Breast Cancer Outcomes in Younger Women: A Systematic Review of the Literature on Locoregional Management

By

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ABSTRACT

Background: Despite significant advances in the treatment and management of breast cancer, young women diagnosed before the age of 40 have worse outcomes as compared to older women with similar cancers. Many posit that this occurrence is related to a propensity to develop more biologically aggressive tumors, while others attribute these differences to the influences of estrogen on this young cohort. Nevertheless, many of the therapeutic measures offered to young women are based on evidence derived from studies of older, post-menopausal women.

Objective: To determine whether locoregional management of early-stage invasive breast cancer is associated with long-term survival outcomes in young women during the era of modern multimodal therapies.

Methods: A systematic review of retrospective cohort studies published within the last 10 years.

Results: Although younger women who undergo breast-conserving therapy (BCT) have higher rates of local recurrence (LR), this review indicates that either there is a slight survival advantage after BCT compared to mastectomy (M), or that there is no survival difference based on these interventions.

Conclusion: Presently, there is insufficient evidence to determine whether younger women should continue to undergo more aggressive local treatment approaches, emphasizing the need for prospective controlled trials to generate more reliable information on the magnitude of survival benefits of BCT and M in young women.

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INTRODUCTION

Management of breast cancer in young women is fraught with a complexity of issues distinct from those encountered in older patients. Young patients experience an abrupt disruption of their menstrual cycle and fertility as a result of chemotherapy. Temporary or premature menopause compounded with hormonal therapy (when indicated) lead to symptoms of fatigue, hot flashes, and increase the risk of uterine cancer, deep vein thrombosis, and depression among others. Some women are not afforded a chance for fertility preservation due to the aggressive nature of the disease in this young cohort or due to the steep costs of this intervention. Body image issues are amplified over the course of treatment as young patients invariably experience multiple side effects of treatment, including hair loss, deforming surgeries, nail changes, steroid-induced weight gain, skin changes and fibrosis related to radiation therapy (XRT), and lymphedema. Patient preferences regarding local management and subsequent reconstruction options allow select patients to have some control during the arduous treatment journey. This option is contingent upon evidence that long-term outcomes associated with breast-conserving therapy (BCT) are not different than those who undergo mastectomy (M).

Scientists, surgeons, and physicians have made great strides in local and systemic treatment of breast cancer over the past three decades. Surgeons have moved beyond the Halstedian era of aggressive surgical interventions as it became apparent that extirpation of the tumor with extensive resection of surrounding tissue, did not improve survival in all patients. The movement towards BCT began in Germany and was slowly adopted by some U.S. surgeons over the following decades. The divergent philosophies of surgeons practicing traditional Halstedian radical mastectomies and those performing breast-conserving therapy catalyzed the call for evidence, ultimately leading to prospective randomized trials comparing BCT to M (1). Six landmark prospective randomized trials compared survival outcomes in patients who underwent BCT versus M. These trials included the MILAN 1 Trial conducted at the Milan

Cancer Institute (1973-1980), the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-06 Trial, the European Organization for Research and Treatment of Cancer (EORTC) 10801 Trial, The Danish Breast Cancer Cooperative Group Trial, the National Cancer Institute Trial, and the Institut Gustave-Roussy Breast Cancer Group Trial, No survival differences were detected in any of the studies; however, only a small percentage of the study subjects were young women. There are no prospective randomized trials that examined the relationship between local treatment approach and long-term survival among young breast cancer patients (2-7).

Chemotherapeutic regimens, including the types of drugs, doses, and frequency of administration continue to be challenged and improved. Chemotherapy for breast cancer has evolved to include cyclophosphamide (C) to the traditional regimen of methotrexate (M), and 5-Flouro Uracil (F), leading to improvement in survival outcomes (8). In the late 1990's, anthracycline-based (A) regimens were shown to further improve survival over CMF, namely in women with hormone receptor negative or triple negative breast cancers (9). More recently, treatment includes the addition of taxanes (T), which are used in both primary and recurrent breast cancer. Polychemotherapy confers considerable benefits in premenopausal patients. Regimens of TAC or TC have mostly replaced the use of CMF (10). In addition, radiation therapy (XRT) approaches, indications, and techniques, have evolved to more precisely irradiate the involved region while decreasing the amount of unwanted radiation to the underlying lungs and heart.

Assays for estrogen and progesterone receptor (ER and PR) positive tumors have been developed during the duration of the studies, and refined since their conclusion. Recommendations for the use of hormonal therapy in young premenopausal women with estrogen receptor-positive cancers lagged behind their older counterparts. Modern assay

techniques allow us to detect over-expression of human epidermal growth factor receptor (HER2/neu) on breast cancer cells (commonly found in young patients), which then identifies women who are eligible for drugs that successfully target affected cells and have improved prognosis in this subgroup (11). Mapping of sentinel lymph nodes safely predicts involvement of remaining lymph nodes and decreases unnecessary surgery in women with early-stage breast cancer (12-14). Thorough evaluation of sentinel lymph nodes became more feasible, since there were fewer nodes to examine with this technique. Improvements in pathologic staging techniques with the addition of immunohistochemistry (IHC) and reverse transcriptase polymerase chain reaction (RT-PCR); both have allowed for discovery of small foci or micrometastasis (15-16). The International Breast Cancer Study Group delineated the association between the presence of micrometastasis and unfavorable long-term outcomes. Prognostic importance of occult axillary lymph node micrometastasis from breast cancers (17). In 2003, the American Joint Commission on Cancer (AJCC) revised the criteria for breast cancer staging to include this indicator (18). These techniques could effectively upstage many women that may have been considered early-stage, prior to the employment of these advanced procedures (19).

METHODS

Search Algorithm

I began this study by searching for prospective controlled trials on the local management of breast cancer in women diagnosed before the age of 35. Notably, the landmark prospective studies on the influence of local management approach on breast cancer outcomes recruited women diagnosed at all ages. Although the landmark trials have abundant long-term follow-up data, systemic therapies, surgical techniques, and radiation approaches have advanced in the last 30 years. Therefore, I developed my search strategy to reflect the influence of local breast

cancer treatment on long-term survival outcomes of young women in the setting of modern evidence-based practice.

I queried the PUBMED database to identify pertinent articles published between January 2003 (to reflect significant changes in chemotherapy regimens and the development of Herceptin in the late 1990s and early 2000s) and January 2013. This would produce a literature database reflecting the most current multimodal treatments. I searched the following Medical Subject Headings (*breast neoplasms/surgery* or *breast neoplasms/therapy)* and *(mastectomy* or *segmental mastectomy)* and *(follow up studies* or *cohort studies)* and *young adult*. I finalized the search terms on April 17, 2013 and finalized the search itself on June 20, 2013. I also supplemented these sources by hand searching bibliographies.

As there were no prospective studies designed to focus specifically on outcomes for young women in the current era of multimodal therapies, I reviewed retrospective analyses published in the last 10 years that examined the effect of local management of early-stage breast cancer on survival in young women who were diagnosed before the age of 35. This search did not yield any literature, so I expanded the search to include women diagnosed before the age of 40. The search was limited to studies conducted in Western nations that are likely to employ similar treatment modalities. **I** excluded studies that included male breast cancer patients and manuscripts that were not written in English. I rejected studies that evaluated the effects of local management in young women diagnosed with advanced breast cancers (T3 or T4 tumors), as they would be unlikely candidates for breast-conserving therapy (BCT). Furthermore, I eliminated studies that focused on the influence of local management on survival after locoregional recurrence. Full inclusion and exclusion criteria are available in **Table 1**.

Data Abstraction and Synthesis

I abstracted the data from each article into a separate appraisal table and rated them for quality of the study and strength of evidence. These data included the study question, study design, the study cohorts evaluated (based on stage, age, and type of local intervention), inclusion/exclusion criteria, comparability of comparison groups, primary and secondary outcomes assessed, author definition of outcomes, length of time allowed for outcome to occur, method of outcome measurement, potential confounders, statistical analysis, and study findings. I assigned quality ratings based on the appropriateness of study cohort and comparison groups, potential for selection and measurement bias (both intervention and outcome), possible confounders and how they were addressed, appropriateness of data analysis, power of the study, clinical relevance, internal and external validity, and overall relevance in relation to the initial study question. I graded the evidence using the composite results of the quality ratings and based on established definitions from the Agency for Healthcare Research and Quality (AHRQ). (**Table 2).** I, then, synthesized the overall outcomes and evidence grades for each of the studies in individual evidence tables according to each of the outcome measures.

RESULTS

The initial search yielded 121 manuscripts, I excluded 113 manuscripts based on both title and abstract. I reviewed the manuscripts of the remaining eight and excluded four for the following reasons: study evaluated the predictors of outcomes among patients undergoing one type of local treatment approach; analysis did not have at least 10 years of follow-up time to outcome occurrence; study did not evaluate survival outcomes; and study evaluated differences in utilization of one type of local management versus the other, but did not assess association of local approach with outcomes. After conducting hand searches, I included one additional manuscript **(Figure 1).**

I compared the influences of local management approaches on survival outcomes for young breast cancer patients in five retrospective cohort studies. The Critical appraisal tables of the literature and quality ratings are available in **APPENDIX A.** I graded and grouped the studies according to primary and secondary outcomes**.** The primary outcomes examined in these studies included overall survival (OS) and cause-specific survival (CSS); secondary outcomes were local recurrence (LR), locoregional recurrence (LRR), and recurrence presenting as distant metastasis (DM). The final grades of the evidence along with the magnitude and direction of effects are presented in Table 3, and in individual outcomes tables in **APPENDIX A**, **Tables 2-7**.

