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CLINICAL TRIAL REPORT

Does the Presence of Cytokeratin Positive Individual Tumor Cells ($N_{0(I+)}$) in Sentinel Lymph Nodes Affect Clinical Outcomes in Breast Cancer Patients Treated with Accelerated Partial Breast Irradiation

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Purpose: To report a primary objective clinical outcome of ipsilateral breast cancer recurrence following accelerated partial breast irradiation (APBI) with $N_{0(i+)}$ (single tumor cells or clusters <2mm) in sentinel lymph nodes. The secondary objective was to observe any incidence of ipsilateral breast failure.

Patients and Methods: Between March 2004 and April 2016, a total of 747 patients were enrolled in one of two APBI (Accelerated Partial Breast Irradiation) breast protocols (Phase II NCT01185145 and Phase III NCT01185132). Nineteen patients with $N_{0(i+)}$ disease were treated between February 2005 and December 2015. Patient eligibility included a primary invasive or DCIS tumor size <3 cm, N0(i+) disease, and margin width of >2 mm. All enrolled patients presented in this report had sentinel lymph node examinations. Clinical outcomes of ipsilateral breast, axillary and combined regional (breast or axillary) recurrences were analyzed.

Results: Median follow-up for all patients was 5 years (1–8 years). No patient experienced either ipsilateral breast or axillary recurrence.

Conclusion: There has been scarce information/reporting of the treatment of patients with cytokeratin positive individual tumor cells $N_{0(i+)}$ with APBI. The authors have presented data which suggest that the successful outcomes of these patients might warrant further study.

Keywords: breast sentinel nodes, breast conservation therapy

Introduction

Accelerated partial breast radiotherapy (APBI) has the benefit of a shortened treatment time and reduced radiation exposure to surrounding tissues when compared to whole breast irradiation (WBI). Currently, it is felt to be an acceptable alternative to breast radiotherapy for the post-lumpectomy adjuvant management of breast cancer.[1–6]

The National Comprehensive Cancer Network (NCCN) panel accepts the updated 2016 version of the American Society of Radiation Oncology (ASTRO) APBI guidelines, which now defines patients "suitable" for APBI to be the following: 50 years or older with invasive ductal carcinoma (IDCA) measuring ≤2 cm (T1 disease) with negative margin widths of ≥2 mm and node negative, no

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lymphovascular invasion, estrogen receptor (ER) positive, and BRCA 1/2 negative. In the ASTRO guidelines patients are categorized into "suitable", "cautionary", and "unsuitable" groups.[1] Recently, these guidelines were revised and expanded to include characteristics previously felt to be "cautionary" into the "suitable" category.[3] Additionally, the GEC-ESTRO Brachytherapy Committee has also published recommended APBI clinical guidelines. These guidelines state that APBI could be offered as standard therapy to node negative eligible patients > 50 years of age who have T_1 invasive ductal carcinoma with a minimum of 2 mm margins.[4] To date there is scarce information regarding the treatment of patients with cytokeratin positive individual tumor cells $N_{0(i+)}$ (single tumor cells or clusters < 2mm) following APBI treatment protocols. Previous analyses of $N_{0(i+)}$ cells range between 10–13% for positive sentinel lymph and 4.9–14.6% in non-sentinel lymph nodes.[7]

This is a retrospective analysis to observe any incidence of ipsilateral breast failure of a total of 747 patients who received APBI. Nineteen of the 747 patients with isolated tumor cells $N_{0(i+)}$ in sentinel lymph node sampling were estrogen and progesterone receptor positive, with HER 2/neu negative T_1 infiltrating ductal tumors. Therefore, other than the isolated tumor cells found in a sentinel node, these patients were generally considered to be in the "suitable" category as defined by ASTRO guidelines. There were 5 exceptions which included 2 women who were younger than 50, 2 with infiltrating lobular carcinoma, and with a 1 mm anterior margin at skin.

Materials and Methods

Between March 2004 and April 2016, a total of 747 patients were enrolled in one of two prospective APBI breast protocols (Phase II NCT01185145 and Phase III NCT01185132). Informed consent according to the Declaration of Helsinki was obtained from every patient for treatment. Patients were treated with 38.5 Gy IMRT or 3D-CRT APBI in 3.85 Gy fraction/BID fractionation for 10 fractions.

