted Date: *08 Feb 2022*
Published Date: *28 Feb 2022*

Citation:
Ghilli M, Fatigante L, Gonnelli A, Mariniello MD, Spagnesi S, Molinari A, et al. IOERT in Breast Cancer: Results of Ten-Year Follow-Up in an Italian Experience Confirm High Local Recurrence Rate. J Plast Surg. 2022; 2(1): 1008.

Introduction

Breast Conserving Surgery (BCS) followed by Radiotherapy (RT) is a valuable treatment for stage I-II invasive carcinoma, able to give the highest contribution in local control. Postoperative RT significantly reduces Local Recurrences (LR) and could be substantially translated into increased survival [1,2].

Pathological analyses revealed that most of the tumor cell density is observed in a 4 cm area around the macroscopic lump or, rather, that the surrounding region has the highest probability of in-breast recurrence [3,4]. Once BCS has been chosen, excision is commonly followed by 3 to 5 weeks of Whole Breast Irradiation (WBI), with a concomitant or sequential boost to the tumor bed, which significantly reduces LR [5].

Despite the proven benefits of adjuvant RT, women sometimes receive incomplete treatment, with no post-operative breast irradiation after lumpectomy [6,7]. Advanced age and distance from RT facilities are identified as the main determinants of RT omission, suggesting that optimization of the therapeutic process could improve disease control [8-11].

These topics have aroused an interest in Accelerated Partial Breast Irradiation (APBI), which can reduce treatment time without compromising survival [10,12,13].

Different APBI techniques have been emerging since the early 2000s and comparing with WBI in randomized, controlled trials, including Intraoperative RT with electrons (IOERT) for early-stage breast cancer. This procedure that is usually performed as single dose at the time of surgery was developed in 1999 by the IEO-Milan (ELIOT trial), ensures an integrated treatment during surgery, with a low incidence of complications [14-16].

In 2009 the American Society for Radiation Oncology (ASTRO) published consensus panel guidelines, partially updated in 2016, on the use of APBI, with patients stratified according to various parameters [17]. Consensus statements were also made available by the Groupe Europeen de Curietherapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) [18]. Both statements identified three categories of patients: "Suitable/ good candidates", "cautionary/possible candidates", "unsuitable/ contraindication candidates" respectively [12,18].

The ELIOT trial demonstrated a high rate of relapse in the IOERT group at 5 [19] and 10 [16] years of follow-up when compared to WBI. According to these results, clinical evidence remains insufficient to consider IOERT as a gold standard treatment in early-stage breast cancer; the indications to IOERT must be discussed in the multidisciplinary group and be limited to accurately selected patients.

The aim of our study was to evaluate, in a real world context, the efficacy of IOERT in a long term follow-up and consequently the primary endpoint was the in-field LR rate (IBTR). The secondary endpoint was the Progression Free Survival (PFS).

Methods

From January 2004 to May 2015 BCS associated with IOERT was used to treat 332 breast cancers, 322 of which underwent monolateral IOERT, while 10 procedures were bilateral. We obtained informed consent from all the patients included in a not-randomized prospective trial (n. 1640/06092003) approved by the local Ethics Committee. At the beginning of our experience, when the scientific knowledge on IOERT was limited, and before the publication of the ASTRO/ESTRO statements, patient selection was based on post-menopausal status and <2 cm unifocal ductal infiltrating carcinoma; tumor biology wasn't considered mandatory and in some cases the diagnosis was exceptionally based only on cytology performed on screen detected tumors. After 2009, recruitment took place strictly following the guidelines. Moreover 96% of patients underwent MRI before surgery and IOERT to exclude multifocality. All lumpectomies revealed negative margins at intraoperative evaluation: indeed, in case of close or positive margins identified at intraoperative pathology consultation, patients were submitted to IOERT as a boost (10 Gy) and were excluded from the population of this experience. Three patients for whom the definitive histology showed some foci of DCIS on the surgical margins were also excluded from this study and submitted to a more frequent follow-up.

