Journal of Cancer Science & Therapy

Salati et al., J Cancer Sci Ther 2019, 11:3
DOI: 10.4172/1948-5956.1000585

Research Article Open Access

Comparing Outcome of Radical Dose Intraoperative Radiotherapy with Electron (IOERT) According to IRIORT Consensus and External Beam Radiotherapy in Early Breast Cancer

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Abstract

Introduction and Hypothesis: The current standard treatment for early breast cancer includes conservative surgery followed by whole breast radiotherapy (WBRT). Recent study findings show that most local recurrences are in the scar tissue area suggesting that whole-breast radiotherapy may not always be necessary. If the volume of breast tissue to be irradiated is limited, radiotherapy may be performed as intraoperative. Intraoperative radiotherapy could in principle substitute the currently used radiation course of external radiotherapy after breast-conserving surgery in selected cases.

Patients and Methods: Patients were enrolled at two center. Khatam Hospital (related to CRC1, SBMU2) patients were delivered intraoperative electron beam during surgery and Azar Clinic (related to CRC) patients received external beam radiotherapy after surgery. Suitable criteria was age>45 y, tumor size ≤ 3 cm, lymphnode negative. Though we included some patients 40-44 y and T=3-4 cm, N=0 and favorable biomarkers as Possible Group.

Results: We applied full dose electron beam intraoperative radiotherapy to 216 patients with early breast cancer and suitable for breast conserving surgery. Afterwards, we compared results with 323 patients with early breast cancer and external beam radiotherapy. Within 4 years for the invasive breast cancer patients, local recurrence was 2 (1.06%) and 1 (0.36%) and also, systemic recurrence was 1and 4 patients in the intraoperative and external radiotherapy groups, respectively. Mortality was 3 cancer related death and the other one, none cancer related death in the external radiotherapy patients. There was not any cancer related death for intraoperative radiotherapy patients.

Conclusion: Comparison of local recurrence in two groups (p-value: 0.335), via demonstrated that IOERT in contrast with EBRT had not inferiority however, it had superiority about systemic recurrence and death. In addition, we can transcend the boundaries of the definition, such as age, tumor size, histology. Invasive lobular carcinoma and DCIS with special characters could be one of these.

Keywords: Intraoperative radiotherapy; Breast cancer; Accelerated partial breast irradiation, Invasive ductal carcinoma; Invasive lobular carcinoma; Ductal carcinoma *in situ*; IORT; Intraoperative Radiotherapy with Electron (IOERT); ABPI

Introduction

The first cases of breast cancer surgery have been reported in "Edwin Smith papyrus", an ancient Egyptian Medical Text, between 3000 and 2500 BC. It is documented that physicians removed breast tumors in ancient Egypt [1]. Galen, "The Greek surgeon 210-129 AC", believed that breast cancer was a systemic disease and the accumulation of bile in the liver and spleen [2]. A very early report of metastatic breast cancer has been reported by Avicenna in the Canon of Medicine [3-5].

In eighteenth and nineteenth centuries, a more aggressive surgical approach was treatment of breast cancer and the Halsted Mastectomy became classic treatment of breast cancer [6].

Further studies demonstrated that there is not outcome difference between Brest Conserving Surgery (BCS), plus radiotherapy and the radical mastectomy. This approach decreased the risk of local recurrence and improved the survival [7,8]. Radiation free radicals remove any residual tumor cells and subsequently cause single or double-stranded breakage of DNA [9,10]. According to studies, most local recurrences after breast conserving surgery occur within tumor bed. This led the apparent benefit of Accelerated Partial Breast Irradiation (ABPI) over whole breast radiotherapy [11]. The advantages of APBI are lower toxicity, decrease the burden of radiation treatment due to fewer fractions and short period of time of radiation and spared the surrounding organs from radiation affects. There are several methods for delivering of radiation to the tumor bed like, IntraOperative RadioTherapy (IORT).

It seems, the first concept of intraoperative radiotherapy is attributed to Comas and his cousin, Prio [12]. They reported a woman with squamous cell carcinoma of cervix treated by direct roentgen therapy after surgery while abdominal wall was open. Abe, the Japanese surgeon, 1960s, began the modern approach about intraoperative radiotherapy at university of Kyoto [13]. Geoffrey Keynes, surgeon at St. Bartholomew's Hospital London, used radium with platinum needles in the treatment tumor bed of breast cancer [10].