Local Recurrence

The effect of local treatment approach on local recurrence (LR) was evaluated in three of the studies **(Table 3)**. Local recurrence was defined as recurrence in the ipsilateral breast, overlying skin, or chest wall. Both Coulombe G, Tyldesley S, Speers C, et al.. and Beadle BM, Woodward WA, Tucker SL, et al. measured time to event from initial diagnosis. However, Van der Sangen MJC, van de Wiel FNM, Poortmans PMP, and colleagues measured time to event from completion of treatment, which would vary significantly depending on whether the patient underwent surgery or began neoadjuvant chemotherapy initially. **Beadle BM, Woodward WA, Tucker SL,** et al. also included an additional comparison group of women who underwent post-mastectomy radiation (MXRT). Both Coulombe G, Tyldesley S, Speers C, et al. and Van der Sangen MJC, van de Wiel FNM, Poortmans PMP, et al. reported 10-year actuarial rates in stage I-IIB breast cancers. Van der Sangen MJC, van de Wiel FNM, Poortmans PMP, and associates reported lower LR rates in the mastectomy (M) group than among those who received breast-conserving therapy (BCT) (6% vs. 18.3% respectively, $p<0.0001$); the risk in the M group actually plateaued at 6% at six years. Conversely, Coulombe G, Tyldesley S, Speers C, et al. did not find clinically or statistically significant differences between the BCT and M groups (14% and 16.6% respectively, $p=0.34$); a subgroup analysis of stage IA patients

revealed less LR among those who underwent M than those who had BCT, 4.9% versus 13.7% respectively, but this was not statistically significant (p=0.30).

Beadle BM, Woodward WA, Tucker SL, and associates included patients with stage I-IIIC breast cancer in their analysis. Patients diagnosed at later stages (stage IIIA or greater) are considered locally advanced, and therefore are not considered part of the traditional cohort included in earlier landmark trials. Furthermore, they did not stratify results for LR by stage; the 10-year actuarial LR rates for stage I-IIIC were 15.8%, 12.5%, and 7.0% for BCT, M, and MXRT respectively, p=0.04. A multivariate analysis to examine the relationship between local management and local recurrence adjusting for known or potential confounders was not performed.

Locoregional Recurrence

Coulombe G, Tyldesley S, Speers C, et al. and Beadle BM, Woodward WA, Tucker SL, et al. compared local regional recurrence (LRR) rates based on local management **(Table 4); they**, defined LRR as time from diagnosis to first ipsilateral local or regional nodal recurrence. Subjects' data were censored at the earliest of the following dates: distant relapse occurring >30 days before local recurrence or local regional recurrence; subsequent contralateral breast cancer occurring before LR or LRR; and date of death or last follow-up. When LR or LRR occurred within 30 days of distant relapse, the relapses were considered concurrent and were recorded as occurring on the date of the earlier events. They found no difference in 10-year LRR rates for patients with stage I-IIB breast cancer after breast-conserving therapy (BCT) versus mastectomy (M) (17.4% and 19.1% respectively, p=0.41). This conclusion was further supported by a subgroup analysis of "ideal" BCT candidates (stage IA), who had LRR rates of 16% in BCT group versus 12.7% in M group, p=0.94. Beadle and colleagues defined LRR as ipsilateral local or regional nodal recurrence (including axillary, supraclavicular, infraclavicular, or internal mammary nodes). All LRRs were considered events regardless of their relationship

in time to distant metastasis in time. They reported a significant difference in 10-year LRR rates among the collective (stage I-IIIC) group 19.8% for BCT, 24.1% for M, and 15.0% for MXRT, p=0.05. After stratifying by stage, LRR rates were no different in the stage I group; 18.0% in BCT versus 19.8% in M, p=0.56 (there were few stage I patients who underwent MXRT, so they were not included). However, there was a significant difference among those with stage II disease 17.7%, 22.8% and 5.7% (p=0.02) in BCT, M, and MXRT respectively. They also conducted a multivariate analysis identifying BCT and M as predictors of LRR among patients with stage II disease, hazard ratio (HR)= 3.40 (95% CI: 0.99-11.7), p=0.052 and HR=4.45 (95% CI: 1.36-14.6), p=0.014 respectively.

Distant Metastases

Distant Metastases (DM) were defined as time from diagnosis to first relapse beyond ipsilateral breast and regional lymph nodes. Coulombe G, Tyldesley S, Speers C, et al. censored subjects at the time of a subsequent contralateral new primary breast cancer occurring before a distant relapse, date of death, or last follow-up. They found no difference in 10-year DM rates among 2,398 patients with stage I-IIB breast cancer; 26.9% in the BCT group versus 27.5% in the M group, p=0.77 **(Table 5).** However, in the subgroup analysis including only "ideal" BCT patients, rates of DM in those who underwent BCT were 14.3% versus 24.6% in patients who underwent M, p=0.17. Although this result was not statistically significant, it may be clinically relevant. Beadle BM, Woodward WA, Tucker SL, and colleagues reported significant differences in DM rates among the entire cohort (n=652) based on local treatment **(Table 5)**. The BCT group had the lowest rates of DM, 25.5% compared with 42.5% and 49.1% in the M and MXRT groups respectively, p<0.0001. Once again, when they stratified by stage, they did not find a difference among women with stage I breast cancer (27.4% in BCT versus 27.7% in M), p=0.15. However, they detected a difference among those with stage II breast cancer, 19.5% versus 33.9% versus 39.4% in the BCT, M, and MXRT groups respectively, p=0.006.

Van der Sangen MJC, van de Wiel FNM, Poortmans PMP, and colleagues also evaluated women with stage I-IIB breast cancer. Using the life-table approach, they measured the interval between the date of primary treatment until diagnosis of DM, rather than the date of initial cancer diagnosis until DM. They found no difference among those treated with BCT compared with M, 29.0% versus 33.0% respectively, p=0.083. Interestingly, they noted that the risk of DM was lower in the BCT group, hazard ratio (HR)=0.75 (95% CI: 0.61-0.93) p=0.009. However, after seven years, risk of DM was lower in the M group and increased in the BCT group, HR= 1.96 (1.02-3.76) p=0.044.

Cause-Specific Survival

Coulombe G, Tyldesley S, Speers C, et al. and Mahmood U, Morris C, Neuner G, et al. searched for differences in cause-specific survival according to the type of local management received. Cause-specific survival (CSS) was defined as time between initial diagnosis and death when breast cancer was the primary or underlying cause of death. They found no difference in CSS according to local treatment among the entire cohort, which included stages I-IIB (BCT= 79.8%, M= 74.9%; p= 0.09); and the subgroup of "ideal" BCT patients with stage IA cancer only (BCT= 90.8%, M= 86.0%; p= 0.41) **(Table 6)**.

Mahmood's group conducted the largest retrospective analysis to date using the Surveillance Epidemiology and End Results (SEER) cancer registry maintained by the National Cancer Institute to determine whether there was a survival difference in patients aged 20-39 who underwent BCT compared to those who had M with or without radiation for stage I-IIB breast cancer. They performed both multivariate and matched pair analyses. Multivariate analysis revealed no difference in CSS between BCT and M, hazard ratio (HR)=0.93 (0.83-1.05), p=0.26 **(Table 6)**. Matched-pair analysis confirmed that local management was not associated with CSS, with identical 10-year rates of 85.5%, p=0.88.

Overall Survival

Overall survival (OS) was defined as death from any cause. The time interval was measured from the date of diagnosis to the date of death or last visit. Beadle BM, Woodward WA, Tucker SL**,** and colleagues found significant differences in overall survival in a pooled analysis of patients with stage I-IIIC breast cancer **(Table 7)**. Patients who underwent breast-conserving therapy (BCT) had 80.0% 10-year OS rates compared with 60.4% in the mastectomy (M) group, and 57.5% in the mastectomy with radiation (MXRT) group, p=0.0003. Stratified analysis revealed a clinically relevant difference in OS among those with stage I disease, with OS rates of 92.4% in BCT group compared to 72.0% in M group, though this was not statistically significant, p=0.19. Among patients with stage II disease, the MXRT group had the highest 10-year OS rates (85.4%), followed by the BCT group (81.0%), and the M group (63.4%), p=0.03. On multivariate analysis of those with stage II cancer, undergoing mastectomy alone associated with a poorer OS (hazard ratio= 1.72 ; 95% CI: 1.11-2.67).

Bantema-Joppe EJ, De Munck L, Visser O, and associates conducted a retrospective analysis using two Dutch cancer registries containing data from 1,453 patients with stage I-IIA breast cancer. They found that women who received BCT had 5% greater 10-year OS rates when compared to those who received mastectomy; p=0.007 **(Table 7)**. Survival analysis controlling for age at diagnosis, time period of diagnosis, pathological T stage, adjuvant chemo, adjuvant hormone therapy, and nodal status concluded that M was associated with poorer OS; HR=1.37 (1.09-1.72).