Surgical and technical procedures in IOERT were carried out as follows: breast tissue was mobilized after surgical excision; a shield in Perspex (1.5 cm to 2 cm thickness) was used to protect the chest wall and the underlying structures; the breast tissue to be irradiated was re-approximated over the shield, and electron beam energy was selected according to breast thickness. An appropriately sized collimator was chosen on the basis of tumor diameter and breast volume; total dose of 21 Gy RT referred to 90% isodose was delivered by mobile linear accelerator (Novac7®); electron energy ranged from 5 to 9 MeV; collimator's range was 5 cm to 8 cm.

A multidisciplinary regular follow-up (every 6 months) of all patients was conducted by radiotherapists, radiologists, oncologists and surgeons.

Statistical analysis

Categorical data were described by frequency and percentage, continuous data by mean and range. The chi-square test was used to compare qualitative variables with low/intermediate and high risk ESTRO groups and variables with suitable, cautionary, unsuitable ASTRO groups. Assessment of the quantitative variables of the ESTRO and ASTRO groups was made using a t-test for independent two-tailed samples and for one-way ANOVA followed by multiple comparisons with the Bonferroni method, respectively.

Survival analysis

Recruitment of the follow-up data was closed on December 31st, 2020. The endpoints evaluated included IBTR, defined as a recurrence within 2 cm from the surgical clips placed on the original tumor bed and PFS. Ten variables were considered in survival analysis: Patient age, tumor size, tumor grading, axillary nodal staging, ER/ PgR status, HER2 status, Mib-1, tumor unifocality, histotype, Extensive Intraductal Component (EIC). The survival curves were calculated using the Kaplan-Meier method and the differences between curves were assessed by means of the log-rank test. All the variables influencing survival in the univariate analysis ($p<0.01$) were analyzed together in a Cox regression model as multivariate analysis, to study the independent contribution of each variable to explain survivorship. The results of the Cox univariate and multivariate models were expressed using both hazard ratios with their related confidence interval and related p-values. Differences were considered significant at $p<0.05$. All analyses were performed by using SPSS v.26 technology.

Results

Median patient age at treatment was 67 (range 48 to 88), with median tumor size of 0.99 cm (range 0.3 to 2.3). Twenty-nine tumors were G1 (8.8%), 191 G2 (57.3%) and 112 G3 (33.9%). All patients were clinically/radiologically N0, while 39 (11.7%) resulted N positive at the final histology. Fourteen women received no adjuvant therapies, 7 received only chemotherapy, 270 only hormonal treatments, 31 patients both treatments. The demographic and pathological characteristics of the patients are detailed in Table 1.

Following the ASTRO criteria, our 332 cases can be classified as follows: 219 "suitable", 74 "cautionary", and 39 "unsuitable" (Table 2).

According to the ESTRO, 271 patients can be considered at "low risk", 50 at "intermediate risk" and 11 at "high risk" (Table 3).

Table 1: Demographic and clinical characteristics of the population and pathological status.

Characteristics	Statistics (332 tumor lesion)
Age	67 (8); 48-88
Tumour size	0.99 (0.4); 0.3-2.3
Tumour grade	
G1	29 (8.8)
G2	191 (57.3)
G3	112 (33.9)
pN	
Neg	290 (88.3)
Pos	39 (11.7)
Missing values	3
ER/PgR (at the final histology)	
Pos/Pos	261 (78.6)
Pos/Neg	53 (16)
Neg/Pos	2 (0.6)
Neg/Neg	16 (4.8)
Mib1(at the final histology)	
<20%	267 (80.1)
21-30%	27 (8.1)
31-60%	33 (9.9)
>60%	5 (1.5)
Status HER2	
Positive	33 (10)
Negative	299 (90)
Unifocal cancer (at the final histology)	
No	7 (2.1)
Yes	325 (97.9)
Histotype(at the final histology)	
IDC	295 (88.9)
DCIS	6 (1.8)
ILC	12 (3.6)
Other	19 (5.7)
EIC (at the final histology)	
Absence	325 (97.9)
Presence	7 (2.1)
Adjuvant treatments (322 patients)	
Chemotherapy alone	7
hormonal treatment alone	270
both	31
none	14