Currently, the Mobetron, LIAC, and NOVAC-7 linear accelerators

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Received January 26, 2019; **Accepted** March 04, 2019; **Published** March 15, 2019

Citation: Salati A, Akbari ME, Nafissi N, Noorian S, Mirzaei H, et al. (2019) Comparing Outcome of Radical Dose Intraoperative Radiotherapy with Electron (IOERT) According to IRIORT Consensus and External Beam Radiotherapy in Early Breast Cancer. J Cancer Sci Ther 11: 063-069. doi: 10.4172/1948-5956.1000585

are used for delivering intraoperative radiation electron beam to tumor bed during surgery. All three units are mobile. The Mobetron was invented in the America in 1997 that has X-band technology and a soft docking system. The LIAC and NOVAC-7 are made in Italy that have S-band technology and a hard-docking system. The NOVAC-7 was developed in the 1990s while the LIAC was presented to clinical use by SORDINA Co. in 2003 [14]. There are many trials and studies about intraoperative radiotherapy. The most important of them are ELIOT [15] and TARGIT-A [16].

This study is about breast cancer patients treating with breast conserving surgery and radical dose of IOERT (IntraOperative Electron RadioTherapy) according to a new protocol for selected cases during four years.

Materials and Methods

1243 breast cancer patients treating with breast conserving surgery were enrolled at two centers between 23 August 2013 and 23 September 2017. 601 patients received External Beam Radiotherapy (EBRT) after breast conserving surgery in Azar Clinic. 642 patients received IntraOperative RadioTherapy (IORT) in another center, Khatan Hospital; 426 patients and 216 patients were treated by boost or full dose, respectively. Eligible criteria was determined according to patients' demographic, pathologic and biologic factors. Patients for receiving IOERT were categorized to three group; Suitable, Possible and Contraindicated (Table 1). For women with documented breast carcinoma in core biopsy, tumor wide local excision and sentinel lymph node biopsy for clinically negative axilla were done. The patients with age ≥ 45, lymph node negative and tumor size <3 cm in frozen section, categorized as suitable group (Table 1), received 21 Gy in one fraction as a radical dose of intraoperative radiotherapy with electron. The rest of patients received 12 Gy as boost dose and they were sent to external radiation after surgery. Sometimes, some patients had specially position as, comorbidity or from remote area and were in possible group with favorable profile of tumor, enrolled for radical dose. Intraoperative radiotherapy was done by using LIAC, a mobile linear accelerated delivery energy levels of electrons (6-12 Mev). The radiation-oncology team calculated the appropriate electron beam energy based on the thickness of the tissue measured by a needle as, 90% of the prescribed dose would cover at least 1.5 cm of tissue close to the margins and at least 1 cm of breast tissue on the chest wall surface in 1-5 min duration. Protection of chest wall was achieved using lead discs. The patients received post-operative adjuvant chemotherapy and /or endocrine therapy according to their clinical and biological findings and pathological staging. Patients were followed every 6 month from the surgery as outpatients. In this study, 216 patients with Radical dose of IOERT compared to 323 selected patients from EBRT group. Selection of patients for control group was according to age (>40-45 y), tumor size (<3-3.5 cm) and negative lymphnode and they received whole breast irradiation, including 50 Gy in 25 fractions using conventional beams, followed by a boost dose of 10 Gy in five fractions after either surgery or 4 month in patients treated with chemotherapy. Overall Survival (OS) and Disease Free Survival (DFS), was defined as the time from diagnosis to last follow up or time of death. The primary outcome was the occurrence of recurrence (Ipsilateral Breast Tumor Recurrence=IBTR, metastases) and death. IBTR included to recurrence either tumor site or ipsilateral axillary. Distance metastases were determined as any recurrence to distant organs. Secondary outcome was complications.

