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CLINICAL INVESTIGATION **Breast**

LOCOREGIONAL RECURRENCE OF BREAST CANCER IN PATIENTS TREATED WITH BREAST CONSERVATION SURGERY AND RADIOTHERAPY FOLLOWING NEOADJUVANT CHEMOTHERAPY

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Purpose: Breast conservation surgery (BCS) and radiotherapy (RT) following neoadjuvant chemotherapy (NCT) have been linked with high locoregional recurrence (LRR) rates and ipsilateral breast tumor recurrence (IBTR) rates. The purpose of this study was to analyze clinical outcomes in patients who exhibited LRR and IBTR after being treated by BCS and RT following NCT.

Methods and Materials: In total, 251 breast cancer patients treated with BCS and RT following NCT between 2001 and 2006 were included. All patients had been shown to be clinically node-positive. Clinical stage at diagnosis (2003 AJCC) was II in 68% of patients and III in 32% of patients. Of those, 50%, 35%, and 15% of patients received anthracycline-based, taxane-based, and combined anthracycline-taxane NCT, respectively. All patients received RT.

Results: During follow-up (median, 55 months), 26 (10%) patients had LRR, 19 of these patients had IBTR. Five-year actuarial rates of IBTR-free and LRR-free survival were 91% and 89%, respectively. In multivariate analyses, lack of hormone suppression therapy was found to increase both LRR and IBTR rates. Hazard ratios were 7.99 ($p < 0.0001$) and 4.22 ($p = 0.004$), respectively. Additionally, pathology stage N2 to N3 increased LRR rate (hazard ratio, 4.22; $p = 0.004$), and clinical AJCC stage III IBTR rate (hazard ratio, 9.05; $p = 0.034$). Achievement of pathological complete response and presence of multifocal tumors did not affect LRR or IBTR.

Conclusions: In patients with locally advanced disease, who were clinically node-positive at presentation, BCS after NCT resulted in acceptably low rates of IBTR and LRR. Mastectomy should be considered as an option in patients who present with clinical stage III tumors or who are not treated with adjuvant hormone suppression therapy, because they exhibit high IBTR rates after NCT and BCS. © 2011 Elsevier Inc.

Breast cancer, Locoregional recurrence, Neoadjuvant chemotherapy, Breast conservation, Radiotherapy.

INTRODUCTION

Neoadjuvant chemotherapy (NCT) is increasingly used to manage breast cancer. Survival of NCT and surgery has been compared to surgery and adjuvant chemotherapy in several studies, but is not increased or decreased compared to patients treated with adjuvant chemotherapy. The ability to convert patients who would otherwise require mastectomy to breast conservation surgery (BCS) is a clearly demonstrated advantage of NCT (1–5). The proportion of patients being treated by BCS following NCT has been reported to be as high as 83% (1). BCS rates are continually increasing for both adjuvant chemotherapy and NCT, due to a combination of convenience, cosmesis, and clinical outcome equivalent to mastectomy.

With adjuvant chemotherapy, although survival outcomes do not differ, patients treated with BCS and radiotherapy (RT) display higher locoregional recurrence (LRR) rates than mastectomy patients (6). Also, for patients with locally advanced breast cancer, performing chemotherapy first is advantageous for systemic disease control but disadvantageous with regard to locoregional disease control. The combined use of NCT and BCS has indeed prompted concerns of high LRR in patients with locally advanced breast cancer. Several groups have reported high LRR rates in patients treated with NCT followed by BCS and RT (7–10).

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Since 2001, we have conducted two prospective clinical trials of NCT for clinically node-positive breast cancer patients at the National Cancer Center (NCC) in Goyang, Korea (11, 12). The goal of these trials was to characterize the response to NCT. To this end, we measured rates of pathological complete response (CR), which has been linked to improved treatment outcomes. Because the study populations in these two trials were patients with locally advanced breast cancer and regional node involvement, increased LRR was anticipated, especially among patients subjected to BCS. The purpose of the current analysis was to report the experience of a single institution using BCS following NCT in clinically node-positive breast cancer patients, focusing on clinical outcomes in patients who suffered LRR and ipsilateral breast tumor recurrence (IBTR), which is part of LRR, and their correlations with clinical and pathological variables.

METHODS AND MATERIALS

Patient selection

Our patient database was used to select patients referred between 2001 and 2006, who were treated with surgery and RT following NCT at the NCC, Korea. During this period, NCT was performed with patients with clinically positive axillary lymph nodes for the purpose of clinical trials to measure a tumor response. A retrospective review of medical records identified 391 patients in total. Of these, 266 (68%) patients had undergone BCS following chemotherapy, and 125 (32%) patients underwent mastectomy. Because our institutional protocol was to perform postoperative RT with all patients with clinically positive axillary lymph nodes irrespective of surgery type, RT was performed with all NCT patients including all patients who underwent mastectomy.