Statistics: Mean: (sd) and range or frequency %; G: Tumour Grade; pN: Lymph Nodes Status; ER: Estrogen Receptors; PgR: Progesteron Receptors; Mib1: Proliferation Index; HER2: Human Epidermal Growth Factor Receptor 2; IDC: Invasive Ductal Carcinoma; DCIS: Ductal Carcinoma *in situ*; ILC: Invasive Lobular Carcinoma; EIC: Extended Intraductal Component

Median time to recurrence was 55 months (range 14 to 161); with a median 10-year follow-up, 27 out of 332 tumors (8.1%) recurred in the same area previously treated by IOERT (IBTR); considering a 5-year follow-up, we observed 16 LR (4.8%). During our long follow-up, we didn't observe any outfield recurrence. During follow-up a total of 37 patients died from any cause, and 10 of these for tumor progression.

Table 2: Demographic and clinical characteristics patients/lesions, according to ASTRO criteria.

Characteristics	Suitable (219)	Cautionary (74)	Unsuitable (39)	p-value
Age	69 (SD7)	61 (8)	67 (9)	°<0.0001*
Tumor size	0.97 (0.39)	0.92 (0.39)	1.17 (0.43)	°°0.003*
Tumor grade				0.007*
G1	19	8	2	
G2	138	40	12	
G3	62	26	25	
N				<0.0001*
Neg	219	74	0	
Pos	0	0	39	
ER/PRG				<0.0001*
Neg/Neg	0	15	1	
Other	219	59	38	
Mib1				0.001*
<20%	189	52	25	
21-30%	12	8	7	
31-60%	17	11	6	
>60%	1	3	1	
Unifocal cancer				0.211
No	2	4	1	
Yes	217	70	38	
Histotype				0.005*
IDC	199	58	38	
No IDC	20	16	1	
EIC				0.002*
Absence	219	69	37	
Presence	0	5	2	

Statistics: Mean: (sd) or frequency; °Suitable *vs.* Cautionary: p<0.0001; Cautionary *vs.* Unsuitable: p<0.0001 (Bonferroni method); °°Suitable *vs.* Cautionary: p=0.006; Cautionary *vs.* Unsuitable: p=0.003 (Bonferroni method). *: Statically significant data; G: Tumour Grade; pN: Lymph Nodes Status; ER: Estrogen Receptors; PgR: Progesteron Receptors; Mib1: Proliferation Index; HER2: Human Epidermal Growth Factor Receptor 2; IDC: Invasive Ductal Carcinoma; DCIS: Ductal Carcinoma *In Situ*; ILC: Invasive Lobular Carcinoma; EIC: Extended Intraductal Component

In the 27 patients with IBTR, median tumor size was 1.13 cm and median age was 66 years (7 patients were ≤ 70, 12 were >70 years old). Tumor grade, evaluated at final histology, was G2 in 12 cases (44.4% of recurrences) and G3 in 15 cases (55.6% of recurrences). Twenty-three patients (85.2% of recurrences) were N0 and 4 (14.8%) resulted N-positive during intraoperative evaluation and were contextually submitted to axillary dissection. Patients' data concerning molecular profile, Mib-1, histotype, and EIC are reported in Table 4.

Six out of twenty-seven recurrences also had distant metastases.

According to the ASTRO criteria, 13 of these 27 pts (48.2%) can be classified as suitable, 10 (37%) as cautionary and 4 (14.8%) as unsuitable. Following ESTRO, there were 21 women (77.8%) at low, 3 (11.1%) at intermediate, and 3 at high-risk (11.1%). We then evaluated the IBTR recurrence rate in the individual subgroups

Table 3: Demographic and clinical characteristics of patients/lesions, according to ESTRO criteria. As shown, intermediate and high risk patients have been grouped together for statistical reasons, considered the small number of high risk patients.

