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Research article

Breast Cancer: Targeted Intraoperative Radiotherapy (INTRABEAM). A Clinical Review from a Developing Country

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Abstract

Aim: The scarcity of radiotherapy centers in developing countries limit the surgical options to mastectomy for the majority of diagnosed breast cancers. This review aims to assess the benefits of using intraoperative radiotherapy (IORT) to promote other treatment options. Materials & Methods: All breast cancer patients were reviewed between December 2011-December 2018. Eligible patients for breast conserving surgery were considered initially as potential candidates for IORT treatment. Strict selection criteria were applied based on demographic data, histological diagnosis, tumor size, tumor grade, lympho-vascular invasion, nodal status, receptor status, treatment with neoadjuvant hormonal\chemotherapy. Results: The total number of patients was 347 patients, BCS was planned in 204 (58.7%) patients. 85 (24.4%) of the BCS were eligible for IORT treatment. Age of the target group ranged between 31-75 years with the median age of 51 years. Histological diagnosis included IDC 74(87%), ILC 3(4%), DCIS 6(7%) Mucinous Carcinoma 1(1%) and papillary carcinoma 1(1%). Tumor size ranged between 0.8 - 4cm. Unfavorable pathological characteristics which could increase the risk of local disease relapse in were 30(41%) Grade III, 49(40%) node positive, 15(19%) Lympho-vascular invasion, 12(14%) positive margins on the initial excision, 19(22%) ER negative, 30(35%) PR negative and 22(26%) Her2 positive, Tumor size > 4cm 8 (9%) with successful neoadjuvant chemotherapy. The total number of patients treated exclusively with IORT were 39 (46%) patients while those who received the IORT as a boost were 46(54%).Disease relapse occurred in the form of index site recurrence in 5(5.8%), Axillary recurrence 3(3.5%) and Distal relapse 2(5.8%). The overall disease-free survival was 88.3 %. Conclusion: IORT emerges as encouraging alternative treatment option in countries with limited resources. It has proven to be a convenient, efficient, cost effective treatment method that may promote early detection strategies.

Keywords: intrabeam, breast cancer, intraoperative radiotherapy

Introduction

Breast cancer treatment had considerably advanced over the last three decades. With the global advent of propagating BCS, Whole Breast Irradiation contributes to the reduction of local recurrence to less than 10% as compared to 30% without radiation at 10 years [1,2]. Many emerging studies reported that radiation boost following WBIR can improve local control with maximum benefit in younger patients, patients who are older than 60 years may be spared the WBIR following BCS [3]. High geographical misses ranging from 20%-90% is linked to WBIR which is delivered many months after BCS. Accurate delineation of the tumor bed is mandatory in optimizing local disease control. Relying on clinical delineation is inaccurate and is discouraged specially with the increasing adoption of oncoplastic surgery were the tumor bed cannot be accurately located. The use of surgical clips or the emerging bioabsorbable martial may to some extent contribute to the accuracy for radiation treatment planning [4-6]. Accelerated Partial breast irradiation (APBI) namely brachytherapy and intraoperative radiotherapy (IORT) has the advantage of eliminating the geographical misses by the direct and targeted treatment to the tumor bed. IORT has an added advantages, in addition to the one-step execution at the time of excision, its radio-biological effect substantiated by exhausting studies indicated that the targeted radiotherapy creates a non-conducive environment for growth leading to tumor cells apoptosis [7].

Materials and Methods

This study was undertaken between December 2011 December 2018. All patients diagnosed with breast cancer were reviewed. Those who were eligible for BCS were considered

initially as potential candidates to be treated with intraoperative radiotherapy. Strict patient selection criteria were applied to this group based on international guidelines for intraoperative radiotherapy treatment. These included demographic data, histological diagnosis, tumor size, tumor grade, lympho-vascular invasion, nodal status, receptor status, and treatment with neoadjuvant hormonal\chemotherapy, applicator size, treatment time and the radiation dose.

Intraoperative ultrasound was used to confirm the circumferential contact of the target tissue with the selected applicator. ZIESS INTRABEAM PRS 500 with XRS4 was used delivering the intended dose of 20 Gy to the target tissue. WBIR arrangements for referral to local radiation oncology center were planned for the potential boost therapy patients prior to the initiation of IORT. The target group of the IORT ongoing follow up ranged between 7 – 84 months to date.

