Editorial

Long term outcomes reporting the safety of breast conserving therapy compared to mastectomy: 20-year results of EORTC 10801

Dalliah M. Black, Kelly K. Hunt, Elizabeth A. Mittendorf

Department of Surgical Oncology, Unit 1484, The University of Texas MD Anderson Cancer Center, 1400 Pressler Blvd. Houston, TX 77030, USA
Corresponding to: Elizabeth A. Mittendorf, M.D. Department of Surgical Oncology, Unit 1484, The University of Texas MD Anderson Cancer Center, 1400 Pressler Blvd. Houston, TX 77030, USA. Email: eamitten@mdanderson.org.

Abstract: Large multicenter clinical trials have demonstrated the safety of breast conserving surgery and radiation (BCT) compared to modified radical mastectomy (MRM). At 20 years follow-up, the European Organization of Research and Treatment of Cancer (EORTC) 10801 trial reports the outcomes of distant metastasis (DM) and overall survival (OS) for stage 1 and 2 breast cancers treated from 1980-1986. Even though BCT had a higher 10 years local-regional recurrence (LRR) at 20% compared to MRM (12%), no significant difference was identified in long term OS (44% in the BCT group and 39% in the MRM group) or time to DM. Factors associated with increased LRR were dependent on biologic characteristics including larger tumor size, lymph node metastasis, and receptor subtype. BCT should be offered in appropriate patients when complete resection can be achieved. Continued research evaluating the heterogeneity of breast cancer subtypes will help further guide local-regional therapy for continued improvement in LRR, DM, and OS.

Key Words: Breast conserving therapy (BCT); modified radical mastectomy (MRM); safety; outcomes; local-regional recurrence (LRR); distant metastasis (DM); overall survival (OS)

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Over the past 40 years, large clinical trials in the United States and Europe have provided the data necessary to safely reduce the extent of surgery in the management of breast cancer from the Halsted radical mastectomy to modified radical mastectomy (MRM) to breast conserving surgery for many patients. Recently, Litiere and colleagues published 20 years follow-up data from the European Organization of Research and Treatment of Cancer (EORTC) 10801 trial which showed that the use of breast conserving therapy (BCT) and mastectomy resulted in similar rates of time to distant metastasis and overall survival (OS) (1).

Briefly, the EORTC 10801 trial accrued patients with stage I or II breast cancer at 8 centers in the UK, the Netherlands, Belgium, and South Africa, from 1980-1986. Patients were randomized to BCT or MRM. BCT included lumpectomy and axillary lymph node dissection (ALND) followed by 5 weeks of whole breast radiation (50 Gy) followed by a 25 Gy boost to the tumor bed. The intent was to obtain 1 cm margins, however 48% of patients in the BCT group were found to have microscopically positive margins. In both treatment arms, internal mammary lymph nodes were irradiated for central and medial cancers or lateral cancers with axillary lymph node metastasis. Patients with lymph node metastasis received adjuvant chemotherapy with cyclophosphamide, methotrexate, and fluorouracil if they were 55 years of age or younger. There were no specific criteria for hormonal therapy and estrogen receptor (ER) status was not recorded. Tamoxifen was administered to postmenopausal patients for 5 years at the discretion of the treating physician. The primary endpoint of EORTC 10801 was time to distant metastasis.

The trial enrolled 868 evaluable patients; 420 assigned to MRM and 448 to BCT. Initial and long-term data from this trial have previously been published (2,3). At a median follow-up of 13.4 years, there were no differences between treatment arms with respect to distant metastasis or OS.

There was, however, a difference in the 10-year local-regional recurrence (LRR) rate favoring the MRM group (12% versus 20% for patients assigned to BCT; P=0.0097) (3). Since the meta-analysis performed by the Early Breast Cancer Trialists' Collaborative Group found that local recurrence has a negative effect on survival, the EORTC investigators performed the current analysis to determine if the difference in LRR at 10 years translated to decreased OS with longer follow-up. In fact, they found that at a median follow-up of 22.1 years, there was no significant difference in OS between the MRM and BCT groups. Fifty-eight percent of all patients had died: 55% [232] in the MRM group and 61% [274] in the BCT group with 20-year OS estimates of 44.5% (95% CI: 39.3-49.5%) in the MRM group and 39% (95% CI: 34.4-43.0%) in the BCT group. On multivariate analysis, clinical tumor size >2 cm, lymph node metastasis and age greater than 50 were associated with increased rates of death, independent of treatment group, with hazard ratios of 1.35 (P=0.013), 1.88 (P<0.0001) and 1.50 (P<0.0001) respectively. There was also an assessment of time to distant metastases with no differences noted between groups.

Beginning in the early 1970s, investigators in the National Surgical Adjuvant Breast and Bowel Project (NSABP) and the Milan Cancer Institute conducted the NSABP B-06 and Milan I-III trials to evaluate the effectiveness of BCT as compared with mastectomy. The NSABP B-06 trial enrolled women with tumors 4 cm or smaller regardless of their clinical nodal status. Patients were randomized to one of three groups: MRM or lumpectomy and ALND with or without radiation. For patients receiving radiation, no boost was delivered to the tumor bed. In 2002, Fisher *et al.* published 20 years follow-up results for B-06 with no significant differences in disease-free survival, distant disease-free survival, or OS between groups (4). The hazard ratio for death when comparing BCT to mastectomy was 0.97. In a series of three trials enrolling clinically node negative patients with tumors <2.5 cm, the Milan group confirmed the safety of BCT. The EORTC 10801 trial differs from NSABP B-06 and the Milan trials in that patients generally had larger tumors (80% with T2 tumors) and 41% of patients had lymph node metastasis. Importantly, although tumor size >2 cm and positive lymph node status predicted an increased risk for distant metastases and death on multivariate analysis, this effect was independent of the surgical treatment. The trial therefore provides important data showing that BCT can be safely performed in patients with larger tumors and positive lymph nodes.