Characteristics	Low risk (271)	Intermediate and high (61)	p-value
Age	67 (8)	68 (8)	0.539
Tumor size	0.96 (0.38)	1.11 (0.45)	0.012*
Tumor grade			0.28
G1	24	5	
G2	161	30	
G3	86	26	
N			<0.0001*
Neg	272	17	
Pos	0	43	
ER/PRG			0.173
Neg/Neg	11	5	
Other	260	56	
Mib1			0.063**
<20%	224	43	
21-30%	17	10	
31-60%	26	7	
>60%	4	1	
Unifocal cancer			0.208
No	2	5	
Yes	268	57	
Histotype			<0.000*
IDC	253	40	
No IDC	18	21	
EIC			<0.0001*
Absence	271	54	
Presence	0	7	

*: Statically significant data; **: A positive trend without, however, statistical significance.
Statistics: Mean (sd) or frequency; G: Tumour Grade; pN: Lymph Nodes Status; ER: Estrogen Receptors; PgR: Progesteron Receptors; Mib1: Proliferation Index; HER2: Human Epidermal Growth Factor Receptor 2; IDC: Invasive Ductal Carcinoma; EIC: Extended Intraductal Component

according to the ASTRO classifications, as follows: Among suitable 13 recurrences out 219 cancers (5.9%); among cautionary 10/74 (13.5%); among unsuitable 4/39 (10.3%). According to ESTRO, inside low risk 21/271 (7.7%), inside intermediate risk 3/50 (6%) and inside high risk 3/11 (27.3%) recurrences.

Univariate and multivariate analysis of the risk factors for LR and Progression-Free Survival (PFS) demonstrates a close correlation with the above-reported prognostic groups (Table 5). Univariate analysis showed that LR is statistically related to tumor grade, mib-1 and all the variables are confirmed at the multivariate analysis.

Patient age, tumor size, tumor grading, lymph-node status and Mib-1 resulted statistically significant for PFS; at multivariate analysis only tumor size, grade and mib-1 are statistically significant.

Discussion

The distinctive feature of our work was represented by the 10 years follow-up of, quite uncommon until the very recent publication

Table 4: Demographic and clinical characteristics of the 27 patients/lesions with infield relapse.

Characteristics	Statistics
Age	66 (9)
Tumor size	1.13 (0.51)
Tumor grade	
G2	12 (44.4)
G3	15 (55.6)
pN	
Neg	23 (85.2)
Pos	4 (14.8)
ER/PgR	
Neg/Neg	2 (7.4)
Other	25 (92.6)
Mib1	
<20%	13 (48.6)
21-30%	6 (22.2)
31-60%	8 (29.6)
HER2	
Neg	23 (85.2)
Pos	3 (11.1)
Missing	1 (3.7)
Unifocal cancer	
No	2 (7.4)
Yes	25 (92.6)
Histotype	
IDC	24 (88.9)
Other	3 (11.1)
EIC	
Absence	26 (96.3)
Presence	1 (3.7)
ASTRO	
Suitable	13 (48.2)
Cautionary	10 (37)
Unsuitable	4 (14.8)
ESTRO	
Low risk	21 (77.8)
Intermediate risk	3 (11.1)
High risk	3 (11.1)

Statistics: Mean (sd) and range or frequency; G: Tumour Grade; pN: Lymph Nodes Status; ER: Estrogen Receptors; PgR: Progesteron Receptors; Mib1: Proliferation Index; HER2: Human Epidermal Growth Factor Receptor 2; IDC: Invasive Ductal Carcinoma; EIC: Extended Intraductal Component

of the long follow-up of the ELIOT study [16]. This trial randomized patients to WBI with conventional fractionation or to IOERT during surgery. The trial was designed assuming a 5-year IBTR rate of 3% in the WBI group and equivalence of the two groups, if the 5-year IBTR rate in the ELIOT group did not exceed a 2.5 times excess, corresponding to 7.5%. After a median follow-up of 12.4 years, was observed an absolute excess of 54 IBTR in the ELIOT group (HR 4.62, p<0.0001). The 5-year IBTR rate was 4.2%, the 10-year rate was 8.1% and the 15-year rate was 12.6% compared to 0.5%, 1.1%, and 2.4%

Table 5: Univariate and multivariate analysis of IBTR (332 tumor lesions) and PFS prognostic factors in 320 patients.