A similar study conducted by Van der Sangen and colleagues evaluating patients diagnosed with stage I-stage IIB breast cancer did not reveal a clinically or statistically significant difference in OS; 71.2% (62.4-71.6) of those who had M were alive at 10-years compared with 74.9% (71.7-78.1) of patients who opted for BCT, p=0.215. It is important to note that in this particular study overall survival was measured from completion of treatment until death from any cause.

A retrospective study conducted by Mahmood U, Morris C, Neuner G, et al. evaluated outcomes for 14,764 young patients with stage I-IIB breast cancer. They performed a multivariate analysis adjusting for year of diagnosis, age at diagnosis, race, histology, tumor grade, area of involvement within the breast, tumor size, number of positive LN, number of evaluated nodes, estrogen receptor (ER), and progesterone receptor (PR) status. They found no difference between the two treatment groups with the HR for BCT being 0.93 (0.83-1.04), p=0.16. Results of a matched pair analysis was consistent with the results of their multivariate analysis; 83.6% OS at 10 years in the M group and 83.5% in the BCT group, p=0.99.

SYNTHESIS: A summation of the findings

Stage I Breast Cancer

With all the shortcomings of a retrospective data analysis, it appears that local management is not associated with statistically significant differences in local recurrence (LR) among young women diagnosed with stage I breast cancer; though the absolute difference between the rates may be clinically relevant, with an 8.8% greater LR rate after BCT. Furthermore, this conclusion is based on data from only one study by Coulombe's group, which reported actuarial rates. Local regional recurrence (LRR) rates are not clinically or statistically different among young women with stage I disease in any of the included studies. Despite the lack of statistically significant differences in rates of distant metastasis (DM), in the two studies that evaluated stage I breast cancers, the mastectomy group had 10.3% higher rates of DM at 10 years in the study by Coulombe and colleagues. The same study failed to reveal any statistically or clinically relevant difference in cause-specific survival (CSS). Breast-conserving therapy was superior to mastectomy in terms of overall survival (OS), the 10 year rates of OS were 20.4% higher among women who opted for BCT versus those treated with M. Although these findings did not reach statistical significance, they remain clinically relevant and imply that the addition of XRT may

actually improve survival even among women with very early-stage breast cancer. In summary, actuarial rates of LR, LRR, DM, CSS and OS were not statistically different based on local management approaches of stage I disease. Interestingly, these results indicate that both rates of DM and OS may actually be better in women undergoing BCT, despite higher rates of local recurrence among young women undergoing BCT. These data imply that young women with stage I breast cancer can safely opt for either local management approach, and some infer that BCT may actually improve long-term overall survival.

Stage II Breast Cancer

Primary and secondary outcomes for the subgroup of women with stage II breast cancer were described in only the Beadle, Woodward and Tucker study. They did not investigate local recurrence (LR) rates among women with stage II breast cancer, but found that actuarial rates of LRR were 5% higher among women who opted for M over BCT (p-0.02) at 10 years. Notably, this reported statistical significance is based on three comparison groups and may represent the difference between mastectomy with adjuvant radiation therapy (MXRT) versus M or MXRT versus BCT. However, upon further analysis, multivariate regression confirmed the elevated risk of LRR among women with stage II cancer undergoing M, with a greater hazard ratio of LRR after M HR=4.45 (95% CI: 1.36-14.6) versus BCT HR= 3.40 (95% CI: 0.99-11.7). Furthermore, actuarial rates of distant metastasis were 14.4% higher in patients treated with M, representing a clinically important and statistically significant difference between the interventions. Cause-specific survival (CSS) was not reported in this study, though overall survival (OS) rates were significantly different among the three groups. Superior rates of OS were reported in women who underwent MXRT, followed by those who received BCT; women who received M alone had the lowest 10-year OS rates Absolute differences in actuarial rates were greatest between M and MXRT groups (22.0% higher in MXRT) and M and BCT (17.6% higher in BCT) groups. In fact, MXRT only conferred a 4.4% improvement in OS over BCT.

Deriving from this single study, it appears that breast conserving therapy provides superior outcomes in terms of LRR, DM, and OS rates among young women with stage II breast cancer.

EARLY-STAGE BREAST CANCER (STAGE I-II)

Investigations that described the influence of local therapy on outcomes of interest in all women with early-stage breast cancer (stage I-II) were generally consistent, though there were some conflicting findings. The evidence compiled in this review indicates that young women with early-stage breast cancer are either as likely or more likely to have local recurrence (LR) after BCT when compared to patients treated with M. (Van der Sangen MJC, van de Wiel FNM, Poortmans PMP et. al. and Coulombe G, Tyldesley S, Speers C, et al.) Coulombe's group found that LRR rates did not differ based on local management approaches in women diagnosed with stage I-II breast cancer. (Coulombe G, Tyldesley S, Speers C, et al.) Similarly, two studies that included distant metastasis (DM) as an outcome of interest failed to find any statistically significant or clinically relevant differences in actuarial rates of DM in those undergoing M versus BCT. (Van der Sangen MJC, van de Wiel FNM, Poortmans PMP et. al. and Coulombe G, Tyldesley S, Speers C, et al.) Van der Sangen and colleagues elucidated an interesting phenomenon wherein the hazard ratio for distant metastasis (DM) was time-dependent. Breast-conserving therapy had an apparent protective effect against DM until year seven, after which BCT was associated with higher hazard ratio for DM. This time dependent interaction warrants further investigation, and was not seen in other similar studies. Cause-specific survival was measured by Mahmood's group and Coulombe et al.; both groups concluded that local management does not influence CSS in stage I-II disease. One of three studies that investigated overall survival in stage I-IIA disease showed a statistically significant difference based on local treatment approach. However, the absolute difference in actuarial 10-year OS rates was <5%, which may not be clinically relevant. (Bantema-Joppe EJ, De Munck L,

Visser O, et al.) The two other studies that examined 10-year overall survival rates included women with stage I-IIB breast cancer. Neither of these studies found any clinically nor statistically significant differences in OS rates. (Mahmood U, Morris C, Neuner G, et al. and Van der Sangen MJC, van de Wiel, FNM, Poortmans, PMP, et al.) In short, women with early-stage breast cancer did not have significant differences in LRR, CSS, and OS. Utilizing the available evidence, young women with early-stage breast cancer should be afforded the option of choosing the local approach of their preference since there is no difference among long-term survival outcomes. However, they should be counseled about the potential for increased risk of local recurrence after BCT.

STRENGTH OF THE AVAILABLE EVIDENCE

Coulombe G, Tyldesley S, Speers C, et al. conducted a retrospective study that included premenopausal breast cancer patients. They stratified these women by age at diagnosis; 20-39 years and 40-49 years of age. Comparison groups included women who had BCT (all of whom had adjuvant radiation) versus those who chose M with or without radiation (XRT). They did not control for XRT as a separate variable since it was strongly correlated with breast conserving therapy; however, this may skew the actual benefit of M. Furthermore, bivariable analysis revealed that women who underwent M had worse baseline prognostic factors than did those undergoing BCT, including more nodal involvement, central or multifocal tumors, and larger tumors. Although the multivariable analysis controlled for baseline prognostic factors, it was based on the entire cohort of women (age 20-49). Essentially, we are provided with actuarial rates of outcomes in women aged 20-39 who underwent M versus BCT. Because the multivariate analysis included women greater than 39 years of age, its results could not be included in the findings of our review nor contribute to recommendations. Actuarial rates do not

provide us with a clear understanding of the weight that mastectomy or breast-conserving therapy have on the outcomes of interest.

Beadle BM, Woodward WA, Tucker SL, et al. retrospectively evaluated a cohort of young women from M.D. Anderson Cancer Center diagnosed between 1976 and 2006. Innovations in local and systemic treatment approaches occurred during this broad span of time. Inclusion of data that was collected more than 20 years ago may not reflect the absolute contribution of either local therapy within the setting of the current treatment patterns. They reported outcomes for the entire cohort by time period, but they did not report the outcomes of the treatment arms by time period. Moreover the authors reported significant findings, but did not clarify which pairs of the three treatment arms were significantly different. Another important limitation of this study is that women with stage IIIA-C cancers were included. Stage IIIA-C cancer is locally advanced disease by definition, and thus these women are not traditional candidates for BCT. Patients requiring radiation therapy after M are more likely to have advanced cancers and a poorer baseline prognosis than are those who are satisfactorily treated with either BCT or M. The high failure rate among those in the mastectomy group might be explained by the inclusion of young women with stage III breast cancer who may have benefitted from post-mastectomy radiation, namely those with large tumors (>5 cm) or those with four or more positive lymph nodes. Lastly, they did not actually answer the question they posed at the beginning of the study; instead, they reported actuarial rates and multivariate analyses only looking for predictors of outcomes (LRR and OS) stratified by stage.

