Int. J. Radiation Oncology Biol. Phys., Vol. 63, No. 5, pp. 1514–1521, 2005

0360-3016/05/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2005.04.045

CLINICAL INVESTIGATION **Breast**

FACTORS ASSOCIATED WITH LOCAL RECURRENCE AND CAUSE-SPECIFIC SURVIVAL IN PATIENTS WITH DUCTAL CARCINOMA *IN SITU* OF THE BREAST TREATED WITH BREAST-CONSERVING THERAPY OR MASTECTOMY

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Purpose: We reviewed our institution's experience treating patients with ductal carcinoma *in situ* (DCIS) of the breast to determine risk factors for ipsilateral breast tumor recurrence (IBTR) and cause-specific survival (CSS) after breast-conserving therapy (BCT) or mastectomy.

Materials and Methods: Between 1981 and 1999, 410 cases of DCIS (405 patients) were treated at our institution; 367 were managed with breast-conserving surgery (54 with lumpectomy alone and 313 with adjuvant radiation therapy (RT) [median dose, 45 Gy]). Of these 313 patients, 298 received also a supplemental boost of RT to the lumpectomy cavity (median dose, 16 Gy). Forty-three patients underwent mastectomy; 2 (5%) received adjuvant RT to the chest wall. A true recurrence/marginal miss (TR/MM) IBTR was defined as failure within or adjacent to the tumor bed in patients undergoing BCT. Median follow-up for all patients was 7 years (mean: 6.1 years).

Results: Thirty patients (8.2%) experienced an IBTR after BCT (25 [8%] after RT, 5 [9.3%] after no RT), and 2 patients (4.7%) developed a chest wall recurrence after mastectomy. Of the 32 local failures, 20 (63%) were invasive (18/30 [60%] after BCT and 2/2 [100%] after mastectomy), and 37% were DCIS alone. Twenty-four (80%) of the IBTRs were classified as TR/MM. The 10-year freedom from local failure, CSS, and overall survival after BCT or mastectomy were 89% vs. 90% ($p = 0.4$), 98% vs. 100% ($p = 0.7$), and 89% vs. 100% ($p = 0.3$), respectively. Factors associated with IBTR on Cox multivariate analysis were younger age ($p = 0.02$, hazard ratio [HR] 1.06 per year), electron boost energy ≤9 MeV ($p = 0.03$, HR 1.41), final margins ≤2 mm ($p = 0.007$; HR, 3.65), and no breast radiation ($p = 0.002$, HR 5.56). On Cox univariate analysis for BCT patients, IBTR, TR/MM failures, and predominant nuclear Grade 3 were associated with an increased risk of distant metastases and a reduced CSS.

Conclusions: After treatment for DCIS, 10-year rates of local control, CSS, and overall survival were similar after mastectomy and BCT. Young age (<45 years), close/positive margins (≤2 mm), no breast radiation, and lower electron boost energies (≤9 MeV) were associated with IBTR. Local failure and predominant nuclear Grade 3 were found to have a small (4%–12%) but statistically significantly negative impact on the rates of distant metastasis and CSS. These results suggest that optimizing local therapy (surgery and radiation) is crucial to improve local control and CSS in patients treated with DCIS.

Ductal carcinoma *in situ*, Breast neoplasms, Local recurrence, Distant metastasis, Cause-specific survival.

INTRODUCTION

Breast-conserving therapy (BCT) remains an accepted option in the management of most patients with ductal carcinoma *in situ* (DCIS) of the breast (1–4). In an effort to optimize treatment outcome in these patients, multiple groups have examined the association of various clinical, pathologic, and treatment-related factors with the development of local recurrence (1, 3, 5–8). In addition, analyses of long-term data also indicate that a small but real percentage of local recurrences after treatment for DCIS contains a component of invasive disease, conferring a potentially increased risk of distant metastases and death. Although there are no randomized trials demonstrating differences in survival between BCT and mastectomy for the DCIS, it is clear that patients who experience local failures (regardless of the treatment regimen) have a reduced rate of survival. Whether or not the prevention of these local failures could have eliminated the risk of a reduced survival remains unclear. To date, there have been very few data specifically

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Presented at the 46th Annual Scientific Meeting of the American Society for Therapeutic Radiation and Oncology (ASTRO), Atlanta, Georgia, October 3–7, 2004.

Received Mar 14, 2005, and in revised form April 19, 2005. Accepted for publication April 20, 2005.

addressing this issue. As a result, we reviewed our institution's experience treating patients with DCIS of the breast with either BCT or mastectomy to examine risk factors for ipsilateral breast tumor recurrence (IBTR) and its impact on outcome.

METHODS AND MATERIALS

Between January 1980 and June 1999, 410 breasts in 405 patients were treated for DCIS of the breast at William Beaumont Hospital, Royal Oak, Michigan. Three hundred sixty-seven cases were treated with breast-conserving therapy, 54 (14.7%, 54/367) with lumpectomy alone, and 313 (85.3%, 313/367) with whole-breast radiation; in 298 patients (81.2%, 298/367), a supplemental radiation boost was added to the tumor bed. The remaining 43 patients underwent mastectomy (2 [5%, 2/32] received adjuvant radiation therapy [RT] to the chest wall).