End-Point: LC (Infield Relapse, N=27)	Univariate Analysis		Multivariate Analysis by Step-Wise Method		
Factor	**HR (95% CI)**	**p-value**	**RC**	**HR (95% CI)**	**p-value**
Eta (continuous)	0.981 (0.933-1.031)	0.449			
Tumor size (continuous)	2.324 (0.968-5.579)	0.059**			0.765
Tumor grade	2.472 (1.234-4.952)	0.011*	0.745	2.106 (1.002-4.428)	0.049*
(1) G1, (2) G2, (3) G3					
N	1.215 (0.420-3.515)	0.720			
(0) Neg, (1) Pos					
ER/PGR	0.584 (0.138-2.466)	0.464			
(0) Neg/Neg, (1) Other					
Mib1	1.586 (1.227-2.051)	0.0004*	0.350	1.419 (1.067-1.887)	0.016*
(0) <20%, (1) 21-30%, (2) 31-60%, (3) >60%					
HER2 status	1.212 (0.363-4.044)	0.754			
(0) neg, (1) pos					
Unifocal cancer	0.136 (0.032-0.578)	0.007*	-2.635	0.072 (0.016-0,331)	0.001*
(0) No, (1) Yes					
Histotype	1.048 (0.315-3.482)	0.939			
(0) no CDI, (1) CDI					
EIC	2.738 (0.371-20.192)	0.323			
(0) Absence, (1) Presence					
End-Point: PFS (Progression, N=25)	**Univariate Analysis**		**Multivariate Analysis by Step-Wise Method**		
Factor	**HR (95% CI)**	**p-value**	**RC**	**HR (95% CI)**	**p-value**
Eta (continuous)	0.947 (0.896-1.001)	0.051**	-0.080	0.923 (0.869-0.980)	0.009*
Tumor size (continuous)	4.559 (1.962-10.59)	0.0004*	1.607	4.988 (1.908-13.04)	0.001*
Tumor grade	2.997 (1.398-6.427)	0.005*			0.336
(1) G1, (2) G2, (3) G3					
N	2.562 (1.068-6.145)	0.035*			0.082**
(0) Neg, (1) Pos					
ER/PGR	0.358 (0.107-1.197)	0.095**			0.409
(0) Neg/Neg, (1) Other					
Mib1	1.711 (1,321-2.217)	<0.0001*	0.361	1.434 (1.091-1.886)	0.010*
(0) <20, (1) 21-30, (2) 31-60, (3) >60					
HER2 status	1.901 (0.646-5.588)	0.244			
(0) neg, (1) pos					
Unifocal cancer	0.385 (0.052-2.850)	0.350			
(0) No, (1) Yes					
Histotype	3.019 (0.408-22.32)	0.279			
(0) No CDI, (1) CDI					
EIC	0.049 (0.001; >100)	0.674			
(0) Absence, (1) Presence					

*: Statically significant data; **: A positive trend without, however, statistical significance. G: Tumour Grade; pN: Lymph Nodes Status; ER: Estrogen Receptors; PgR: Progesteron Receptors; Mib1: Proliferation Index; HER2: Human Epidermal Growth Factor Receptor 2; IDC: Invasive Ductal Carcinoma; DCIS: Ductal Carcinoma *In Situ*; ILC: Invasive Lobular Carcinoma; EIC: Extended Intraductal Component

respectively of the WBI group. The long-term results of this study confirmed the higher rate of IBTR in the ELIOT group, with no differences in overall survival [16].

Our results confirm the high rate of IBTR, 8.1% at 10-year follow-up, in a monocentric Italian real world experience, where patient where accurately selected and controlled after the treatment. Given that our prospective not randomized study started in 2004 when the data of IOERT were absent, we adopted rigorous enrolment criteria, subsequently confirmed by the recommendations of ASTRO and ESTRO. Nevertheless, our data on IBTR, as that of the much more relevant study by Orecchia et al. [16] demonstrates a 10-year local relapse rate of over 8%, against a LR rate of around 1% to 3% in the WBI reported in literature [20].

Another experience on a bigger population of patients after a shorter follow-up period (5 years) reported an IBTR ranging between 1.8% and 11.6% in suitable and unsuitable patients respectively [21].