Van der Sangen MJC, van de Wiel FNM, Poortmans PMP, and colleagues used the life-table approach in their retrospective study. All outcomes were measured from the time of treatment completion to the time of the “event”. The time to completion of therapy is variable as it is dependent on timing and requirement for adjuvant therapy. The authors of the other studies in

this review measured outcomes as time from diagnosis to the occurrence of the event. Moreover, follow-up time for patients that underwent BCT was one year longer than for those who underwent M, though the authors did not explain the rationale for the discrepancy in follow-up time. The authors discovered a change in the trends of distant metastasis rates after BCT and M. Initially, BCT was superior to mastectomy, though the trends cross at year 7 post-treatment. Despite this clear violation of the proportional hazards rule, they conducted a multivariate regression analysis including both time periods. This approach is statistically unfavorable as it diminishes the true magnitude and direction of the findings. It would have been more appropriate to create two regression models to represent the individual time intervals and report the respective hazard ratios instead.

Mahmood U, Morris C, Neuner G, and colleagues conducted a secondary analysis using the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) database. The authors conducted both multivariate regression followed by a sensitivity analysis matching cases and controls. Multiple limitations of this study are attributed to the paucity of specific data in the SEER database. For example, the database provides information on whether patients received radiation therapy; however, the targets and doses are not provided. Also, the SEER database does not collect information on which patients received chemotherapy nor the drug regimens prescribed. The authors carried out the analysis under the assumption that approximately the same proportion of patients in both treatment arms received chemotherapy. Although the SEER data provides estrogen and progesterone receptor status, prescriptions for hormonal therapy and patient compliance is not reported. HER2/neu status is not captured in the SEER database. Patients with unfavorable prognostic factors such as HER2/neu positivity or triple negative status are more likely to undergo more aggressive treatment (mastectomy) giving this study arm worse baseline prognosis that is unaccounted for. Despite the fact that

many of the study limitations are due to the shortcomings of the database and not the study design itself, they are unable to answer the study question with certainty.

DISCUSSION

. The results of this review are uniform among the sub-group of patients with stage I breast cancer and among the cohort of all patients with early-stage breast cancer. Due to the quality of the single study that evaluated stage II alone, we may assume that BCT and M are not different at the least, and that the requirement for XRT in BCT is potentially associated with improved survival patients at best. These findings may seem counterintuitive in light of the pooled analysis, which demonstrated inferior outcomes in the MXRT group; however, it is important to consider that the pooled analysis included women with locally advanced breast cancer (stage III). Women with locally advanced breast cancer are more likely to receive adjuvant radiation therapy after mastectomy than women with early-stage breast cancer due to larger tumor sizes and/or involved lymph nodes. Moreover, the baseline prognosis for advanced breast cancer is inferior to those with early-stage cancers. The relationships between advanced breast cancer, increased likelihood of requiring post-mastectomy radiation, and unfavorable baseline prognosis are likely to cause confounding.

As evidenced in this review, BCT is associated with equal or greater risk of local recurrence at 10 years when compared with their counterparts who opt for mastectomy. (Van der Sangen MJC, van de Wiel FNM, Poortmans PMP, et al.). Numerous studies have suggested that younger women have higher rates of LR after BCT than do older women (e.g. 20). Other studies comparing young women under 35 to women 35 or older who undergo BCT find that the rates of LRR are higher among those in the younger age group (21-22). Excessive LR rates following BCT may be explained by differences in tumor biology and pathologic findings that are more characteristic of breast cancers diagnosed in young women. A study by P. Karlson et. al.

illustrates this point well, as they find higher LRR rates after M in young women (under 40) than in their older counterparts (23). Taken collectively, these studies suggest that age, or the typical "behavior" of young breast cancers may contribute to local failure after BCT and M.

Interestingly, it seems that development of LR does not translate into inferior survival outcomes. This may be explained by the salvage option of M at the time LR is discovered. The absence of a link between LR and long-term survival outcomes was confirmed in NSABP-06. However, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) conducted a retrospective analysis of evidence derived from prospective randomized trials with long-term follow-up. They found that when surgery or radiation could attain at least 10% absolute reduction of local disease recurrence, significant reductions in cause-specific mortality followed (24-25).
The divergent conclusions derived from the EBCTCG article and this study may partially be explained by the greater length of follow-up time.

The studies in this review suggest that DM and OS rates are similar in young women treated with BCT. M. Van der Saangen's group found an interaction between time and long-term DM rates. The presence of a time interaction has important implications and should be explored further in future studies. It is also possible that long-term outcomes are not captured until after the 10-years of follow up provided in these studies.

LIMITATIONS

I encountered many obstacles in attempting to identify the association between local management and long-term outcomes for young women with early-stage breast cancer. This The foundation of this review was created built upon results from retrospective cohort studies and the inherent limitations that come with secondary data analyses. Variations in selection of

study cohorts, definition of exposures and outcomes, covariates included in analysis, and statistical analysis strategies are not uniform across investigations. Inconsistencies in the numerous layers of breast cancer diagnostics and treatments exist within and among the reviewed studies dilute the magnitude and certainty of our results.

Selection of Comparison Groups. The authors define "ideal BCT candidate" differently, emphasizing the importance of appropriate comparison group selection. Some investigators defined these candidates as patients with stage I disease, stage I and II disease, and one of the studies even included patients with stage III disease. Landmark randomized trials of BCT vs. M did not include stage III breast cancer, which is considered locally advanced. Women with advanced breast cancers are not typical candidates for BCT unless they have a good response to neoadjuvant chemotherapy.

Management of the axilla. Axillary nodal status is one of the most important predictors of prognosis in breast cancer. Innovations in axillary management and staging complicated secondary analyses that included patients treated before, during, and/or after the adoption of sentinel lymph node biopsies. Aggressive axillary dissections were carried out in all patients prior to this practice; sentinel lymph node biopsy has largely saved women without clinical evidence of axillary disease from a highly morbid procedure. Conversely, some sampled sentinel nodes with small foci of micrometastasis and small macrometastasis could have been missed by traditional staining methods prior to the use of advanced immunohistochemistry techniques.. Women with undetected micrometastasis or small macrometastsis received no further surgical intervention, even though the guidelines would have recommended that these women undergo complete axillary dissection.

Surgical margins and radiation therapy. The extent of surgical resection varied in both BCT and M within and among studies. Some examined simple mastectomy, which includes the breast mound and nipple areolar complex, versus modified radical mastectomy, which also includes full axillary dissection. The extent of margins in breast-conserving therapy likely varied within studies since they were derived from registry data. Breast-conserving therapy includes lumpectomy, quandrantectomy, and in some cases multiple lumpectomies within the same breast. Quandrantectomy,is a resection of the breast quadrant that includes both tumor and healthy tissue, often employed in patients with multifocal disease. On the other hand, lumpectomy, involves taking a minimal amount of healthy tissue around the tumor in order to obtain clean margins; recommended margins also differ between institutions (usually 1mm-2mm). Targets for radiation include tumor bed and axillary nodal levels; dosing and boost treatments varied over the time of the studies, as did the protocols.

Neoadjuvant chemotherapy. A majority of the studies did not include women that were treated with neoadjuvant chemotherapy (chemotherapy before surgery), which is can effectively downstage patients and influence local treatment approach. This sequence is often employed in order to make a tumor more amenable to treatment with BCT. Chemotherapy (either neoadjuvant and adjuvant) is also known to reduce local and locoregional recurrence rates in women who have BCT significantly, even in node negative patients (26). Moreover, patients with close or positive margins who are treated with conservative surgery and radiation have an increased risk of breast recurrence that is delayed by adjuvant systemic therapy (27). Failure to adjust for chemotherapy and other systemic treatments may confound results, attributing survival benefit to local treatment rather than the additional contribution of systemic therapy.

Hormone receptor status and targeted therapy. Assays for hormone receptor overexpression on cancer cells has led to targeted therapies in breast cancer. Hormone receptor status was taken into account in a few of the studies. Some of the authors included hormone receptor status in the analysis even though this information was available for recently diagnosed study subjects. Most of the studies did not control for use of adjuvant hormonal therapy or types of hormonal therapy. Younger breast cancer patients are more likely to have triple negative disease; triple negative cancer status was not included in any analysis despite its known unfavorable prognosis.

Data analysis. The largest limitation I encountered was in interpreting actuarial rates, since they fail to account for potential confounders, the influence of local management on the baseline natural history of breast cancer, and in light of current adjuvant therapies. Although actuarial rates help us identify trends, they do not allow us to explore possible confounders that may be the driving forces behind these observations. The aforementioned discrepancies could potentially decrease the magnitude of any appreciated variances between the two groups, thus decreasing the internal validity. Nonetheless, they may illustrate a more accurate picture of true effectiveness and applicability of the interventions over a diverse spectrum of clinical practice.

CONCLUSION

Investigational studies intended to improve clinical and patient decision-making should demonstrate the absolute benefit provided by the intervention of interest, while also providing probabilities, relative risks, and hazard ratios. The absolute benefit of BCT compared with mastectomy in young women with breast cancer should be discussed in terms of their baseline risk based on clinical factors and tumor characteristics; this discussion needs to be accompanied by discussion of any additional benefits from adjuvant chemo and hormonal therapy.