Results

The total number of patients presented breast cancer for the above period was 347 patients out which BCS was planned in 204 (58.7%) patients. Following the strict selection criteria only 85 (24.4%) of the BCS were eligible to be treated with IORT. The remaining (34.2%) patients were treated with BCS followed by the standard WBIR. As summarized in Table 1, age of the target group ranged between 31-75 years with the median age of 51 years. Histological diagnosis of IDC in 74 (87%), ILC 3(4%), DCIS 6 (7%) Mucinous Carcinoma 1(1%) and papillary carcinoma 1(1%). Tumor size ranged between 0.8-4cm. Despite the lack of national structured breast cancer programs and to our surprise 34(40%) of the tumor size were <2cm and node negative in 51(60%). Tumor grade I in 10(12%), Grade II in 40(47%) and Grade III in 30(41%). Lympho-vascular invasion was absent in 60(81%). Margins were reported as negative in the initial excision in 73(86%). Receptor status was completed in 73 (86%) of cases and was reported as: ER positive in 63(74%). PR positive in 53(62%), Her2 and negative in 55 (65%). Unfavorable pathological characteristics which could increase the risk of disease relapse in this review were included: Grade III 30(41%), 49(40%) node positive, Lympho-vascular invasion 15(19%), Positive margins on the initial excision 12(14%), ER negative 19(22%), PR negative in 30(35%) and Her 2 positive 22(26%). Tumor size > 4cm 8 (9%) with successful neoadjuvant chemotherapy prior to treatment initiation. These were ER 3(4%) PR 1(1%) and Her2 8(9%). The unknown results of receptor status 12(14%) may contribute to the undesirable results. The total numbers of patients treated exclusively with IORT were 39 (46%) patients while those who received the boost were 46(54%).

Disease relapse occurred in the form of index site recurrence in 5(5.8%), Axillary recurrence 3(3.5%) and Distal relapse 2(5.8%) Table 2. In the local relapse group 5(5.8%), high tumor grade III was seen in 3(60%) patients, extensive intraductal component in 2(40%), 1(20%) was reported with positive margin on initial excision and 1(20%) patient was post successful chemotherapy for a 4 cm lesion. The calculated dose administered ranged between 14.7-24.4Gy in this group. Of the index site relapse 3(3.5%) were noncompliant with intended additional WBRT as planned. 1(1.1%) was from the boost group who

Table 1. Summarizes patient's clinical data

N=85	
<45	25 (29%)
45-60	40 (47%)
>60	20 (24%)
Tumor size	
0.8- 2 cm	34 (40%)
2.1- 3 cm	28 (33%)
3.1 -4cm	15 (18%)
>4cm	8 (9%)
#Lymph node Involved	
N0	51 (60%)
N1-2	18 (21%)
N 3	4 (5%)
N>3	12 (14%)
Pathology	
IDC	74 (87%)
ILC	3 (4%)
DCIS	6 (7%)
Mucinous carcinoma	1 (1%)
Papillary carcinoma	1 (1%)
ER	
Positive	63 (74%)
Negative	19 (22%(
NA	3 (4%)
PR	
Positive	53 (62%)
Negative	30 (35%)
NA	1 (1%)
Her2	
Positive	22 (26%)
Negative	55 (65%)
NA	8 (9%)
Ki67	
<14%	9 (11%)
>14%	41 (48%)
NA	35 (41%)
Tumor Grade	
I	10 (12%)
II	40 (47%)
III	33 (39%)
Lympho-vascular invasion	
Positive	16 (19%)
Negative	69 (81%)
Margins on first excision	
Positive	12 (14%)
Negative	73 (86%)
Neoadjuvant Chemotherapy	
Positive	8 (9%)
Negative	77 (91%)

Paget's disease and extensive DCIS component (Table 3).

It is worth noting that almost half of the target patients were 48 (56%) for followed for 5 years. Disease relapse at the index site occurred between 12-36 moths of follow up. The overall disease-free survival was 88.3 % with total disease relapse 11.7%. Thus, looking at these results that was subjected to strict selection criteria if coupled by equally strict patient compliance, the true index site recurrence rate is in this review would have been only 1 (1.1%) which occurred at 36 months of follow up.

Table 2. Sites and timing of disease relapse.

N=11

Site	Number of patients
Breast	
8-12 months	1
13-30 months	0
30-36 months	4
>36 months	0
Axillary nodes	
8-12 months	1
13-24 months	2
25-36 months	0
>36 months	0
Distant Relapse	
8-12 months	1
13-24 months	0
25-36 months	0
>36 months	1

Discussion

With the global initiatives on breast cancer, health education and the wide spread of screening programs early detection strategies have been recognized and accepted in many developing countries. Overzealous efforts are needed to clear the hindrance of early detection based on the deeply rooted cultural barriers [8]. Understandably, wrong and incomplete messages on the early detection strategies, the lack of hope for cure and the liberal adoption of mutilating mastectomies that accounts for 80% of breast cancer surgical procedures in developing countries deter women from seeking early advice [9].

If these women are promised BCS when they follow early detection methods and present early adjuvant radiotherapy should be available. It remains a cornerstone in the treatment of breast cancer as 90% of local recurrences occur at the proximity of the tumor bed following BCS, thus it can aid in reducing the index site recurrence rate by two-thirds [10].

The routine WBIR delivers 45 - 50 Gy fractions daily for 5 weeks in addition to the additional boost of 10 -16 Gy to the tumor bed. This tends to lower the tumor recurrence rates to 6% at 10 years [11]. Such results are very rewarding for women in many conservative societies were body image plays a major role in life style and survival.