Patients factors	Suitable	Possible	Contraindicated
Age	≥ 45	44-40	<40
Tumor Size	<3 cm	3-3.5 cm	>3.5 cm
Margins	Negative	Negative	Positive
Grade	1 or 2	Any	-
LVI[1]	Negative	Any	Positive
ER Status	Positive	Any	-
Multicentricity	No	No	Yes
Multifocality	No	Yes	-
IDC	Yes	-	-
ILC	Yes	-	-
Pure DCIS	≤ 3 cm	3-4 cm	>4 cm
EIC[2]	<25%	≥ 25%	Diffuse
HER2	Any	-	-
Ki67	<30%	≥ 30%	-
LCIS Associated	Any	Any	Any
Nodal Status	Negative	Negative (i-, i+)	Positive
Axillary Surgery	SLNB[3]	SLNB or ALND[4]	-
Neoadjuvant Th	Not allowed	Not allowed	If used

[1]Lymphovascular invasion, [2]Extensive *in situ* component, [3]Sentinel lymphnode biopsy, [4]Axillary lympnode dissection

Table 1: IRIORT consensus for radical IOERT.

This is a case-control study that aims to show that local recurrence and distance metastasis at 48 months in the intraoperative radiotherapy with electron group and the external radiotherapy group. Cumulative Hazard Function and survival plots were drawn using the Kaplan-Meier method. The log-rank test was used to evaluate the survival difference between the two treatment radiotherapy groups, as well. All of analysis were done with SPSS.

Results

As mentioned above, 216 patients with radical dose intraoperative radiotherapy were compared to 323 selected patients with external radiotherapy. The median follow up time in the intraoperative radiotherapy and external radiotherapy groups was 670 days (23 months) and 623 days (21 months), respectively.

According to Table 2 the characteristics of patients and tumors in the intraoperative radiotherapy and the external radiotherapy groups was collected. The maximum and minimum age for a patient was 93 and 39 years old respectively in the intraoperative radiotherapy group. They were in the external radiotherapy group, 81 and 40 years old, respectively. Most patients had an invasive ductal carcinoma (60.6% for the intraoperative radiotherapy group *vs*. 81.6% for the external radiotherapy group), invasive lobular carcinoma was 19.4% for the intraoperative radiotherapy group *vs*. 5.1% for the external radiotherapy group and pure ductal carcinoma *in situ* was 13.4% *vs*. 12.7%, respectively. Most tumors had a size <3 cm (87.8%=IOERT *vs*. 80.3%=EBRT) in both groups. Tumors were most commonly estrogen receptor (ER) positive (83.5%=IOERT *vs*. 80.9%=EBRT), progesterone receptor (PR) positive (80.0%=IOERT *vs*. 72.2%=EBRT), HER2 (human epidermal growth factor 2) receptor nonamplified (95.2%=IOERT *vs*. 83.7%=EBRT) and Ki67<20% (58%=IOERT *vs*. 61.9%=EBRT). Most women had tumors of grade 1 or 2 (76.9%=IOERT *vs*. 69.1%=EBRT) with no LVI (lymphovascular invasion), (89.0%=IOERT *vs*. 85.6%=EBRT) and EIC (extensive *in situ* component) <25%, (50.0%=IOERT *vs*. 74.0%=EBRT). In the intraoperative radiotherapy group 9.2% patients received chemotherapy alone, 37.6% patients received endocrine treatment alone, 50.4% had both treatment. Again, in the external radiotherapy group 3.3% patients received chemotherapy alone, 27.2%

Patients Factors	IOERT	EBRT	p-value
Total	216	323	
Age			
<40	3 (1.4%)	0 (0%)	0.000
40-44	11 (5.1%)	53 (17.2%)	
≥ 45	202 (93.5%)	255 (82.8%)	
Tumor size			
< 3	187 (87.8%)	257 (80.3%)	0.063
3-3.5	24 (11.3%)	55 (17.2%)	
>3	2 (0.9%)	8 (2.5%)	
Grade			
1	34 (18.7%)	63 (22.1%	0.101
2	106 (58.2%)	134 (47.0%)	
3	42 (23.1%)	87 (30.5%)	
LVI			
Negative	162 (89.0%)	231 (85.6%)	0.321
Positive	20 (11.0%)	39 (14.4%)	
ER			
Positive	177 (83.5%)	241 (80.9%)	0.485
Negative	35 (16.5%)	57 (19.1%)	
PR			
Positive	168 (80.0%)	213 (72.2%)	0.047
Negative	42 (20.0%)	82 (27.8%)	
HER2			
Negative	121 (64.7%)	143 (55.4%)	0.101
1+	33 (17.6%)	34 (13.2%)	
2+	24 (12.8%)	39 (15.1%)	
3+	9 (4.8%)	42 (16.3%)	
Ki67			
<20%	98 (58.0%)	70 (61.9%)	0.128
20%-30%	41 (24.3%)	21 (18.6%)	
>30%	30 (17.8%)	19 (16.8%)	
EIC			
<25%	12 (50.0%)	37 (74.0%)	0.065
≥ 25%	12 (50.0%)	13 (26.0%)	
Histology			
IDC	131 (60.6%)	258 (81.6%)	0
ILC	42 (19.4%)	16 (5.1%)	
IDC+ILC	14 (6.5%)	0 (0.0%)	
DCIS	29 (13.4%)	40 (12.7%)	
Adjuvant treatment (Invasive tumors)			
Chemotherapy alone	13 (9.2%)	6 (3.3%)	--
Endocrine Treatment alone	53 (37.6%)	50 (27.2%)	
Both of them	71 (50.4%)	126 (68.5%)	
None of them	3 (2.1%)	2 (1.1%)	
NeoAdjuvant	1 (0.7%)	0 (0.0%)	