The development of predictive models that include both clinical and pathologic characteristics and therapeutic interventions tools to predict benefits of adjuvant therapy are available online (28-29). Although a prospective randomized control trial in survival outcomes after BCT versus mastectomy in young breast cancer patients would certainly help us answer this question, it is not feasible. An acceptable alternative prospective observational study to study this unique population of breast cancer patients would either confirm or challenge the conclusion that local management in early-stage breast cancer is not different, even in young patients. The advantage of a prospective observational study lies in its ability to pre-emptively define important patient demographic information, tumor characteristics, and adjuvant therapies that are known to influence long-term survival. Ultimately, the value of observational and outcomes studies lie heavily in their ability to give us theories and a foundation for further bench and clinical research, rather than in a definitive answer to our questions

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REFERENCES

1. Veronesi, U., & Zurrida, S.. Breast cancer surgery: a century after Halsted. *Journal of cancer research and clinical oncology* 1996;*122*(2):74-77.

2. Arriagada R, Le MG, Rochard F, et al. Conservative treatment versus mastectomy in early breast cancer: patterns of failure with 15 years of follow-up data. Institut Gustave-Roussy Breast Cancer Group. J Clin Oncol 1996;14:1558-1564.

3. Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med 2002;347:1227-1232.

4. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 2002;347:1233-1241.

5. Poggi MM, Danforth DN, Sciuto LC, et al. Eighteen-year results in the treatment of early breast carcinoma with mastectomy versus breast conservation therapy: the National Cancer Institute Randomized Trial. Cancer 2003;98:697-702.

6. van Dongen JA, Voogd AC, Fentiman IS, et al. Long-term results of a randomized trial comparing breast-conserving therapy with mastectomy: European Organization for Research and Treatment of Cancer 10801 trial. J Natl Cancer Inst 2000;92:1143-1150.

7. Blichert-Toft M, Rose C, Andersen JA, et al. Danish randomized trial comparing breast conservation therapy with mastectomy: six years of life-table analysis. Danish Breast Cancer Cooperative Group. J Natl Cancer Inst Monogr 1992;(11):19-25.

8. Fisher B, Dignam J, Mamounas EP, et al. Sequential methotrexate and fluorouracil for the treatment of node-negative breast cancer patients with estrogen receptor-negative tumors: eight-year results from National Surgical Adjuvant Breast and Bowel Project (NSABP) B-13 and first report of findings from NSABP B-19 comparing methotrexate and fluorouracil with

conventional cyclophosphamide, methotrexate, and fluorouracil [see comments]. J Clin Oncol 1996;14:1982-1992.

9. Polychemotherapy for early breast cancer: an overview of the randomized trials. Early Breast Cancer Trialists' Collaborative Group. Lancet 1998;352(9132):930-942.

10. Jones SE, Moon TE, Bonadonna G, et al. Comparison of different trials of adjuvant chemotherapy in stage II breast cancer using a natural history database. Am J Clin Oncol 1987;10:387-395.

11. Slamon DJ, Leyland-Jones B, Shaks S, et al. Use of chemotherapy plus a monoclonal antibody against Her 2 for metastatic breast cancer that overexpresses Her 2. N Engl J Med 2001;344(11):783-792.

12. Giuliano AE, Kirgan DM, Guenther JM, Morton DL. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. Ann Surg 1994;220:391-401.

13. Krag DN, Anderson SJ, Julian TB, et al.; National Surgical Adjuvant Breast and Bowel Project. Technical outcomes of sentinel-lymph-node resection and conventional axillary-lymph-node dissection in patients with clinically node-negative breast cancer: results from the NSABP B-32 randomised phase III trial. Lancet Oncol 2007;8(10):881-888.

14. Veronesi U, Paganelli G, Viale G, et al. A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. N Engl J Med 2003;349:546-553.

15. Turner RR, Ollila DW, Krasne DL, Giuliano AE. Histopathologic validation of the sentinel lymph node hypothesis for breast carcinoma. Ann Surg 1997;226:271-276.

16. Noguchi S, Aihara T, Motomura K, Inaji H, Imaoka S, Koyama H. Detection of breast cancer micrometastases in axillary lymph nodes by means of reverse transcriptase-polymerase chain reaction: comparison between MUC1 and mRNA and keratin 19 mRNA amplification. Am J Pathol 1996;148:649-656.

17. International (Ludwig) Breast Cancer Study Group [see comments]. Lancet 1990;335:1565-1568.)

18. Singletary E, Allred C, Ashley P, Bassett LW, Berry D, Bland KI, Borgen PI, Clark G, Edge SB, Hayes DF, Hughes LL, Hutter RVP, Morrow M, Page DL, Recht A. Revision of the American Joint Committee on Cancer Staging System for Breast Cancer. J Clin Oncol 2002;20:3628-3636.

19. Giuliano AE, Dale PS, Turner RR, et al. Improved axillary staging of breast cancer with sentinel lymphadenectomy. *Ann Surg* 1995;222:394-9.

20. Kurtz J, Jacquemier J, Amalric R, et al. Why are local recurrences after breast-conserving therapy more frequent in younger patients? J Clin Oncol 1990;8:591-598.

21. S.H. Kim, A. Simkovich-Heerdt, K.N. Tran *et al.* Women 35 years of age or younger have higher locoregional relapse rates after undergoing breast conservation therapy**.** J Am Coll Surg, 187 (1998), pp. 1–8.

22. A. Recht, J.L. Connolly, S.J. Schnitt *et al.* The effect of young age on tumor recurrence in the treated breast after conservative surgery and radiotherapy. Int J Radiat Oncol Biol Phys, 14 (1988), pp. 3–10.

23. P. Karlsson, B.F. Cole, K.N. Price *et al.* The role of the number of uninvolved lymph nodes in predicting locoregional recurrence in breast cancer. J Clin Oncol, 25 (2007), pp. 2019–2026.

24. Clarke M, Collins R, Darby S, et al.; Early Breast Cancer Trialists' Collaborative Group (EBCTCG) Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;366(9503):2087-2106.

25. Brooks JP, Danforth DN, Albert P. Early ipsilateral breast tumor recurrences after breast conservation affect survival: an analysis of the NCI randomized trial. Int.J. Radiat. Oncol. Biol. Phys. 2005.

26. Elkhuizen,P.H.; van Slooten,H.J.; Clahsen,P.C.; Hermans,J.; van de Velde,C.J.; van den Broek,L.C.; van de Vijver,M.J. High local recurrence risk after breast-conserving therapy in node-negative premenopausal breast cancer patients is greatly reduced by one course of

perioperative chemotherapy: A European Organization for Research and Treatment of Cancer Breast Cancer Cooperative Group Study. J.Clin.Oncol., 2000, 18, 5, 1075-1083.

27. Freedman G., Fowble B., Hanlon A,, Nicholaou N., Fein D., Hoffman J., Sigurdson E., Boraas M., Goldstein, L. Patients with early stage invasive cancer with close or positive margins treated with conservative surgery and radiation have an increased risk of breast recurrence that is delayed by adjuvant systemic therapy. Int J Radiat Oncol Biol Phys 1999 July 15; 44(5): 1005-1015.

28. Ravdin PM, Siminoff LA, Davis GJ, et al. Computer program to assist in making decisions about adjuvant therapy for women with early breast cancer. J Clin Oncol 2001;19(4):980-991.

29. Olivotto IA, Bajdik CD, Ravdin PM, et al. Population-based validation of the prognostic model ADJUVANT! for early breast cancer. J Clin Oncol 2005;23(12):2716-2725.

TABLES AND FIGURES

Table 1. Systematic Review Inclusion and Exclusion Criteria

	Inclusion Criteria	Exclusion Criteria
Population	Females Age <35 or <40 a the time of diagnosis with early stage invasive breast cancer	DCIS Advanced breast cancer Males
Interventions	BCT	
Comparisons	Mastectomy +/-XRT	
Outcomes	Survival	
Timing	≥10 years	Less than 10 years of survival outcomes
Settings	Western Nations Published in the English language	
Study Design	Retrospective cohort studies published within the last 10 years	

*DCIS- Ductal Carcinoma; BCT- Breast conserving therapy; XRT- radiation therapy

Table 2. AHRQ Grades of Evidence

GRADE	DEFINITION
High	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit estimation of an effect.
Sources: {Owens, JCE 2009}{AHRQ 2007}	

EVIDENCE TABLES

Table 3. Effect of Local Management on Local Recurrence (LR)

EVIDENCE PROFILE: COMPARATIVE 10 YEAR LR AFTER BCT VS. MASTECTOMY IN YOUNG BREAST CANCER PATIENTS				
NO. OF PATIENTS	**STUDY DESIGN**	**STUDY QUALITY**	**MAGNITUDE OF EFFECT (AND/OR PRECISION)**	**OVERALL GRADE OF THE EVIDENCE**
STUDY: Coulombe G, Tyldesley S, Speers C, et al.				
540	Fair	Poor	**Stage I-IIB: (20-39 yo)** BCT= 14% MRM= 16.2% P= 0.34 **Stage IA: (20-39 yo)** BCT= 13.7% MRM= 4.9% P= 0.30	Low
STUDY: Beadle BM, Woodward WA, Tucker SL, et al.				
652	Poor	Poor	**Stage I-IIIC:** BCT=15.8% M=12.5% MXRT=7.0% P=0.04 *LR not stratified by stage	Low
STUDY: Van der Sangen MJC, van de Wiel, FNM, Poortmans, PMP.				
1451	Poor	Poor	**Stage I-IIB:** BCT: 18.3% (14.9-21.7) M: 6.0% (3.5-8.5) p<0.0001	Low

