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Prognostic Indicators Following Ipsilateral Tumor Recurrence In Patients Treated With Breast Conserving Therapy

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Introduction

Breast cancer remains the most frequently diagnosed malignancy in women with an estimated 182,460 new cases of invasive cancer diagnosed in 2008 and an estimated 40,480 deaths expected to occur this year alone 1. Correspondingly, incidence rates continue to rise due to improved screening. Fortunately, this has allowed a greater proportion of early stage breast cancers to be detected and consequently allows a greater percentage of women to be eligible for breast conserving therapy (BCT).

Whereas, seminal randomized trials have shown equivalent overall survival and distant disease-free survival rates with BCT as compared to mastectomy in treating early stage invasive breast cancer (1-4), local failure rates tend to be higher with BCT (5-7). Indeed, in a retrospective analysis of five National Surgical Adjuvant Breast and Bowel Project (NSABP) trials by Wapnir et al., 9.7% of patients experienced IBTR (8). Taken together, this certainly raises questions regarding the implications of IBTR.

Several studies have attempted to elucidate the relative prognostic significance of IBTR following breast conservation, yet the data is often conflicting, especially with regard to routine surveillance following initial treatment. Herein, we attempt to determine significant predictors of systemic recurrence following IBTR, which may provide insight into optimal clinical management following initial treatment, as well as recurrence of breast cancer.

Materials/Methods

With Institutional Review Board approval, we conducted a retrospective single institution chart review of all newly diagnosed breast cancer patients treated between 1981 and 2007 to identify women treated with breast conserving surgery. Of these, all patients who received adjuvant radiation therapy and subsequently developed IBTR were identified. IBTR was defined as an adenocarcinoma recurrence within the conserved breast. Breast conserving surgery consisted of wide local excision of the tumor in an attempt to obtain

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macroscopically negative margins of 1 cm in combination with sentinel lymph node biopsy and/or axillary lymph node dissection at the discretion of the surgeon. Radiation therapy was delivered by external beam to the whole breast using opposed tangential fields. Doses ranged from 4500 cGy to 5400 cGy in 180 cGy to 200 cGy daily fractions. The lumpectomy cavity was then boosted with en-face electrons to doses ranging from 1000 cGy to 1200 cGy. Chemotherapy was administered to patients with initial lymph node involvement, tumors greater than 1 cm or other high-risk features of disease, as deemed appropriate by the treating medical oncologist. A selective estrogen receptor modifier, e.g. tamoxifen, was given to in the adjuvant setting to post-menopausal women with estrogen receptor (ER) positive tumors at the discretion of the medical oncologist.

Patients were seen by a treating physician for history, physical and clinical breast exam every 6 months following treatment for five-years, and annually thereafter if they remained without clinical or radiographic evidence of disease. Generally, mammograms were obtained at 6 and 12 months post-radiation therapy and annually thereafter if they remained normal. MRI was obtained at the physician's discretion. All IBTRs were biopsy proven. Patients who presented with synchronous recurrent local and metastatic disease, or distant disease within thirty days of local recurrence, were excluded from analysis. Charts were reviewed for demographics, clinical presentation, time to diagnosis, method of detection, American Joint Committee on Cancer stage, histopathology, types of therapy, margin status and patient status as of last follow-up for both the primary and recurrent tumors. All patients not currently receiving routine office follow-up visits were interviewed in person or by telephone to assess most current status.

Primary outcome was distant metastases-free survival. The following variables were identified and analyzed as potential predictors of DMFS: initial T stage, initial nodal status, initial receptor status, initial margin status, adjuvant RT, age at time of recurrence, location of recurrence, histology of recurrence, time to recurrence, method of detection of recurrence and management of recurrence. A multivariate analysis using the Cox proportional hazards model was performed to evaluate independent predictors of DMFS.

Results

A total of 1733 patients were treated with breast conserving surgery of whom 199 (11%) developed IBTR (Table 1). One hundred and fifty seven patients of 199 also received adjuvant radiation therapy. Median time from initial diagnosis to recurrence was 44 months (range 7 to 242 months). Median follow-up after recurrence was 27 months (range 1 to 231 months). At time of initial diagnosis, 98% of patients had T1 or T2 tumors, 80% were node negative and 67% of resections were to negative margins (Table 1). One hundred and thirty one of 157 (83%) patients had recurrences within 3 cm of the initial tumor bed and 65% of all IBTRs were detected radiographically (mammography and/or MRI). Median time from IBTR to DM was 151 months. Overall 5-year DM-free survival following IBTR was 69.5%.

Univariate analysis revealed the type of IBTR management, younger age, lymph node positivity at initial diagnosis, higher initial T stage, shorter time to IBTR, histology of recurrence (invasive > mixed invasive and DCIS > DCIS) and method of detection (clinical

> radiographic) of IBTR were significant predictors of lower DM-free survival (Table 2). In contrast, location of tumor recurrence, initial margin status and initial tumor receptor status were not significant predictors of DM-free survival by univariate analysis. Subsequent multivariate Cox regression analysis to ascertain the independent prognostic effect of these variables on DM-free survival showed that method of detection of local recurrence remained significant (Figure 1). Median DM-free survival for clinically and radiographically detected IBTRs was 54 months and 231 months, respectively. Adjusted relative risk for clinically detected IBTRs was 2.2.

Conclusions

Several studies have suggested that development of IBTR following BCT for early stage cancer predicts for a poorer outcome including distant metastases (5, 6, 9). Based upon follow-up data from NSABP-B06, Fisher et al. found that the risk of distant disease was 3.41 times greater following IBTR after adjusting for co-variables (5). Moreover, Whelan et al. found that IBTR predicted for an increased mortality risk ($RR = 2.18$), as well as higher risk of distant relapse (9). Given these findings, the importance of identifying risk factors and defining characteristics before and after IBTR becomes self-evident. However, the literature is conflicting and individual management is thus challenging.