Table 2: Clinical, pathologic and treatment related characteristics for the IOERT and EBRT groups.

patients received endocrine treatment alone, 68.5% patients received both treatment. One patient with bilateral disease and history of heart disease treated by neoadjuvant therapy received radical dose for left side whereas she received boost dose for right breast. Due to difference in the nature of invasive and noninvasive tumors, their analysis and their outcome were performed separately.

In the patients with invasive tumors, there were 2 occurrence of local recurrence in the intraoperative radiotherapy patients (1patient with invasive ductal carcinoma and the other one with invasive lobular carcinoma) and 1 patient had liver metastasis with ER positive tumor that she had not taken recommended endocrine therapy. However, 1 patient had local recurrence along with metastasis and 3 patients had pure metastasis in the external radiotherapy group (1.08%=IOERT *vs*. 1.82%=EBRT p-value: 0.9009) and with consideration of just local recurrence, it was 1.06% *vs*. 0.36% (p-value: 0.355), respectively (Table 3). The number of death attributable to cancer was 3 case in the external radiotherapy group whiles there was no mortality related to cancer in the intraoperative radiotherapy patients. The number of recurrences (local and systemic) were 3 of 188 (1.59%) of intraoperative radiotherapy patients and 4 of 284 (1.40%) of external radiotherapy patients. In the intraoperative radiotherapy group, all of recurrent tumors were ER, PR, receptors positive and HER2 receptor negative, while, except for 1 patient, all of them had triple negative tumors in the external radiotherapy group. None of patients with tumor recurrence in both groups, had not EIC (External *In situ* Component) >25%.

The mean of survival time for patients in the intraoperative radiotherapy group was about 1570/76 days and for whom in the external radiotherapy group was 1790/07 days. The mean of time to have a recurrence in the external radiotherapy group was more than the intraoperative radiotherapy group (Table 4). To illustrate the significant difference, we used the "Log-Rank test". According to this test (Table 5) the p-value was 0.686. Therefore, there was not a significant difference in survival distribution between the intraoperative radiotherapy and the external radiotherapy groups. The p-value was 0.063 and it was more than 0.05. Thus, survival distributions for the different levels of two groups was acceptable.

Figures 1 and 2 illustrate the Survival and Cumulative Hazard functions for the patients of two groups. According to these plots, the survival function of the patients with external radiotherapy (red line) is almost similar to the survival function of the patients with intraoperative radiotherapy. So the distribution of survival time is homogeneous. The 2 years disease free survival (DFS) was 100% for the patients with intraoperative radiotherapy and 99.22% for the patients with external radiotherapy. The 4 years disease free survival was 96.15% for the intraoperative radiotherapy group and 96.94% for the external

Recurrence (Invasive)	IOERT	EBRT	p-value
Invasive Ca			
Total	188 (78.03%)	284 (87.9%)	--
IBTR	2 (1.06%)	1 (0.36%)	0.355
Metastasis	1 (0.53%)	4 (1.45%)	0.346
Total Recurrence	3 (1.60%)	4 (1.4 5%)[a]	0.9009
DCIS			
Total	29 (13.4%)	39 (12.7%)	--
IBTR	4 (13.7%)	2 (5.1%)	--
Metastasis	-	1 (2.5%)	--
Total recurrence	4 (13.7%)	3 (7.69%)	--
Total Death			
Cancer related	-	3[b]	--
Non cancer related	1	1	--
Total patients	216	323	--

[a] One of them had both of recurrence, local and systemic, [b] One of them died of colon cancer and the other ones from breast cancer

Table 3: Local, systemic recurrence and death in the IOERT and EBRT groups.