Table 4. Effect of Local Management on Local Regional Recurrence (LRR)

EVIDENCE PROFILE: COMPARATIVE10 YEAR LRR AFTER BCT VS. MASTECTOMY IN YOUNG BREAST CANCER PATIENTS				
NO. OF PATIENTS	**STUDY DESIGN**	**STUDY QUALITY**	**MAGNITUDE OF EFFECT (AND/OR PRECISION)**	**OVERALL GRADE OF THE EVIDENCE**
STUDY: Coulombe G, Tyldesley S, Speers C, et al.				
540	Fair	Poor	**Stage I-IIB: (20-39 yo)** BCT= 17.4% MRM= 19.1% p= 0.41 **Stage IA: (20-39 yo)** BCT= 16.0% MRM= 12.7% p= 0.94	Low
STUDY: Beadle BM, Woodward WA, Tucker SL, et al.				
652	Poor	Poor	**Stage I-3C:** BCT= 19.8% M= 24.1% MXRT=15.0% p=0.05 **Stage I:** BCT= 18.0% M= 19.8% MXRT= Not included p= 0.56 **Stage II:** BCT= 17.7% M= 22.8% MXRT= 5.7% p= 0.02 **Multivariate for Stage II:** M HR= 4.45 (1.36-14.6); p=0.014 BCT: HR= 3.40 (0.99-11.7); p= 0.052	Low

Table 5. Effect of Local Management on Distant Metastasis (DM)

EVIDENCE PROFILE: COMPARATIVE 10 YEAR DM AFTER BCT VS. MASTECTOMY IN YOUNG BREAST CANCER PATIENTS				
NO. OF PATIENTS	**STUDY DESIGN**	**STUDY QUALITY**	**MAGNITUDE OF EFFECT (AND/OR PRECISION)**	**OVERALL GRADE OF THE EVIDENCE**
STUDY: Coulombe G, Tyldesley S, Speers C, et al.				
540	Fair	Poor	**Stage I-IIB: (20-39 yo)** BCT= 26.9% MRM= 27.5% p=0.77 **Stage IA: (20-39 yo)** BCT= 14.3% M= 24.6% p= 0.17	Low
STUDY: Beadle BM, Woodward WA, Tucker SL, et al.				
652	Poor	Poor	**Stage I-IIIC:** BCT= 25.5% M=42.5% MXRT= 49.1% p<0.0001 **Stage I:** BCT= 27.4% M= 27.7% MXRT= Not included p= 0.15 **Stage II:** BCT= 19.5% M= 33.9% MXRT= 39.4% p= 0.006	Low
STUDY: Van der Sangen MJC, van de Wiel, FNM, Poortmans, PMP.				
1451	Poor	Poor	**Stage I-IIB:** M: 33.0% BCT: 29.0% p= 0.0831 **Treatment- year 7:** BCT: HR= 0.75 (0.61-0.93) p=0.009 **Year 7 onwards:** BCT: HR=1.96 (1.02-3.76) p=0.044 **Multivariate** BCT: HR=0.97 (0.78-1.20) p= 0.771	Low

Table 6. Effect of Local Management on Cause-Specific Survival (CSS)

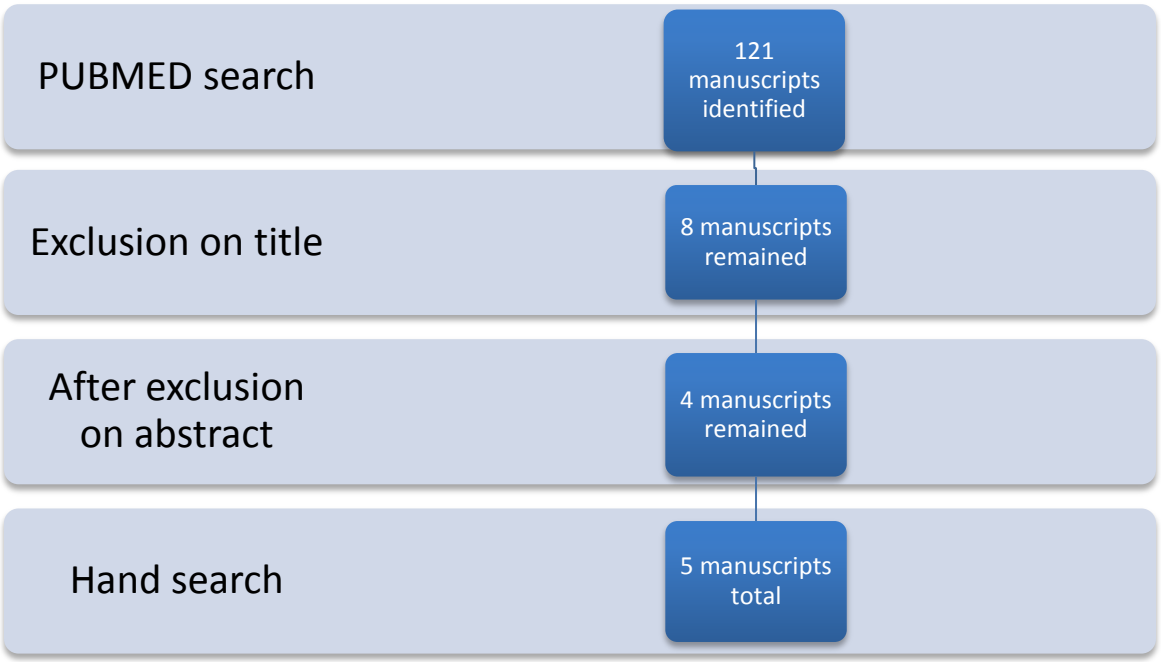
EVIDENCE PROFILE: COMPARATIVE 10 YEAR CSS AFTER BCT VS. MASTECTOMY IN YOUNG BREAST CANCER PATIENTS				
NO. OF PATIENTS	**STUDY DESIGN**	**STUDY QUALITY**	**MAGNITUDE OF EFFECT (AND/OR PRECISION)**	**OVERALL GRADE OF THE EVIDENCE**
STUDY: Coulombe G, Tyldesley S, Speers C, et al.				
540	Fair	Poor	**Stage I-IIB: (20-39 yo)** BCT= 79.8% MRM= 74.9% P= 0.09 **Stage IA: (20-39 yo)** BCT= 90.8% M= 86.0% P= 0.41	Low
STUDY: Mahmood U, Morris C, Neuner G, et al.				
14,764	Fair/Poor	Poor	**Stage I-IIB:** M: HR=1.00 BCT: HR= 0.93 (0.83-1.05) p=0.26 **Matched pair analysis:** M= 85.5% BCT= 85.5% p=0.88	Low/Moderate

Table 7. Effect of Local Management on Overall Survival (OS)

EVIDENCE PROFILE: COMPARATIVE 10 YEAR OS AFTER BCT VS. MASTECTOMY IN YOUNG BREAST CANCER PATIENTS				
NO. OF PATIENTS	**STUDY DESIGN**	**STUDY QUALITY**	**MAGNITUDE OF EFFECT (AND/OR PRECISION)**	**OVERALL GRADE OF THE EVIDENCE**
STUDY: Beadle BM, Woodward WA, Tucker SL, et al.				
652	Poor	Poor	**Stage I-IIIC:** BCT= 80.0% M=60.4% MXRT= 57.5% P=0.0003 **Stage I:** BCT= 92.4% M= 72.0% MXRT= Not included P= 0.19 **Stage II:** BCT=81% M= 63.4% MXRT= 85.4% p= 0.03 M: HR= 1.72 (1.11-2.67) p=0.015	Low
STUDY: Bantema-Joppe EJ, De Munck L, Visser O, et al.				
1453	Poor	Poor	**Stage I-IIA:** M: 78% BCT: 83% p=0.007 M: HR= 1.37 (1.09-1.72)	Low
STUDY: Van der Sangen MJC, van de Wiel, FNM, Poortmans, PMP.				
1451	Poor	Poor	**Stage I-IIB:** M: 71.20% (62.4-71.6) BCT: 74.9% (71.7-78.1) p=0.215	Low
STUDY: Mahmood U, Morris C, Neuner G, et al.				

14,764	Fair	Fair/Poor	**Stage I-IIB:** **Matched pair analysis** M= 83.6% BCT= 83.5% p=0.99 **Multivariate analysis** M=1.00 BCT= 0.93 (0.83-1.04) p=0.16	Low/Moderate

Figure 1. Search Results



APPENDIX A. APPRAISAL TABLES

Table 1. Coulombe, et al.