In two reviews and metanalysis, the authors concluded that APBI was associated with significantly higher odds for LR compared to WBI [22,23]. Furthermore, Korzets et al. [23] in their subgroup analysis by APBI modality showed that the highest risk of LR was observed with IORT, whereas when External Beam RT (EBRT) was used the odds for LR were equivalent to WBI.

In our experience, we particularly focused on IBTRs, considering them as the "real" failure of IOERT. Our 5-year follow-up recurrence data appear quite consistent with those of other studies. In the ELIOT study, the 5-year recurrence rates with IOERT and WBI were 4.4% and 0.4% respectively ($p<0.0001$); the analysis of recurrence showed that IBTR was correlated with some specific tumor characteristics: tumors >2 cm, ≥ 4 positive nodes, G3, ER negative, triple-negative biology and high Mib-1 [19].

Another Italian non-randomized study on 1822 non-selected patients treated with IOERT showed a 5-year IBTR rate of 6%; when analyzed according to ASTRO and ESTRO for 'suitable' or 'low-risk' patients, the 5-year IBTR rates decreased to 1.5% and 1.9%, respectively [24].

In our study a number of cases were classified as unsuitable both by ASTRO (out of 332, 39 unsuitable and 74 cautionary) and ESTRO (11 high and 50 intermediate risks) because our enrolment had started before the ASTRO/ESTRO statement publication. However, a rigorous selection of patients had been made by a complete preoperative assessment of the tumor and by a frequent use of MRI to exclude multifocality. Only a very small number of patients with only positive cytology had originally been enrolled; moreover, at a further stage we excluded subjects with lobular cancers and we also required the patients' biological profile before surgery, to exclude high Mib-1, luminal-B, triple-negative or HER2-positive cancers. Despite a negative clinical stage, axillary evaluation at surgery resulted in some cases N-positive (13.1%), thus leading to axillary dissection. Furthermore, even some patients with G3 tumor (33%) underwent IOERT treatment because the grade of the tumor could not be established preoperatively. Likewise, for their biological profile some patients with ER-/PgR-tumors (4.8%) were included in the study because of the impossibility to obtain information in the preoperative context; for the same reason, 10% of tumors presented with Mib-1 ≥ 30%. In some final pathological reports we found discrepancies between preoperative and postoperative data, although almost all patients had been carefully selected according to age, menopausal status, unifocality, tumor size, and axillary involvement. In our experience, according to the ASTRO criteria (Table 2), age, tumor size, grade, lymph-node status, ER/PgR, Mib-1, histotype and EIC resulted to be statistically significant. Furthermore, according to ESTRO tumor size, lymph-node status, histotype and EIC resulted to be statistically significant (Table 3).

Speculatively, we may hypothesize that if we had started to apply the ASTRO/ESTRO criteria in our study in 2004, anyway there would have been 13 and 21 in-field-recurrences at 10 years, with a recurrence rate of 3.9% and 6.3% respectively.

According to ASTRO, in our trial 13 of the 27 IBTR (48.2%) are classified as suitable, 10 (37%) as cautionary, and 4 (14.8%) as unsuitable. Following ESTRO, there were 21 women (77.8%) at low, 3 (11.1%) at intermediate-, and 3 at high-risk (11.1%). We then evaluated the IBTR recurrence rate in the individual subgroups according to ASTRO, as follows: Among suitable 13 recurrences out 219 cancers (5.9%); among cautionary 10/74 (13.5%); among unsuitable 4/39 (10.3%). According to ESTRO, inside low risk 21/271 (7.7%), inside intermediate risk 3/50 (6%) and inside high risk 3/11 (27.3%) recurrences.

Also Orecchia et al. [16] found that the ideal candidate for IOERT should be selected more strictly than that described in the ASTRO suitable category. Indeed, they observed a high rate of IBTR after IOERT in ASTRO-suitable patients. In this group, intraoperative treatment should be evaluated on a case-by-case basis and offered after obtaining fully informed consent during a care discussion with the patient.