Patient Code	Mean[a]				Median			
	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
IORT	1570.762	22.388	1526.881	1614.642	.	.	.	.
Control	1790.074	17.719	1755.344	1824.803	.	.	.	.
Overall	1783.557	15.883	1752.427	1814.688	.	.	.	.

Table 4: Means and medians for survival time.

Variables	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	.163	1	.686
Breslow (Generalized Wilcoxon)	.313	1	.576
Tarone-Ware	.010	1	.921

Table 5: Test of equality of survival distributions for the different levels of patients.

radiotherapy group. According to above mentioned test, there was no statistical difference in disease free survival between two groups.

13.4% and 12.7% patients had pure DCIS histology in the both intraoperative radiotherapy and external radiotherapy groups, respectively. The mass size <3 cm, was 93.1% in the intraoperative radiotherapy group and 90.0% in the external radiotherapy group, as well. Most of patients with pure DCIS had high grade tumors (59.3%=IOERT, 41.7%=EBRT), ER (65.5%=IOERT, 55.3%=EBRT) and PR (58.6%=IOERT, 47.4%=EBRT) positive receptors (Table 6).

In patients with DCIS, the occurrence of local recurrence was significantly greater in the intraoperative radiotherapy group than in the external radiotherapy group (17.2% *vs.* 5.4%).

Information about complications of radiotherapy was not available for all patients. The most common complication was seroma in both groups. The other ones are in the Table 7. Overall, for patients with data available (29 patients in the intraoperative radiotherapy group, 45 patients in the external radiotherapy group), there was not statistical significant difference between two group (p-value: 0.62). However, skin burns was significant in the external radiotherapy group (25 patients).

Discussion

This is the first study to evaluate the use and outcome of patients treated with radical dose of intraoperative radiotherapy with electron for early breast cancer in Iran. In women with early breast cancer, radical dose of intraoperative radiotherapy with electron resulted similar to the external whole breast radiation with a brief differences. In the patients with invasive breast cancer, the external radiotherapy group had one ipsilateral breast tumor recurrence (IBTR) however, there was two patients with IBTR in the intraoperative radiotherapy group (p-value: 0.35). Two great studies; ELIOT and TARGIT-A trials were based on electron high voltage beam and low Kv X-ray energy, respectively. The results of them were evaluated according to local recurrence as the final outcome. For ELIOT, it was 4.4% versus 0.4% in the patients who received intraoperative radiotherapy and external radiotherapy, respectively, in compared to 3.2% and 1.3% for the other one. Further analysis of ELIOT trial according Society of Therapeutic Oncology guidelines for IORT use, the local recurrence risk was 1.5% in the intraoperative radiotherapy group [15-17]. The other comparison in this field, reported local recurrence rate less than 1.9% in the low risk group of ELIOT study [18]. In our study, local recurrence was 1.06% versus 0.36% in the intraoperative radiotherapy and external radiotherapy, respectively.

To explain that, one of patients with IBTR in the intraoperative radiotherapy group had invasive lobular carcinoma (ILC) histology.

Patients Factors	IOERT	EBRT	p-value
Total	**29**	**39**	
Age			
<40	2 (6.9%)	0 (0%)	
40-44	3 (10.3%)	8 (21.6%)	
≥ 45	24 (82.8%)	29 (78.4%)	0.147
Tumor Size			
< 3	27 (93.1%)	38 (97.4%)	
3-4	0 (0.0%)	0 (0.0%)	
>4	2 (6.9%)	1 (2.56%)	0.751
Grade			
Low-Int	11 (40.7%)	17 (47.3%)	
High	16 (59.3%)	15 (41.7%)	
Missing	0 (0.0%)	4 (11.1%)	0.249
ER			
Positive	19 (65.5%)	21 (55.3%)	
Negative	8 (27.6%)	9 (23.7%)	
Missing	2 (6.9%)	8 (21.1%)	0.273
PR			
Positive	17 (58.6%)	18 (47.4%)	
Negative	9 (31.0%)	11 (28.9%	
Missing	3 (10.3%)	9 (23.7%)	0.358
Endocrine treatment			
Yes	19 (65.5%)	21 (53.8%)	
No	7 (24.1%)	3 (3.0%)	--
Missing	3 (10.3%)	15 (38.4%)	

Table 6: Clinical, pathologic, and treatment related characteristics for the DCIS patients.