STUDY INFOMRATION	
Study Citation	Coulombe G, Tyldesley S, Speers C, et al. Is Mastectomy superior to Breast-conserving treatment for young women? Int. J. Radiation Oncology Biol. Phys. 2007; 67(5): 1282-1290.
Funding	No COI reported
Country of Origin	Canada (B.C.)
STUDY QUESTION	
QUESTION	Is Modified Radical Mastectomy (MRM) superior to Breast Conserving Therapy (BCT) in terms of local recurrence, local regional recurrence, distant recurrence and breast cancer specific survival in a cohort of young women with early-stage invasive breast cancer?
POPULATION	Young women diagnosed with early-stage breast cancer in British Columbia
Inclusion criteria	
Age	20-49
Stage	Stage I-II (AJCC Stage I-IIB)
T	pT1/T2
N	N0/1/NX
Histologic Subtypes	Ductal, Lobular, Other
Exclusion criteria	Locally advanced or metastases (T3-4; N2-N3; M1), neoadjuvant chemo or RT, primary breast sarcomas or lymphomas, prior DCIS or LCIS or other cancers, nodal RT
INTERVENTION	BCT – defined as any open surgery of the breast less than a total mastectomy
COMPARISON	Modified Radical Mastectomy (MRM) (+/-XRT)
OUTCOME	Local recurrence (LR) Local recurrence (LRR) Distant relapse-free survival (DRFS) Breast cancer specific survival (BCSS)
TIMING	
Years of diagnosis	1989-1998
Stratified?	No
TIME FORWARD	10 years Median: 9 years
STUDY DESIGN	Retrospective Cohort study
SELECTION OF COHORTS	British Columbia Breast Cancer Outcomes Unit (BCOU) database BCT vs. MRM, early stage patients
POPULATION CHARACTERISTICS	
N	2,398 (BCT= 1597; MRM=801-> 64/801=+XRT) 20-39 years old (N=540; BCT= 356; MRM= 184)
Age	Range: 20-49 Stratified: yes Stratification: 20-39 40-49

Race	Not reported/controlled for
SES	Not reported/controlled for
HR status assessed	ER ONLY
Hormone therapy	Yes
Chemotherapy	Yes, adjuvant only
POTENTIAL FOR SELECTION BIAS? (+, ++, +++)	++
(Based on appropriate selection of cases or cohorts and controls, descriptive demographics, eligibility criteria (and how chosen), and initial comparability of groups)	Logistic regression was carried out only on patients without missing data for the included variables and with a minimum of 10 years follow-up.
OUTCOME MEASUREMENT	
Definition of outcome	**LR**: time from diagnosis to recurrence in ipsilateral breast, overlying skin, or chest wall. **LRR:** time from diagnosis to first ipsilateral local or regional nodal recurrence. Censored at the earliest of the following dates: distant relapse occurring >30 days before LR or LRR, subsequent contralateral breast cancer occurring before LR/LRR, date of death or last follow-up. When LR/LRR occurred within 30 days of distant relapse, the relapses were considered concurrent and were recorded as occurring on the date of the earlier events. **DRFS**: time from diagnosis to first relapse beyond ipsi breast and regional lymph nodes. Censored at the time of a subsequent contralateral new primary breast cancer occurring before a distant relapse, date of death, or last follow-up. **BCSS:** time between initial diagnosis and death when breast cancer was the primary or underlying cause of death.
Method of Outcome Assessment **How often?**	Outcome data reported in database
Equal, valid, reliable?	Unclear since voluntary data.
Length of follow-up time	+++
POTENTIAL FOR MEASUREMENT BIAS? (+, ++, +++)	+/++; Measurement of exposure: No set definition of ”extensive DCIS”. BCOU includes centrally reviewed and non-centrally reviewed path reports. One of variables is absence or presence of “noticeable DCIS”? Again unclear how this is measured/defined. XRT does differed between groups and within groups
CONFOUNDING	
Quality of intervention	Not likely to be different
Confounders and how each was addressed	1. DID NOT CONTROL FOR XRT in mastectomy group since strongly related to surgery, kept all mastectomy +XRT in analysis-> controlled for margin status since patients requiring post-M XRT are likely to have positive chest wall margins. 2. MRM patients had worse prognostic factors: larger tumors, ore nodal involvement,

	"noticeable DCIS", central or mutifocal lesions.
POTENTIAL FOR CONFOUNDING? (+, ++, +++)	++
STATISTICAL ANALYSIS	
Statistical Analysis	Conducted a subgroup analysis on "ideal BCT candidates"= tumor size ≤ 2cm, pN0, clear surgical margins, no extensive DCIS= AJCC Ia Survival analysis for using forward binary logistic regression (b/c violated proportional hazards). Type of surgery was last to include in regression mode-> includes women 40-49. Those with minimum of 10 year follow-up and no missing values.
Powered to show difference?	Not stated a-priori
Variables controlled for in regression model	Age, size of tumor, tumor location, number of positive nodes, ER status, grade, LV status, margin status, primary histology, presence or absence of noticeable DCIS, and +/- of initial adjuvant chemo or hormone therapy.
RESULTS	
LRFS	
Results	**In young study cohort (20-39)** BCT= 86% MRM= 83.8% P= 0.34 **In ideal candidates (20-39)** BCT= 86.3% MRM= 95.1% P= 0.30
Magnitude	3.8% in study cohort; 8.8% in ideal
Direction	Study (I-IIB): slightly favors BCT; ideal(IA) favors MRM
Statistically significant?	No
Clinically relevant?	Yes, in ideal subgroup
LRRFS	
Results	**In young study cohort (20-39)** BCT= 82.6% MRM= 80.9% P= 0.41 **In ideal candidates (20-39)** BCT= 84.0% MRM= 87.3% P= 0.94
Magnitude	I-IIB: 1.7%; 1a: 3.3%
Direction	I-IIB group favors BCT; IA group favors MRM
Statistically significant?	No
Clinically relevant?	No
DRFS	
Results	**In young study cohort (20-39)** BCT= 73.1% MRM= 72.5% P=0.77

	In ideal candidates (20-39) BCT= 85.7% M= 75.4% P= 0.17
Magnitude	I-IIB: <1%; IA: 9.3%
Direction	Favors BCT in ideal candidates (1a)
Statistically significant?	No
Clinically relevant?	Yes
BCSS	
Results	**In young study cohort (20-39)** BCT= 79.8% MRM= 74.9% P= 0.09 **In ideal candidates (20-39)** BCT= 90.8% M= 86.0% P= 0.41
Magnitude	Stage I-IIB: 4.9%; Stage IA: 4.8%
Direction	Favors BCT in both groups
Statistically significant?	Almost in I-IIB group
Clinically relevant?	Yes
CONCLUSIONS/COMMENTS	
Overall conclusions/interpretation (include consistency with other studies; biologic plausibility; conflicts of interest; selective endpoint reporting; costs; potential harms; patient decision making preferences)	Logistic regression was carried out only on patients without missing data for the included variables and with a minimum of 10 years follow-up.
QUALITY RATING OF STUDY: GOOD, FAIR, POOR	
Selection of cohorts	++
Adjustment for Confounding	+
Measurement	+
Statistical analysis	+
Internal validity	++
External validity/Generalizability	+
STUDY QUALITY SCORE	Poor
STRENGTH/GRADE OF EVIDENCE: HIGH, MODERATE, LOW	
Study Design	++
Study Quality	+
Consistency	+
Directness	+
Precision	Unknown
STRENGTH OF EVIDENCE (GRADE)	Low

Table 2. Beadle, et al.

STUDY INFOMRATION	
Study Citation	Beadle BM, Woodward WA, Tucker SL, et al. Ten-Year recurrence rates in young women with breast cancer by locoregional treatment approach. Int. J. Radiation Oncology Biol. Phys. 2009; 73(3): 734-44.
Funding	No COI reported
Country of Origin	USA
STUDY QUESTION	
QUESTION	Effect of local management comparing Breast-cnserving therapy (BCT) vs. Mastectomy (M) vs. Mastectomy + radiation (MXRT) on 10 year rates of local recurrence (LR), local regional recurrence (LRR), distant metastases (DM) and overall survival (OS) survival in a cohort of young women with early-stage invasive breast cancer?
POPULATION	Young women treated for early-stage breast cancer at MD Anderson hospital.
Inclusion criteria	
Age	<35 years old at dx
Stage	Stage I-III (using 2002 AJCC-> Stage I-IIIC) *patients who got neoadjuvant chemo-> most advanced stage used (clinical or pathological) patients with adjuvant chemo-> pathologic stage used
T	T: 1-4
N	N: 1-3
Histologic Subtypes	Invasive ductal Invasive lobular Invasive mixed Unknown/other
Exclusion criteria	Inflammatory breast cancer DCIS Sarcoma Unknown primary BCT (without XRT) Mets within 6 months of diagnosis Did not receive a definitive surgery
INTERVENTION	BCT
COMPARISON	M vs. MXRT
OUTCOME	Local recurrence (LR) Local recurrence (LRR) Distant metastases (DM) Overall survival (OS)
TIMING	
Years of diagnosis	1973-2006
Stratified?	Yes, by decade of treatment: 1973-1979 1980-1989 1990-1999 2000-2006
TIME FORWARD	10 years Range: 2-411