In a large cooperative effort of the Dutch Study Group on Local Recurrence after Breast Conservation, Voogd et al. identified 266 patients who developed local recurrence after BCT (10). Cox regression analysis revealed that initial lymph node involvement, histologic grade of primary tumor, skin involvement of recurrent tumor, as well as size of recurrent tumor were significant predictors for distant metastases in patients. In our study, while initial lymph node involvement was a significant predictor of DMFS on univariate analysis, it was not significant after multivariate analysis. Additionally, unlike our study, patients with non-invasive recurrence were excluded from final analysis, which could have contributed to poorer outcomes. Whereas, follow-up of their patient cohort was limited, the study proved to be an important step forward in attempting to risk stratify patients who develop recurrence (10, 11).

Contrary to our study and that by Voogd et al., Doyle et al. were unable to identify any factors that predicted for freedom from distant metastases. They did find that interval from diagnosis to local recurrence was the only independent predictor of overall survival at 5 years (12). This has been further confirmed in a study by Haffty et al. who found recurrences within 4-yr of initial diagnosis portend a poorer DMFS and OS (6). Given that most patients present with distant disease, the authors concurred with other studies in suggesting that rapidly recurring tumors are likely to be more biologically aggressive, and such patients should be considered for systemic therapy (6, 9, 12, 13). We found time to recurrence to be a significant predictor of DMFS on univariate but not multivariate analysis, and the outcome of OS was not analyzed in our study. Additionally, given patients with longer time to recurrence have better outcomes, increasing effort should be made to diagnose at earlier stages (14). Abner et al. found that histology of recurrent tumor predicted for subsequent relapse, as patients with purely non-invasive or focally invasive recurrences had excellent prognosis following salvage mastectomy (15). Similarly, in our study,

histology of recurrence predicted for improved DMFS on univariate analysis, yet this did not hold true following multivariate analysis (16).

Orel et al. specifically attempted to address the prognostic implications of method of detection of IBTR following BCT and found a statistically significant association between mammographically detected tumors and their size (17). Whereas the authors noted a trend towards improved RFS or OS, it was not statistically significant. Mammographic diagnosis of LR was made in 47% of patients and there was a trend towards higher percentage of non-invasive disease detection. We also identified a trend toward higher number of non-invasive recurrences detected by mammography as compared to clinical exam, which could likely be attributed to the presence of microcalcifications and the high sensitivity of mammographic detection of DCIS (18). Therefore, although mammographically detected tumors were smaller, this did not portend a more favorable outcome. Based on these and other data, the authors recommended mammogram at 9-12 months post-radiation and annually thereafter unless otherwise indicated (19-21).

Interestingly, in a recent study of IBTR following BCT for DCIS, 97% of recurrences were mammographically detected (16). In this study, post-BCT surveillance consisted of mammograms at 6, months, 12 months and annually thereafter. This favorably compares to 65% in our study and 47% in the the study by Orel et al., given 72% of recurrences were mostly DCIS and 75% of all recurrences had calcifications noted on mammography. In spite of a mean time to recurrence of 4.5 years, 91% of tumors were minimal and all were stage 0 or 1. Unfortunately, whereas ample information was provided regarding mammography and imaging assessment, the authors failed to provide follow-up history and physical information regarding clinical breast examination, which could potentially confound results.

Voogd et al. found tumor recurrences larger than 1 cm to be a significant predictor for development of distant metastases on multivariate analysis. However, this only loosely correlated with method of detection, as only 34% of mammographically detected tumors were ≤ 1 cm. In contrast, only 18% of tumors detected by physical examination were ≤ 1 cm ($P = 0.04$). The authors also noted a higher rate of mammographic detection of local recurrences in women older than 45, as would be expected. Given the larger percentage of smaller tumors detected by mammography, as well as the higher rate of distant metastases in patients with IBTR > 1 cm, the authors contend that annual mammography appears to contribute to early detection, which in turn, may improve treatment outcomes. In spite of this, method of detection was not found to be a significant predictor of distant metastases following multivariate analysis. Indeed, in a systematic review of the literature, Montgomery et al. analyzed whether method of detection of relapse influenced outcome and concluded that an increasing proportion of IBTRs were being detected mammographically (14). Additionally, they found that patients with clinically detected IBTRs tended to have worse outcomes. The importance of post-treatment surveillance mammography was further highlighted by Doubeni et al. who found its use among breast cancer survivors decreased significantly over time following treatment, especially in women of age 55 or more with comorbid illnesses or late stage disease (22). Given the prognostic significance of post-treatment mammography in our study, combined with median time to recurrence of 44

months, we believe that routine long-term mammographic surveillance is indicated following BCT.

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None

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Figure 1.

Table 1

Patient Characteristics	No. of Patients
Local recurrence	119/173
Adjuvant RT initial tumor	
Yes	157/199
No	42/199
Site of IBTR	
< 3 cm from tumor bed	131/157
> 3 cm from tumor bed	26/157
Method of detection	
Clinical	103/157
Radiographic	54/157
Intital T Stage	
T1	103/157
T2	51/157
T3	2/157
T4	1/157
Intital nodal status	
N0	125/157
N1	26/157
N2	6/157
Intital margin status	
Negative	105/157
positive	19/157
Unknown	33/157

Table 2

Variable		P value <.05
Initial T stage		Yes
Initial nodal status		Yes
Initial receptor status		No
Initial margin status	—	No
Adjuvant Rt	—	No
Younger age at IBTR		Yes
Location of recurrence		No
Histology of recurrence		Yes
Time to recurrence		Yes
Method of detection		Yes
IBTR management		Yes