Reminds that, IRIORT (Table 1) defined ILC as a suitable criteria, strongly. Univariate and multivariate analysis in the other our study showed that there was no significant statistical difference between invasive lobular carcinoma and invasive ductal carcinoma patients. The results of Cox regression analysis showed that the AHR for patients with invasive lobular carcinoma compared to patients with invasive ductal carcinoma was 1.34 (95% CI: 0.12-14.73) with the p-value equal to 0.813 [19]. So there is no significant difference in risk of recurrence between patients with invasive lobular carcinoma and patients with invasive ductal carcinoma. In Leonard's study, treated breast cancer patients and invasive lobular carcinoma (252; 11.6%) were compared to those with invasive ductal carcinoma (1921; 88.4%). The 5 and 10 years IBTR rate were 7.5% and 21.8%, respectively for invasive lobular carcinoma patients versus 5.5% and 14.4%, respectively for invasive

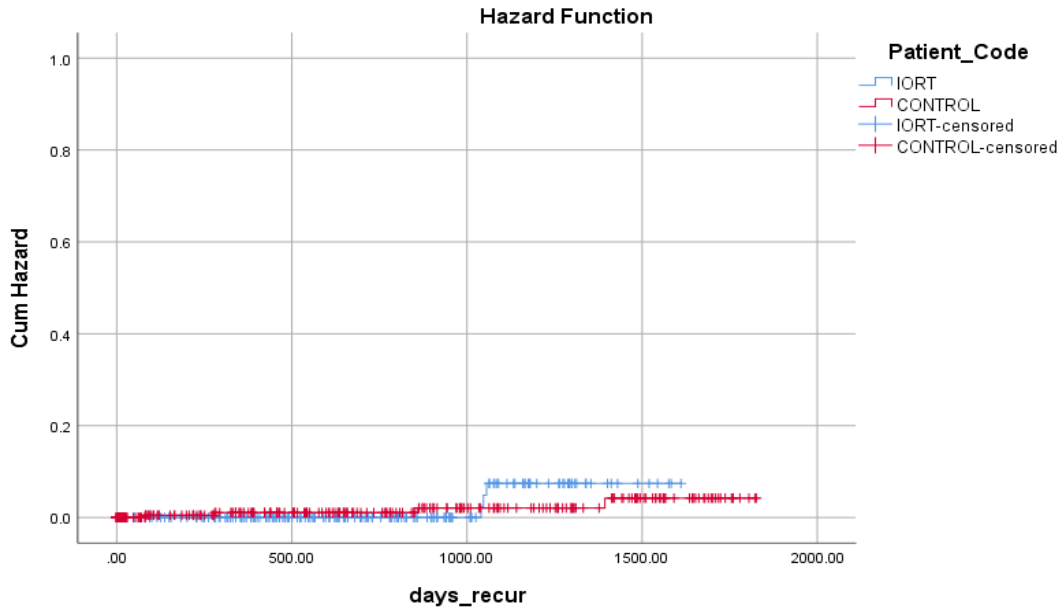

Figure 1: Hazard functions comparison in the intraoperative radiotherapy and external radiotherapy groups.

