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Application of 21-gene recurrence score results and ASTRO suitability criteria in breast cancer patients treated with intraoperative radiation therapy (IORT)

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ABSTRACT

Background: American Society for Radiation Oncology (ASTRO) suitability criteria for accelerated partial breast irradiation (APBI) and the 21-gene recurrence score (RS) were evaluated for prognostic and predictive benefit in IORT patients.
Methods: Outcomes of 184 patients completing IRB approved IORT protocol were retrospectively reviewed. Data included demographics, histopathology, RS, adjuvant therapy, locoregional (LRR) and distant recurrences (DR), and breast cancer-specific survival.
Results: There were 10 (5.4%) breast cancer recurrences, including one breast cancer-specific death. All 184 patients were classified by ASTRO suitability criteria (suitable: 64% (5 LRR), cautionary: 30% (3 LRR), unsuitable: 6.0% (1 LRR, 1 DR leading to death). RS were available in 114 estrogen receptor positive patients (<11: 22% (1 LRR), 11–25: 63% (1 LRR), 26–30: 9%, >30: 6%). Mean follow-up was 55 months.
Conclusions: ASTRO suitability criteria for APBI and RS were useful in making prognostic and therapeutic recommendations for patients considering IORT.

Introduction

IORT has allowed for delivery of a single fraction of radiation following lumpectomy for early stage breast cancer while in the operating room. Use of intraoperative brachytherapy was widely reported in two prospective, randomized multi-institutional studies. The ELIOT trial reported the results of 1246 patients receiving either whole breast radiation (WBRT) or intraoperative electron beam radiotherapy (IOERT) using the NOVAC 7(R) (Hythesis, Latina, Italy) or Liac(R) (Info and Tech, Rome, Italy) device.[1] At 5.8 years, overall recurrence rates for this non-inferiority non-risk adapted trial were reported as 4.4% for IOERT versus 0.4% for WBRT. Low 50 kV intraoperative electronic beam brachytherapy (IORT) was reported in the TARGIT-A trial, using the Intrabeam(R) (Carl Zeiss Meditec, Oberkochen, Germany) device.[2] The trial accrued 3451 patients, including 1222 patients followed for 5 years. Using Kaplan-Meier estimates, recurrence rates in this prospective randomized non-inferiority risk adapted trial were 4.2% for IORT versus 2.0% for WBRT. Both trials included patients who would not be treated with IORT by today's standards. Recurrence rates were reported in two additional nonrandomized retrospective studies using Intrabeam(R) technology. Targit-R, a North American study (mean follow-up of 23.3 months) reported a recurrence rate of 2.4% (537 patients) when IORT was used as the primary therapy.[3] A 2% recurrence rate was noted in 100 patients at mean follow-up of 24 months in a study which evaluated outcomes related to age.[4]

Four IORT registry studies using a Xoft(R) Axxent(R) disposable

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balloon applicator brachytherapy device (Axxent, a subsidiary of iCAD, Nashua, New Hampshire) were published. A 0.15% recurrence rate was reported in a multi-institutional study of 667 patients at mean follow-up of 11 months.[5] A 0.8% recurrence rate was noted in 261 IORT patients with average follow-up of 15.6 months.[6] A 1.9% recurrence rate was reported in 702 IORT patients with a median time to local recurrence of 24.2 months,[7] while a 6% recurrence rate was reported at 5 year follow-up in 69 patients treated with IORT.[8]

IORT and IOERT were considered subsets of a broader treatment spectrum utilizing APBI. In 2008, the APBI Consensus Statement Task Force of the Health Services Research Committee of ASTRO provided guidelines for the application of APBI outside of clinical trials, based on literature review and expert opinion.[9] This task force, which established 3 patient groups (suitable, cautionary, unsuitable) for off-protocol ABPI use published in 2009, provided an update of their categories in 2016.[10] The updated ASTRO suitable category included women at least 50 years of age with estrogen receptor (ER) positive (+) T1 unicentric and/or unifocal invasive tumors of any grade and favorable histologic subtype having margins of at least 2 mm without lymphovascular invasion or an extensive intraductal component. Pure ductal carcinoma in situ (DCIS) was considered suitable if it was screen-detected, low to intermediate nuclear grade, no larger than 2.5 cm in diameter, and had resected margins of at least 3 mm. The updated ASTRO cautionary group included women 40–49 years of age if all other criteria for the suitable category were met. It otherwise included women age 50 or higher if the tumor was 2.1–3.0 cm in greatest diameter, had close (less than 2 mm) margins, had limited lymphovascular invasion, was ER negative (−), or had invasive lobular histology. DCIS measuring no more than 3 cm was considered cautionary if the suitable criteria for DCIS were not fully met. The updated ASTRO unsuitable category included women less than 40 years of age who were BRCA 1/2 mutation positive and had tumors of at least 3 cm with positive margins, extensive lymphovascular invasion, extensive intraductal component of greater than 3 cm, multicentricity and/or multifocality and positive lymph nodes. DCIS in this category measured at least 3 cm in size.