All women had American Joint Committee on Cancer clinical Stage 0 (Tis, N0, M0) DCIS of the breast. Patients with the following findings were excluded: (*1*) invasive carcinoma of the breast, (*2*) microinvasive carcinoma of the breast, and (*3*) metastatic lymph nodes at the time of diagnosis. Five patients (1.2%) with previous or simultaneous contralateral DCIS were included in the study population. However, previous or simultaneous contralateral invasive breast cancers were excluded from all survival analyses ($n = 18$).

The surgical treatment in all cases included at least an excisional biopsy, defined as an excision of tissue around the tip of the needle localization wire. The initial excision was guided by needle localization in 320 of breast-conserving cases (87.3%). Two hundred eighty-six cases (77.9%, 286/367) underwent a re-excision of the primary tumor site because of close (<2 mm), positive, or uncertain margins or at the discretion of the surgeon or radiation oncologist. In some cases, postexcisional (preirradiation) mammograms were obtained (37.7%) to exclude residual microcalcifications in the breast.

Since 1990, surgical staging of the axilla in cases of DCIS has not been performed routinely at William Beaumont Hospital. Nonetheless, pathologic lymph node data were available for 115 cases (28%, 115/410). All excised lymph nodes were free of metastasis. The median number of lymph nodes removed was 12 (range, 1–28 nodes).

Our radiation technique has been previously reported (9). Briefly, RT was initiated at a median interval of 30 days after the last surgical procedure (range, 7–170 days). The entire breast was irradiated with tangential fields in 313 cases with 4–6-MV photons to a median dose of 45.0 Gy (mean, 46.5 Gy; range, 43.1–56.0 Gy). Whole-breast irradiation was followed by a supplemental boost to the tumor bed in 298 cases (95.2%, 298/313), for a median total dose of 61 Gy (range, 45.0–71.8 Gy). In 266 cases (89.3%, 266/298), this was delivered with direct electron beam teletherapy, in 30 (10%, 30/298) with an interstitial implant, and in 2 cases (0.7%, 2/298) with photon beams. Regional lymphatics were not treated in any patient, and no adjuvant chemotherapy was administered. Thirty-three patients (9.0%, 33/367) received adjuvant tamoxifen.

All specimen slides were reviewed for this study by the department of pathology at our institution. The following information and pathologic features were recorded for the initial biopsy and re-excision specimens: (*1*) total number of slides examined from each specimen; (*2*) maximum specimen dimensions; (*3*) maximum DCIS tumor dimensions; (*4*) predominant histologic subtype (comedo, cribriform, papillary, micropapillary, solid, clinging, or cystic); (*5*) predominant nuclear grade; (*6*) highest nuclear grade; (*7*) margin status [positive, close (≤2 mm from the margin), negative (>2 mm from margin), or uncertain (specimen was not inked or was fragmented such that the specimen margin could not be determined)]; (*8*) distance from the tumor edge to the margin (mm); (*9*) presence or absence of residual malignancy at re-excision.

Treatment-related and clinical factors analyzed included: (*1*) surgery type (lumpectomy vs. mastectomy); (*2*) radiation administration for breast-conserving cases; (*3*) initial radiation photon energy, fraction size, and dose; (*4*) radiation boost administration, energy, and type (electrons vs. other); (*5*) patient's age; (*6*) menopausal status; and (*7*) palpable abnormality. Mammographic findings were recorded from a retrospective review of reports on patient charts. Results were categorized as follows: (*1*) mass alone (with no calcifications), (*2*) calcifications alone, and (*3*) both a mass and calcifications. The vast majority of patients underwent standard screening mammography with two-view film (craniocaudal and mediolateral oblique) and magnification views of suspicious calcifications or masses. Preradiation mammogram was done in 37.7% of patients to assess the completeness of removal of any suspicious calcifications.

After completion of breast irradiation, patients were evaluated every 3 months for the initial 2 years of follow-up and at 6-month intervals thereafter. Patients frequently alternated follow-up visits between their surgeon and radiation oncologist. Mammograms were performed 6 months after completion of treatment and annually thereafter unless a given mammographic finding warranted earlier follow-up.

An ipsilateral failure was defined as the reappearance of cancer in the treated breast before or at the time of metastases. Ipsilateral failures were classified according to the criteria described by Recht *et al.* (10). A true recurrence/marginal miss (TR/MM) was defined as a recurrence within or immediately adjacent to the boost volume (or the primary tumor site in patients who did not receive radiation or a boost). TR/MM was not evaluated for patients after mastectomy. Twenty-seven of the 30 cases of IBTR were managed with salvage mastectomy, whereas the remaining 3 were managed with wide local excision with or without additional RT.

Rates of IBTR, TR/MM, distant failure, overall survival, and cause-specific survival (CSS) were calculated using the Kaplan–Meier method (11). Significance of differences of the curves for numerous risk factors was determined using the log–rank test. The Cox proportional hazards model was used for univariate and multivariate analysis to determine significant risk factors for IBTR and TR/MM (12). A two-tail p value of ≤0.05 was considered to be statistically significant for all tests. All time intervals were calculated from the date of initial surgery. Statistical analysis was performed using Systat version 10.0 (SPSS Inc., Chicago, IL).

The median follow-up period for all patients is 6.1 years (range, 1–18.5 years). Two hundred forty-four (59.5%) have been followed up for a minimum of 5 years, and 102 patients (24.9%) have been followed up for more than 10 years.

RESULTS

Characteristics of patients treated with all forms of BCT are shown in Table 1. There were no statistically significant differences in any variables between patients treated with lumpectomy alone ($n = 54$) or lumpectomy followed by