Of the BCS patients, 1 patient with systemic metastasis at presentation, a second patient with an unidentifiable primary tumor, and 13 other patients with clinically negative axillary lymph nodes were excluded from the analysis. The remaining 251 patients were analyzed in this retrospective study, which was performed in accordance with the guidelines of the institutional review board of the NCC.

Before NCT was initiated, all patients had been clinically staged according to 2003 American Joint Committee on Cancer (AJCC) staging guidelines. All patients had palpable axillary lymph nodes on physical examination. Clinical T (cT) and N (cN) stages were evaluated by ultrasonography, fluorodeoxyglucose-positron emission tomography/computed tomography (PET/CT), and chest computed tomography (CT). Although identification of positive axillary nodes was not routinely confirmed through pathology analyses, ultrasonography-guided biopsy confirmed pathologically positive axillary lymph nodes in 23 (9.2%) patients. These 23 patients were also identified as having positive axillary nodes on ultrasonography and/or PET/CT. Among 228 patients who did not undergo axillary biopsy, an imaging study with a single modality was performed with 140 (56%) patients, two modalities were used for 85 (34%) patients, and three modalities were used for 3 (1.2%) patients. The number of patients evaluated with PET/CT only was 112 (45%); 14 (5.6%) patients were evaluated with ultrasonography only, and 14 (5.6%) patients were evaluated with chest CT only. PET/CT combined with ultrasonography was performed in 69 (28%) patients. No sentinel lymph node procedure was performed before NCT.

Treatment

A total of 245 (98%) patients was treated with one of the two prospective institutional clinical trials. Full details of the regimens used have been reported previously (11, 12). NCT consisted of four to six courses of intravenously administered anthracycline-based (n = 126 patients [50%]), taxane-based (n = 87 patients [35%]), or combined anthracycline-taxane-based (n = 38 patients [15%]) therapy.

General guidelines for BCS eligibility criteria included lack of initial extensive skin or chest wall involvement, absence of extensive microcalcifications or multifocal disease, anticipated adequacy of residual breast tissue following BCS, and other contraindications for RT. In the BCS procedure, residual primary tumors were excised, with clear margins to healthy tissues being determined from frozen biopsy specimens. In cases in which the final pathology examination indicated persistence of positive margins, patients underwent re-excision to produce negative margins, or they were considered for mastectomy. Ten patients with positive resection margins declined further surgical resection. No further revision surgery was attempted for 16 patients with close resection margins (<2mm). Standard level I and II axillary lymph node dissections were performed with or without sentinel lymph node biopsy. Eight patients underwent sentinel lymph node biopsy without axillary dissection. Most patients exhibited pathology stage T1 (n = 119 [47%]), T2 (n = 78 [31%]), N0 (n = 89 [36%]), or N1 (n = 100 [40%]) disease. Fifty (20%) patients achieved a pathologically CR in their primary tumors or exhibited residual ductal carcinoma *in situ* only. Of these, 17 patients displayed residual invasion of the axillary lymph nodes. Thus, a pathologically CR in both the primary tumor and axillary lymph nodes was achieved in 33 (13%) patients. Final pathology stages are shown in Table 1.

Following BCS, comprehensive radiation treatment was administered to all patients. Breast RT was performed with tangential fields at a median dose to the breast of 50.4 Gy, delivered in 28 fractions over 5.5 weeks. All patients received an electron boost to the tumor bed (median dose, 10 Gy, in 5 fractions). An additional 4 to 10 Gy boost dose was applied to patients with close or positive pathology resection margins. Regional nodal RT was delivered, including to the supraclavicular fossa, to all patients (median dose, 45 Gy). Internal mammary nodal RT was administered to only 1 patient with PET-positive internal mammary lymph nodes. In all cases, the initial planned dose of RT was completed.

Adjuvant hormone suppression therapy was offered to patients with estrogen receptor (ER)-positive or progesterone receptor (PR)-positive tumors. Some patients displayed changes in ER and PR expression before and after NCT, but hormonal suppression therapy was administered to all patients whose tumors were shown to be ER or PR positive in one or more tests. Following RT, trastuzumab (Herceptin) was administered for 1 year to 16 of 57 patients with c-erbB2-overexpressing tumors.

Statistical methods

Endpoints were LRR and IBTR, distant metastasis, and disease-free survival. IBTR was defined as recurrent disease in the ipsilateral breast or chest wall. LRR was defined as recurrent disease in the ipsilateral breast, chest wall or axillary, supraclavicular, infraclavicular, or internal mammary nodes. Recurrence at any other site was considered distant metastasis. All LRR and IBTR were considered events, regardless of whether they represented the primary site of recurrence or followed distant metastasis. Five-year actuarial rates of LRR–free, IBTR-free, distant metastasis-free, and disease-free survival were estimated by the Kaplan-Meier method; comparisons