The 2016 consensus statement, which acknowledged IORT, stated that low-energy x-ray IORT for partial breast irradiation should be used within the context of a prospective registry or clinical trial due to higher reported recurrence rates and should be restricted to women with invasive cancer considered “suitable” for partial breast irradiation.

The 21-gene recurrence score (RS) assay quantified the prospective benefit of chemotherapy in minimizing risk of LRR and DR in ER + patients with invasive breast cancer treated with adjuvant endocrine therapy. The likelihood of DR in patients treated with tamoxifen versus placebo was demonstrated using archival tissue from patients enrolled in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 clinical trial.[11] Archival tissue was evaluated using a reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay for 21 prospectively selected genes and correlated to the likelihood of DR in patients with node-negative, tamoxifen-treated breast cancer. The Kaplan-Meier estimates of the DR rates at 10 years was 6.8% in the low risk group (RS 0–18), 14.3% in the intermediate group (RS 19–30) and 30.5% in the high risk group (RS > 30). RS and high tumor grade were significant predictors of recurrence, although there was substantial variability in assignment of tumor grade by the three central trial pathologists. LRR was thought to be a significant predictor of DR in these patients. The association between RS and the risk of LRR was subsequently demonstrated in 895 tamoxifen-treated patients (NSABP B-14 and B-20), 355 placebo-treated patients (NSABP B-14) and 424 chemotherapy plus tamoxifen-treated patients (NSABP B-20).[12] In tamoxifen-only treated patients, LRR was significantly higher in the high RS group (>30), which had a 15.8% LRR risk using 10 year Kaplan-Meier estimates. The TAILORx study further evaluated 1629 (15.9%) patients, categorized into a newly assigned low risk RS group (<11), also placing 6907 (67.3%) patients into a midrange RS group (11–25), and 1736 (16.9%) patients into a high RS group (>25).[13] At median follow-up of 69 months, the patients in the low risk RS group who were compliant with their adjuvant medical therapy had a rate of freedom from LRR or DR of 98.7% when treated with adjuvant endocrine therapy alone without chemotherapy.

Benefit from receiving any radiation therapy has been questioned. The PRIME II study, randomizing women aged at least 65 years with low-risk breast cancers (hormone receptor +, axillary node-negative, T1-T2 of no more than 3 cm, clear margins, and grade 3 or lymphovascular invasion but not both) to adjuvant endocrine therapy with (658 women) or without (668 women) WBRT demonstrated the prognostic significance of grade.[14] At 5 years, ipsilateral breast tumor recurrences (IBR) were 4.1% in the adjuvant therapy group versus 1.3% in the group also receiving WBRT. Patients with low ER status and grade 3 tumors were of borderline significance in prediction of LRR in those patients not receiving WBRT. The Cancer and Leukemia Group B (CALGB) 9343 study reported long term follow-up of 636 women (aged at least 70 years with ER + early stage breast cancer) in a prospective randomized trial comparing tamoxifen alone to tamoxifen plus WBRT.[15] At 10 years, 90% of patients receiving tamoxifen were free from LRR versus 98% of patients receiving tamoxifen plus WBRT. There was no difference in breast cancer-specific deaths or overall survival. The CALGB 9343 study did not report compliance with medical therapy or stratification by grade.

Short term data now exists in regards to IORT LRR and DR rates, along with information about breast cancer-specific deaths and overall survival. It is unknown whether use of the current ASTRO suitability criteria, defining APBI eligibility, or RS, which predicts benefit from chemotherapy, has application in IORT patient outcomes.

Methods

Two hundred twenty-one patients were accrued prospectively to voluntarily enroll in this physician-sponsored non-randomized trial approved by the HCA-HealthONE Institutional Review Board. The trial patients were to receive a single fraction of 50 kV electronic brachytherapy immediately following lumpectomy while still in the operating room.

Women at least 40 years of age with a single focus of biopsy-proven infiltrating ductal carcinoma no larger than 2.5 cm were eligible for this trial. Tumor size no larger than 3.0 cm and DCIS were added to the eligibility criteria after the first 51 subjects enrolled. Inclusion criteria included all breast cancer molecular subtypes. Pre-operative work-up included a mammogram, ultrasound and bilateral breast MRI. Axillary lymph nodes were screened for metastatic disease radiographically and by examination prior to surgery.

Exclusion criteria were patients with biopsy-proven multifocal breast cancer, lymphovascular invasion, radiographic or biopsy-proven positive lymph nodes, extensive intraductal component of 25% or more, metastatic disease, a history of ipsilateral breast cancer and/or irradiation to the same breast or thorax. Patients receiving neoadjuvant chemotherapy, neoadjuvant endocrine therapy or who had surgical and/or radiation therapy already performed for this cancer were excluded. Additional exclusion criteria included: BRCA 1/2 mutation positivity, pregnancy, lactation, scleroderma, systemic sclerosis or active lupus, an ipsilateral pacemaker, serious psychiatric or addictive disorders.

Once in the operating room, each patient underwent a sentinel

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