Unfortunately, in the ill-prepared developing countries with its limited resources and scarcity of radiation oncology centers merely denotes that BCS remains farfetched, thus limiting the offered surgical treatment options.

The concept of APBI has gained popularity over recent years rendering it a treatment of choice in breast cancer in a selected group of women. When used as a targeted boost to the tumor bed in addition to WBR, it may further reduce the local recurrence independent of age [12]. The scarcity of services in rural area finds IORT an attractive option for senior women with early breast cancer who are incapable to travel long distances to cities [13]. IORT emerges as a breakthrough for the challenged developing world. It may aid in overcoming the delays incurred by the long waiting lists and reduce the inflicted burden on the scarce radiation oncology centers when given as a boost or exclusive therapy.

In view of perceived small number of patients presenting with early breast cancer, acquiring the IORT in our institution was initially intended for boost therapy with its added benefits on the tumor bed micro-environment, it certainly was aimed to reduce the burden on the single radiation oncology center in the our area. In this current study to our surprise, despite the scarcity of early detection programs, early breast cancer was diagnosed in 39 (46%) patients and were treated exclusively with IORT, while 46(54%) received IORT as boost therapy based on the selection criteria. Not all patients eligible for BCS surgery (58.7%) were suitable for IORT treatment. (24.4%) only fit the strict selection criteria and received the treatment.

The overall disease-free survival was 88.3 % with total disease relapse 11.7% in the form of index site recurrence in 5(5.8%), Axillary recurrence 3(3.5%), Distal relapse 2(5.8%). Two mortality occurred at > 36 months. Causative factors for local relapse in this study included high tumor grade, extensive intraductal component, and positive margin on initial excision non-compliance with the prescribed WBIR. Prescribed doses of

Table 3. Demonstrates prognostic factors and timing of relapse

Age	Diagnosis	SIZE	Grade	Margins	Nodes	LVI	Dose (Gy)	ER	PR	Her2	Ki67	Neo-Adjuv.	RX	Relapse (Months)	Intended EBR
42	IDC	3.3X3.0	II	-ve	0\13	-ve	14.7	+ve	+ve	+ve	5%	-ve	IORT	30	No
41	IDC + DCIS	2.3x2.2	III	-ve	0\2	-ve	17.6	-ve	-ve	-ve	50%	-ve	IORT	36	Yes
37	IDC	1.9x1.2	II	-ve	0\2	-ve	24.4	+ve	+ve	+ve	20%	-ve	IORT	33	Yes
51	IDC+ DCIS	NA	III	+ve	0\2	-ve	20.1	-ve	-ve	+ve	30%	-ve	IORT +WBR	12	Done
47	IDC	3.4X2.6	III	-ve	3\9	-ve	18.53	+ve	-ve	+ve	50%	+ve	IORT	25	Yes

14.7- 24.5Gy both were noted in index site relapse group. Based on strict selection criteria, the intended planned and executed treatment only if coupled by patient's compliance our true recurrence would have been is only 1 (1.1%) which occurred at 36 months of follow up.

Despite the less than 5 year follow up, this initial result are quite encouraging considering the limited early detection programs. Our results thus far are similar to reported results of 4.3% in EORTC study, and with results using IORT with low recurrence of 1.5% in the targeted boost therapy [14-16]. From the technical aspects, the intrabeam radiotherapy system is mobile easy to operate equipment that can be used in safely in the conventional operating rooms. It delivers radiation through specially designed round easy handled applicators to fit the target area of the tumor bed in a one-step procedure while the patient is under anesthesia [17]. Staff safety is not jeopardized as patient is monitored during the radiation delivery as the scattered dose around shielding accounts for 1%, around the source with minimal shielding [18].

Further, the cycle of local repair is interrupted due to the radio-biological effect of the focused IORT that is known to alter both the molecular configuration and biological activity of wound fluid creating a non conducive environment for cell growth [19]. It was also reported that the targeted focused beam moderates the expression of microRNA involved in the expression of the growth factors that regulate of cancer cell growth and motility [20]. Further, as an alternative to salvage mastectomy, due to the unique targeted nature of the IORT on the breast, it may be administrated in previously irradiated breast with WBIR in an eligible subset of women for second BCS [21]. In developing countries and countries with limited resources it may also be propagated as a new modality of treatment in promoting early detection strategies [22]. Furthermore, it can be a breakthrough for those subset of women who resist early disclosure of symptoms and refuse treatment because of the limited surgical options, in addition, it may encourage oncologists to liberally utilize Neo-adjuvant treatment options thus promoting BCS [23].

Conclusion

IORT emerges as encouraging alternative in treating more patients with BCS in countries with limited resources. It provides a practical solution to the breast cancer treatment dilemma. It has proven to be a convenient, efficient, cost effective method that may aid in endorsing early detection strategies.

Conflict of Interest

None

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