Planning volumes were constructed using the following methods. Gross target volumes (GTV) encompassed the surgical bed as defined by the CT/ultrasound, clinical target volumes (CTV) included the GTV with an additional 1 cm, planning target volume (PTV) included the CTV with an additional 1 cm. The CTV was drawn 5mm from the lung-chest wall interface, and both the CTV and PTV were drawn a minimum of 5mm from the surface of the skin. Both contralateral and ipsilateral breasts were contoured to include all breast tissue from the inframammary fold to the clavicle in the medial-lateral direction (approximately mid-axillary line to midsternal line) and the cranial-caudal direction. With the patients lying supine on a spine board, the first CT slice contoured the heart from the pulmonary artery inferiorly to the apex and both lungs were entirely contoured using a Varian Eclipse or ADAC inverse planning nodule. Standardized restrictions for plan optimization were followed according to previously published protocols*. Therapy administration used 6-MV or 15-MV from Varian linear accelerators. Patients' dose-volume histograms were individually calculated and quantified. Approval of all paired orthogonal and treatment fields occurred before treatment initiation. All patients received treatment in 10 equal fractions administered twice daily over 5 consecutive days.

Nineteen patients with $N_{0(i+)}$ disease were treated between February 2005 and December 2015. Patient eligibility included a primary invasive or DCIS tumor size < 3 cm, N0 or $N_{0(i+)}$ disease, margin width of > 2 mm and planning volume < 25% of ipsilateral breast volume. All enrolled patients presented in this report had sentinel lymph node examinations performed either by Tc_{99}lymphoscintigraphy or injection of 5cc lymphazurin blue dye injection. Two 4mm sections of positive sentinel lymph nodes were embedded in paraffin for analysis, then sectioned at 4 μm thickness. At least three H and E levels as well as adequately controlled pan-cytokeratin staining were performed on each block for evaluation by the pathologist. Clinical outcomes of ipsilateral breast, axillary and combined regional (breast or axillary) recurrences were analyzed.

Results

Patient characteristics are noted in Table 1 and treatment characteristics are listed in Table 2. Median follow-up for all patients was 5 years (1–8 years). Seven patients were enrolled onto a Phase II protocol examining the use of intensity modulation for accelerated partial breast irradiation (NCT01185145). Twelve patients were subsequently enrolled in a phase III protocol which randomized patients to one of two accelerated partial breast treatment arms, intensity modulation or 3-dimensional planning. The majority of patients (14/19) were >60 years of age (median, 65). The majority of patients were postmenopausal (17/19). Most of this patient population did not receive

Table 1 Patient Characteristics

Variable	
Age	
Median (range)	65 (44–83)
Menopausal Status	
Premenopausal	2
Postmenopausal	17
Primary Histology	
IDCA	17
ILCA	2
Margin	
Median (cm) (range)	0.6 (0.1–2)
Estrogen receptor status	
Negative	0
Positve	19
Progesterone receptor status	
Negative	0
Positve	19
HER2/neu status	
Negative	18
Positve	1
Unknown	
T stage	
$T1_{mic}$	
T1a	2
T1b	5
T1c	9
T2	3
Lymph Nodes sampled	
Median (range)	2 (1–8)
Lymph Nodes positive	
Median (range)	1 (1–2)
Surgery-XRT interval	
Median (range)	63 (32–80)
Hormone Therapy	
Femara	2
Arimedex	7
Letrozole/Aromasin	1
Arimedex/Femara	4
Arimidex/Tamoxifen	1
Tamoxifen	3
Femara/aromisin	1
Chemotherapy	5

chemotherapy (14/19) and all were administered hormone therapy. Tumor size ranged from 0.2 cm to 2.5 cm (median, 1.3 cm). Seventeen of the 19 patients had infiltrating ductal histologies and two patients had infiltrating lobular tumors. All but one patient were estrogen and progesterone positive; this patient was estrogen receptor positive but progesterone receptor negative. Two patients were HER2/neu positive and seventeen patients were HER2/neu negative. The median margin size was 6 mm (range 1–20 mm). There were three patients with T_2 tumors and the remaining patients were T_1. All patients had pathologically proven involvement of at least one node with isolated tumor cells and were staged by sentinel node procedure and examination. The number of dissected nodes ranged from 1–8 with a median number of 2 lymph nodes removed. Only one patient had more than one positive lymph node (that patient had a total of 2 positive lymph nodes).

No patient experienced either ipsilateral breast or axillary recurrence nor is any patient deceased.