Although the LR-rate after 5 and 10 years recorded in our experience is not negligible, in some cases the choice to perform IOERT instead of WBI was conditioned by reasons such as distance from RT facilities, very advanced patient age, social problems and concomitant disabling diseases (e.g. scleroderma, multiple sclerosis, advanced psoriasis, neurological deficit).

Therefore several guidelines today include IOERT as a possible technique for APBI in very carefully selected patients, considering some important advantages such as:

- Utmost precision in dose delivery by avoiding tumor geographic miss and temporal delay of external RT;
- High Relative Biological Efficacy (EBR) of electron beam, high-dose delivered in a single fraction in a very short time;
- Favourable results in terms of cosmetic outcome, thanks to complete skin sparing combined with the small breast volumes irradiated [18].

Therefore IOERT should be assessed on a case-by-case basis only in a group of patients at particularly low risk, as recently indicated by IEO-Milan that found IOERT feasible in very low risk tumors: Small (<1 cm), well-differentiated, luminal A tumors, with a proliferative index ≤ 14%. The importance of tumor size was also underlined by the NSABPB-39/RTOG0413 trial which found a favourable outcome for APBI when given to patients with tumors up to 1 cm [25].

On these premises, the question arises whether RT can be completely omitted in such a selected group of patients. Many trials comparing BCS alone to BCS plus radiation confirmed a substantial decrease in the risk of recurrence in RT-treated women [26,27] but it remains unclear whether surgery alone without IOERT or any other RT would be the best option in elderly patients [28]. In our opinion, in the older patients, even if not suitable, IOERT could be justified to contain the risk of local relapse, considering the life expectancy of these patients and the fact that a considerable number of IBTRs occurred ≥ 5 years after treatment.

Finally, best clinical management and outcome of IBTR after IOERT are topics of great interest. Salvage surgery consists of either mastectomy or repeated lumpectomy, with or without axillary lymph-node investigation. In a recent study, external re-irradiation was offered in several cases, and resulted in a statistically significant improvement not only in local control but also in DFS and OS compared to quadrantectomy alone [29].

Even if, according to literature, the IBTR does not seem to impact

OS, however it is beyond question that the IBTR impacts on the quality of life of patients, care-givers and it is an additional burden to the health-care system [16].

In our experience, the salvage therapies consisted in 5 wide tumor excisions, 6 second quadrantectomies, and 12 mastectomies. External beam re-irradiation to the chest wall or residual breast was performed in 4 patients after 1 mastectomy and 3 quadrantectomies. Four patients, particularly old and with relevant comorbidity, refused any supplementary local treatment at recurrence diagnosis.

This is a small single institution trial of 322 breast cancer patients who underwent intra-operative radiation therapy for a total of 332 early breast cancers.

Despite the small number of patients, this is a monoinstitutional study that provides good quality 10 years follow up and uniformity of data, and is therefore strength of this study. The non-randomized trial setting, which is a limitation, could be also viewed as strength, since it provides "real world" data.

According to our data, although a 5-year follow-up demonstrates an acceptable relapse rate in patients treated with IOERT, the assessed LR rate over a longer follow-up period reveals the occurrence of a significant number of relapses. Our results are consistent with the more important ones revealed by randomized trials.

In the era of treatment de-escalation for low risk breast cancer, IOERT can be considered a valid approach on a case-by-case basis only in patients at particularly low risk of relapse: Small, well-differentiated, luminal-A tumors, with a low Mib-1, that represent a subgroup of the suitable/low risk classification. It remains to be seen however that is now possible to omit axillary dissection in sentinel-node positive patients treated with BCS, but only in case WBI is planned. In this subset of patients IOERT and the other PBI techniques cannot be considered.

Highlights

- IOERT: Acceptable approach indicated only in particularly low risk patients.
- At 10 years follow-up, 27/332 patients (8.1%) had in-field breast recurrence.
- These results are consistent with other recently published important experiences.
- Strength of this study: Good quality 10 year follow up and uniformity of data.
- Limitation: Non-randomized trial, which however provides "real world" data.

Acknowledgment

Our thanks for this trial go to the RT technicians and breast center's nursing staff, to the breast surgeons and to the dedicated breast radiologists and oncologist.

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