This updated analysis of the EORTC 10801 trial did not find that the differences in LRR at 10-year between the MRM (12%) and BCT (20%) translated into OS differences. The same was true for the NSABP B-06 trial where the ipsilateral breast tumor recurrence rate was 14.3% in the 20-year follow-up report (4). As suggested by Litiere *et al.*, this could be due to the relatively small numbers of patients in each trial or to the effectiveness of salvage mastectomy (4). Local-regional recurrences may still have a negative impact on breast cancer patients, however, due to the need for additional treatments as well as the psychological impact that recurrence can have on the individual patient. Since the EORTC 10801 and NSBP B-06 trials were initiated, indications for adjuvant systemic therapy, including endocrine therapy and chemotherapy, have expanded and the use of systemic therapies has been shown to decrease local-regional recurrences. In addition, there have been improvements in diagnostic imaging, surgical techniques and pathologic evaluation of specimens leading to lower local-regional failure rates overall. We have recently reviewed our experience at The University of Texas MD Anderson Cancer Center with a cohort of 2,331 patients undergoing BCT to include lumpectomy and whole-breast irradiation (50 Gy to the breast in 25 fractions followed by electron boost to the tumor bed) between 1987 and 2005 (5). The pathologic stage of disease in this cohort was: stage I in 66%, stage II in 30% and stage III in 4%. At MD Anderson, our goal is to obtain a negative margin of 2 mm, which was accomplished in 96% of patients. A close margin (<2 mm) was identified in 3% and a positive margin in 1%. This contrasts with the EORTC 10801 trial where 48% had a microscopically positive margin (1) and the NSABP B-06 trial where 10% of patients had a positive margin (4). Although the exact margin width required for BCT is a matter of debate, it is generally accepted that it should be clear with no tumor present at the inked margin (6). Adjuvant chemotherapy was administered in 42% of patients in our study and adjuvant endocrine therapy was given to 78% of patients with ER-positive disease. With a median follow-up of 8 years, the 5-year LRR-free survival rate was 97% [95% confidence interval (CI): 96-98%], and the 10-year rate was 94% (95% CI: 93-95%). This is consistent with other contemporary studies which have reported 10-year rates of local recurrence being less than 5% (reviewed by Recht and Solin) (7).

In the earlier report from the EORTC 10801 trial, the incidence of local recurrences was higher in patients with larger tumors in the BCT group but not in the

MRM group (2). Positive nodal status was also a significant predictor of recurrence. In our study from MD Anderson, factors associated with increased risk for LRR following BCT included: clinical stage III disease, grade 3 disease, ER-negative disease or ER-positive disease without receipt of endocrine therapy, close or positive margins, multifocal disease and age <50 (5). From these data, we concluded that LRR recurrence is driven largely by biologic factors. As Litiere and colleagues discuss, there is an increased appreciation for breast cancer as a heterogeneous disease with different prognoses associated with biologic subtypes defined by gene expression profiling or approximated using immunohistochemistry evaluating ER, progesterone receptor and HER2 status. This was recently evaluated in a study by Solin and colleagues that assessed the prognostic value with respect to local-regional control of different subtypes and the 21-gene recurrence score in patients treated with BCT that had enrolled on the Eastern Cooperative Oncology Group 2197 trial (8). Briefly, this trial was investigating 2 chemotherapy regimens in patients with tumors >1 cm, with node negative disease or with 1-3 positive lymph nodes. At a median follow-up of 9.7 years, the 10-year rates of local recurrence and LRR were 5.4% and 6.6%, respectively. Neither the biologic subtype nor the recurrence score predicted for local or LRR recurrence. This is in contrast to the findings of Nguyen *et al.* who evaluated 793 patients treated with BCT between 1998 and 2001 (9). Ninety percent of patients received systemic therapy. At a median follow-up of 70 months, the 5-year incidence of LRR was 0.8% for patients with hormone receptor (HR)+/HER2- tumors, 1.5% for HR-/HER2+ tumors and 7.1% for HR-/HER2- tumors. On multivariate analysis using HR+/HER2- as the referent, the HR-/HER2+ and HR-/HER2- subtypes were associated with higher LRR rates.

In conclusion, the current report from Litiere *et al.* is important in that it provides long-term follow-up data that is consistent with the previous data from the NSABP and Milan trials showing that BCT and MRM are equivalent with respect to OS. As breast surgical oncologists, we remain committed to optimizing the local-regional management of breast cancer. It is likely that as we continue to improve our understanding of the biology of the disease, there will be biologic factors that will help guide surgical decisions and local-regional therapies for the individual patient. In the future, it's possible that the decision may not be just mastectomy versus lumpectomy with radiation but could include less invasive approaches such as cryoablation, which is being investigated in the American College of Surgeons Oncology Group Z1072 trial, or perhaps even no surgery in patients with favorable biologic characteristics. In the meantime, we encourage consideration of BCT in appropriately selected patients in whom complete resection can be achieved with a negative margin.

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