Discussion

The majority of previous reports have also shown that the presence of $N_{0(i+)}$ disease has not shown any impact on overall survival.[11–17,19] There has also been evidence that there is no impact on distant relapse, axillary recurrence or local recurrence.[8–13,15–19] However, treatment has not been homogenous. Some patients have had axillary dissections, sentinel node evaluations only or both.[8,11–13,15–17] Axillary regional irradiation as well as chemotherapy have also been utilized to treat $N_{0(i+)}$ patients.[8,11–13,16,17,19] Patient cohorts have also included a varied mix of patients undergoing breast conservation or mastectomy.[11,15–17,19,20] To date, none of these reports concern the use of accelerated partial breast radiotherapy. However, because of this exploratory analysis, further research of this $N0_{(i+)}$ patient group might be warranted, and pertinent for their inclusion into conservative breast cancer treatment with accelerated partial breast irradiation.

Conclusion

The small scale of this study prevents definitive conclusions to be taken. However, the significance of these results in combination with the reasonable follow-up time suggests that accelerated partial breast irradiation may be appropriate in patients with $N_{0(i+)}$ disease, supporting continued research in these patients. These data suggest that APBI in combination with hormonal treatments after sentinel lymph nodes biopsy could effectively treat breast cancer patients with $N_{0(i+)}$ sentinel lymph nodes who have estrogen and progesterone receptor positive,

Table 2 Treatment Characteristics

Age	Chemo	Hormone Therapy	Tumor Size (cm)	T Stage	ER	PR	Her2	Margin Size	Histology	Menopause Status	Sentinel Nodes Removed	Positive Sentinel Nodes
81	No	Femara	1.8	T1c	Pos	Pos	Neg	0.5	IDCA	Post	2	1
63	No	Arimidex	1.8	T1c	Pos	Pos	Neg	0.5	IDCA	Post	2	1
65	Yes	Arimidex	2.5	T2	Pos	Pos	Pos	1.0	IDCA	Post	4	1
68	Yes	Femara/ Aroisin	0.5	T1a	Pos	Pos	Neg	0.6	IDCA	Post	1	1
71	No	Arimidex	0.2	T1b	Pos	Pos	Neg	0.8	ILCA	Post	2	1
65	No	Arimidex	0.8	T1b	Pos	Pos	Neg	1.0	IDCA	Post	8	1
60	No	Arimidex	1.5	T1c	Pos	Neg	Neg	0.1	IDCA	Post	2	1
75	No	Tamoxifen	1.1	T1c	Pos	Pos	Neg	2.0	IDCA	Post	2	1
48	Yes	Tamoxifen	1.5	T1c	Pos	Pos	Neg	0.6	ILCA	Pre	1	1
67	No	Arimidex	0.7	T1b	Pos	Pos	Neg	0.6	IDCA	Post	4	1
68	No	Arimidex	2.5	T2	Pos	Pos	Neg	0.5	IDCA	Post	2	1
62	No	Letrozole/ Aromasin	2.3	T2	Pos	Pos	Neg	0.5	IDCA	Post	2	1
56	No	Arimidex/ Femara	0.9	T1b	Pos	Pos	Neg	0.5	IDCA	Post	5	1
55	Yes	Arimidex/ Femara	1.3	T1c	Pos	Pos	Neg	0.3	IDCA	Post	3	2
65	No	Femara	0.5	T1a	Pos	Pos	Neg	1.0	IDCA	Post	1	1
65	No	Arimidex/ Femara	1.5	T1c	Pos	Pos	Pos	0.5	IDCA	Post	2	1
59	Yes	Arimidex/ Femara	1.3	T1c	Pos	Pos	Neg	1.0	IDCA	Post	2	1
83	No	Arimidex/ Tamoxifen	1.2	T1c	Pos	Pos	Neg	1.0	IDCA	Post	4	1
44	No	Tamoxifen	0.6	T1b	Pos	Pos	Neg	0.5	IDCA	Pre	3	1

HER 2/neu negative T_1 infiltrating ductal tumors. The patients from this study will continue to be monitored for any recurrence. The preliminary findings from this novel study warrant future studies involving larger sample sizes, particularly focused on the clinical outcomes of the newly "suitable" treatment of $N_{0(i+)}$ disease using APBI protocols.

Data Sharing Statement

All patient data including all history/physical as well as protocol treatment and follow-up are reposed and stored indefinitely in an electronic database as well as paper chart here at Rocky Mountain Cancer Centers. Deidentified records/files are available for sharing.

Ethics Statement

All patients were enrolled/consented for one of two treatment protocols approved by WIRB (initial approval 7/7/09) – 20091193, WIRB (initial approval 1/30/04)-2004 0075).

Disclosure

The authors report no conflicts of interest in this work.

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