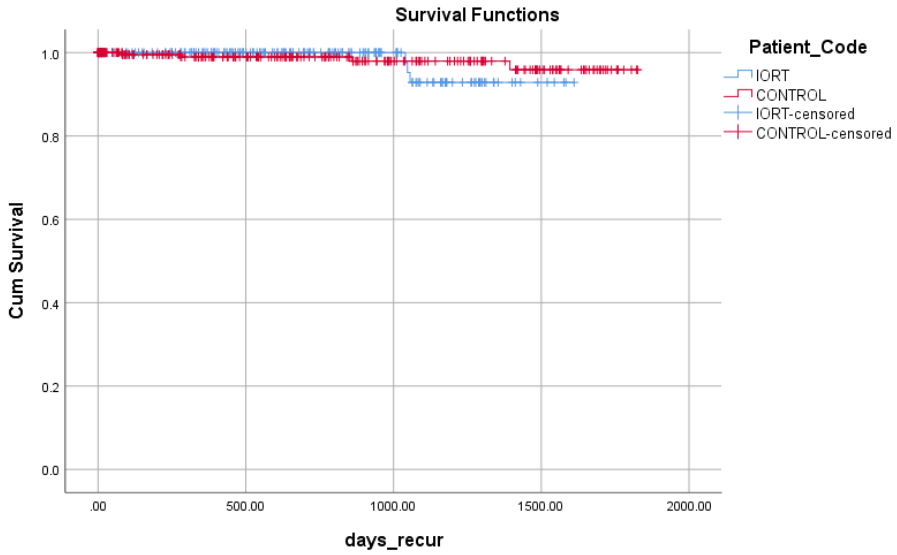

Figure 2: Comparison of survival function in the intraoperative radiotherapy and external radiotherapy groups.

ductal carcinoma patients. They resulted that selection of patients with invasive lobular carcinoma for intraoperative radiotherapy must be done, cautiously [20].

According to researches, 20% of breast cancers pathology is ductal carcinoma *in situ* (DCIS) [21]. DCIS inherently is nonlethal but could be precursor of invasive breast cancer with the ability to provide the metastasis and consequently death. Therefore, over the years, due to a change in the knowledge about nature and biological behavior of DCIS, it's diagnosis and treatment was distinguished from invasive breast cancer. First, mastectomy became the standard of therapy for DCIS. Later, developing of postoperative radiotherapy and hormonal treatment allowed to preserve the breast in the DCIS patients [22].

The prospective randomized trials of postoperative radiotherapy after breast conserving surgery showed a reduction of the risk of local recurrence, 26% to 36%, compared to patients with breast conserving surgery alone [21,23-26]. The other randomized trials about tamoxifen use for patients with DCIS, demonstrated the radiotherapy and hormonal treatment after breast conserving surgery, decreased local recurrence 50% and 30%, respectively [21,23-27].

So, breast conserving surgery is considered standard treatment for

Complications	IOERT	EBRT	p-value
Fat necrosis	4 (1.9%)	3 (0.9%)	--
Induration	9 (4.2%)	1 (0.3%)	--
Abscess	2 (1.0%)	0 (0.0%)	--
Wound Dehiscence	1 (0.5%)	0 (0.0%)	--
Burn	3 (1.4%)	25 (7.5%)	--
Erythema	1 (0.5%)	1 (0.3%)	--
Edema	1 (0.5%)	1 (0.3%)	--
Wound Infection	1 (0.5%)	1 (0.3%)	--
Fibrosis	2 (1.0%)	1 (0.3%)	--
Nipple Necrosis	1 (0.5%)	0 (0.0%)	--
Lymphedema	0 (0.0%)	2 (0.6%)	--
Mastitis	1 (0.5%)	1 (0.3%)	--
Hyperpigmentation	1 (0.5%)	3 (0.9%)	--
Cardiac	2 (0.9%)	0 (0.0%)	--
Telangiectasia	0 (0.0%)	1 (0.3%)	--
Blister	0 (0.0%)	2 (0.6%)	--
Fatigue	0 (0.0%)	2 (0.6%)	--
Respiratory	0 (0.0%)	1 (0.3%)	0.062

Table 7: Complications of IOERT and EBRT groups.

Name	Age	Pathology	Mass size	Grade	ER	Endocrine therapy	Local Recurrence
M.M	56	DCIS	0.7 cm	High	Positive	Yes	Breast
F.S.M	53	DCIS		High	Positive	Yes	Breast
Z.A	33	DCIS		High	Positive	Yes	Breast
M.B	50	DCIS		High	Positive	No	Breast
T.Kh	64	DCIS		High	Positive	Yes	Breast

Table 8: DCIS recurrence patients.

DCIS. Today, the benefits of intraoperative radiotherapy after breast conserving surgery have been confirmed for invasive breast cancer, as the ESTRO and ASTRO guidelines have accepted. However, they did not offer DCIS as a suitable criteria for intraoperative radiotherapy whereas, the ASBS and the ABS considered unifocal DCIS in the suitable category (Table 8) [28].

In a study of 300 patients with DCIS treated with breast conserving surgery and APBI, local recurrence was 2.6% [29]. However, in the other study of 35 patients with DCIS treated by breast conserving surgery and APBI at the California university, local recurrence rate 5.7% was reported [30].

We found an excess of local recurrence in the patients with DCIS treated with intraoperative radiotherapy compared to the external radiotherapy group (17.2% *vs.* 5.4%). Five patients with DCIS had IBTR in the intraoperative radiotherapy group. All of them were ER receptor positive and received endocrine treatment after surgery except one. However, all patients had high grade tumor and two patients had 3 cm and 4.5 cm size of DCIS, as well. One of them was under 40 years of age (Table 8). In other word, these patients had not been selected according to IRIORT consensus (Table 1) and they were not suitable for radical dose of intraoperative radiotherapy except for a patient who, apart from high grade tumor, had no other conflict with the IRIORT consensus. There was two patients with DCIS had IBTR in the external radiotherapy group and they had low grade tumors. However, there was not any IBTR in patients with low grade DCIS in the intraoperative radiotherapy group. And this is while, one of two patients belongs to the external radiotherapy group also had systemic recurrence (spleen). The patient died four years after diagnosis because of colon cancer. Conversely, there was no systemic recurrence in the intraoperative radiotherapy group. Another issue is that, most of patients had high grade DCIS in the two group and didn't relapse. Thus, It seems that, apart from grade of DCIS, size of mass and age play an important role in local recurrence.

The main goal of DCIS treatment is to reduce the rate of local recurrence. So, surgical decisions will be depending on age and tumor characteristics; size, margin, width and pathologic classification.

Van Nuys index (VNPI) was introduced in an effort to determine the invasiveness of DCIS and possibility of local recurrence and prevention of unnecessary mastectomy and radiotherapy [31]. Later, USC/Van Nuys was presented by adding age, margin width and pathology as effective factors in the recurrence [32].

It seems the size of DCIS and margin status are statistically significant factors in local recurrence. DCIS <1 cm with negative margins have a lower risk for local recurrence however, DCIS>2.5 cm consider high risk for it and additional treatment is necessary [33].

The result of a cohort study of 140, 000 women with ductal carcinoma *in situ* (DCIS) reported by Giannakeas V, and colleagues showed that the 15 years breast cancer related mortality in patients treated by breast conserving surgery followed by radiotherapy were lower than patients treated by lumpectomy alone or mastectomy, as well. They concluded that there should be some systemic effects of radiation like a kind of immune system stimulus, of course the effects of endocrine treatment should not be ignored [34].

We found that, all of IBTR were in breast at two groups except one in axilla. Overall, systemic recurrence in the external radiotherapy group was greater than intraoperative radiotherapy group (5 patients *vs.* 1 patient). It perhaps represents that intraoperative radiotherapy can play a major role in systemic disease control.

Definition of abscopal effect means calling out extra tumor response like the immune system after using local radiotherapy, was considered 50 years ago [35-37]. In 1953 Dr. RH Mole introduced the term of abscopal effect as the antitumor effects of radiotherapy in other site than tumor location [36,37]. In our study, three patients with recurrence and intraoperative radiotherapy were Luminal A however, the patients with recurrence in the external radiotherapy had triple negative tumors.

Several clinical trials are ongoing based on undertaking results of preclinical trials representing the abscopal effects of radiotherapy. We also founded fewer complications in the patients treated by IOERT, however, this analysis was done on limited number of patients because the data about complications was not fully recorded. Therefore, this is a bias issue.

Conclusion

The rational conclusion is that intraoperative radiotherapy should be as one of options to decide about radiation treatment along with breast conserving surgery because it makes patients needless to attend in radiotherapy center every day after surgery, and it has fewer complications than external radiotherapy with the same survival and local recurrence rate. So, IOERT could be a personalized treatment regimen in breast cancer patients. Radical dose of IOERT should be limited to suitable patients. But we can transcend the boundaries of the definition, such as age, tumor size, histology. Invasive lobular carcinoma and DCIS with special characters could be one of these. In addition to some patients with possible criteria could be a candidate for radical dose of IOERT.

Citation: Salati A, Akbari ME, Nafissi N, Noorian S, Mirzaei H, et al. (2019) Comparing Outcome of Radical Dose Intraoperative Radiotherapy with Electron (IOERT) According to IRIORT Consensus and External Beam Radiotherapy in Early Breast Cancer. J Cancer Sci Ther 11: 063-069. doi: 10.4172/1948-5956.1000585

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