	Median: 91 months
STUDY DESIGN	Retrospective Cohort study
SELECTION OF COHORTS	MD Anderson database <35 years old at dx grouped into BCT vs. M vs. MXRT Women with MXRT probably not candidates for BCT, should this comparison group be included?
POPULATION CHARACTERISTICS	
N	652 (BCT= 196; M=237; MXRT=234)
Age	Range: 16-35 Median: 33 Stratified: yes Stratification: ≤19 20-24 25-29 30-35
Race	White/Caucasian (62%) Black/AA (14.8%) Hispanic (20.2%) Other (3.0%)
SES	Not reported/controlled for
HR status assessed	ER and PR Most patients not evaluated for her-2 status, so not reported
Hormone therapy	Yes
Chemotherapy	Yes
POTENTIAL FOR SELECTION BIAS? (+, ++, +++) **(Based on appropriate selection of cases or cohorts and controls, descriptive demographics, eligibility criteria (and how chosen), and initial comparability of groups)**	++, comparison groups are not equivalent. Patients requiring MXRT are not likely candidates for BCT. Furthermore "ideal BCT candidates" have smaller tumors (<5cm); this analysis includes patients with T3 (>5cm) who have inherently worse prognosis.
OUTCOME MEASUREMENT	
Definition of outcome	All pathologic endpoints were calculated as interval between pathologic diagnosis of primary cancer and event of interest. **LR:** Recurrence in ipsilateral breast chest wall or overlying skin. **LRR:** ipsilateral local or regional nodal recurrence (including axillary, supraclavicular, infraclavicular, or internal mammary nodal beds). All LRRs were considered events regardless of their relation to DM in time. **DM:** recurrence in any other site. **OS:** death from any cause
Method of Outcome Assessment **How often?** **Equal, valid, reliable?**	Reviewed records. No info on institutional follow-up protocols or changes in surveillance over different time periods.
Length of follow-up time	**+++**
POTENTIAL FOR MEASUREMENT BIAS? (+, ++, +++)	**++**
CONFOUNDING	
Quality of intervention	++, all patients seen and treated at one of the best cancer hospitals in the nation.
Confounders and how each was addressed	Only controlled for variables that were borderline/significant on bivariate analysis (p≤0.1) Stage I patients who had MXRT were few so not included in

	subgroup analysis (Stage I: M vs. BCT only)
POTENTIAL FOR CONFOUNDING? (+, ++, +++)	+++
STATISTICAL ANALYSIS	
Statistical Analysis	10 year actuarial rates of LRR, DM, OS were calculated using KM statistic and comparisons between groups were calculated using log-rank test. Multivariate analysis using forward stepwise Cox regression (violated proportional hazards assumption). Only controlled for variables that were borderline/significant on bivariate analysis (p≤0.1))
Powered to show difference?	Not stated a-priori
Variables controlled for in regression model	Unclear which univariate analysis was used to determine variables to be included in multivariate analysis.
RESULTS	
LR	
Overall population (n=652; BCT= 196; M=237; MXRT=234)	
10 year actuarial rates	BCT=15.8% M=12.5% MXRT=7.0% P=0.04 **Did not stratify by stage for LR
Magnitude	8.8% for BCT; 5.5% for M
Direction	Favors MXRT
Statistically significant?	Yes
Clinically relevant?	Yes
LRR	
Overall population (n=652; BCT= 196; M=237; MXRT=234)	
10 year actuarial rates	BCT= 19.8% M= 24.1% MXRT=15.0% P=0.05
Magnitude	4.8% for BCT; 9.1% for M
Direction	Favors MXRT
Statistically significant?	Yes
Clinically relevant?	Yes
Stage I (n=101; BCT=53; M=42)	
10 year actuarial rates	BCT= 18.0% M= 19.8% MXRT= Not included P= 0.56 <u>Stratified by chemo:</u> No Chemo: BCT= 33.3%; M= 25.5% P=0.23 Chemo: BCT= 12.0%; M= 9.0% P= 0.72 (chemo group had more high grade tumors; p=0.005) said all other factors not sig different but didn't report HRs)
Multivariate analysis	No adjuvant chemo: HR=2.73 (1.06-7.04); p=0.037 No hormone therapy HR= 2.54 (0.98-6.56); p= 0.055
Magnitude	Only when stratified by chemo
Direction	No chemo favors BCT; +Chemo favors M

Statistically significant?	No
Clinically relevant?	Yes
Stage II (n= 296)	
10 year actuarial rates	BCT= 17.7% M= 22.8% MXRT= 5.7% (despite advanced N stage (p=0.004); and use of neoadjuvant chemo (p<0.0001)) P= 0.02
Multivariate analysis	**M Alone: HR= 4.45 (1.36-14.6); p=0.014** **BCT: HR= 3.40 (0.99-11.7); p= 0.052** (34 got neoadjuvant chemo, 68 no neoadjuvant; p= 0.29) Grade 3: HR= 2.24 (1.19-4.23); p=0.012
Magnitude	12% for BCT; 17.1% for M
Direction	Favors MXRT>BCT>M
Statistically significant?	Yes
Clinically relevant?	Yes
Stage III (n=262)	
10 year actuarial rates	BCT= 28.4% M= 23.9% MXRT= 18.4% P= 0.13
Multivariate analysis	**M Alone: HR= 2.37 (1.24-4.51); p=0.009** ≥10 +LN: HR= 2.50 (1.36-4.60); p= 0.003 older age: HR= 0.91 (0.85-0.99); p=0.021 No neoadjuvant chemo: HR= 0.59 (0.31-1.09); p=0.094
Magnitude	10% for BCT; 5.5% for M
Direction	Favors MXRT>M>BCT
Statistically significant?	No
Clinically relevant?	Yes
DM	
Overall population (n=652; BCT= 196; M=237; MXRT=234)	
10 year actuarial rates	BCT= 25.5% M=42.5% MXRT= 49.1% P<0.0001
Magnitude	17.0% for M; 24.4% for MXRT
Direction	Favors BCT>M>MXRT
Statistically significant?	Yes
Clinically relevant?	Maybe, but patients with MXRT tend to be more advanced than candidates for BCT
Stage I (n=101; BCT=53; M=42)	
10 year actuarial rates	BCT= 27.4% M= 27.7% MXRT= Not included P= 0.15
Multivariate analysis	Did not report
Magnitude	0.3%
Direction	Favors M
Statistically significant?	No
Clinically relevant?	No
Stage II (n= 296)	
10 year actuarial rates	BCT= 19.5% M= 33.9% MXRT= 39.4%

	P= 0.006
Multivariate analysis	Did not report
Magnitude	14.4% for M; 20.1% for MXRT
Direction	Favors BCT
Statistically significant?	Yes
Clinically relevant?	Yes?
Stage III (n=262)	
10 year actuarial rates	BCT= 36.2% M= 58.3% MXRT= 54.0% P= 0.08
Multivariate analysis	Did not report
Magnitude	22.1% for M; 17.8% for MXRT
Direction	BCT>MXRT>M
Statistically significant?	almost
Clinically relevant?	Yes
OS	
Overall population (n=652; BCT= 196; M=237; MXRT=234)	
10 year actuarial rates	BCT= 80.0% M=60.4% MXRT= 57.5% P=0.0003
Magnitude	22.5% for BCT; 2.9% for M
Direction	BCT>M>MXRT
Statistically significant?	yes
Clinically relevant?	Yes
Stage I	
10 year actuarial rates	BCT= 92.4% M= 72.0% MXRT= Not included P= 0.19
Multivariate analysis	+Hormone therapy: HR= 2.17 (0.90-5.23); p=0.084
Magnitude	20.4%
Direction	Favors BCT
Statistically significant?	No
Clinically relevant?	Yes, maybe just not powered to show a difference
Stage II (n= 296)	
10 year actuarial rates	BCT=81% M= 63.4% MXRT= 85.4% p= 0.03
Multivariate analysis	**M alone: HR= 1.72 (1.11-2.67); p=0.015** +LN: HR= 1.52 (0.97-2.37); p= 0.067
Magnitude	-4.3% for BCT; -22.0% for M
Direction	MXRT>BCT>M
Statistically significant?	Yes
Clinically relevant?	Yes
Stage III (n=262)	
10 year actuarial rates	BCT= 64.4% M= 46.6% MXRT= 48.4% P= 0.16
Multivariate analysis	**M alone: HR= 1.58 (1.02-2.45); p= 0.041**

	≥ 4+ nodes: HR= 2.29 (1.42-3.67); 0.001 ≥ 10+ nodes: HR= 1.47 (0.95-2.26); p=0.082 No adjuvant chemo; HR= 1.70 (1.00-2.87); p=0.049 ER negative: HR= 1.92 (1.28-2.87) **BCT: 0.54 (0.29-0.99)** No neoadjuvant chemo: 0.41 (0.25-0.66); p<0.0001
Magnitude	-16.8% for M; -16% for MXRT
Direction	BCT>MXRT>M
Statistically significant?	yes
Clinically relevant?	Yes for BCT but no big diff b/w M and MXRT
CONCLUSIONS/COMMENTS	
Overall conclusions/interpretation (include consistency with other studies; biologic plausibility; conflicts of interest; selective endpoint reporting; costs; potential harms; patient decision making preferences)	Although it would be helpful to determine benefit based on subgroups with each combination of local management, it is inappropriate to do so retrospectively since the decision for type of local management results from clinical and pathologic characteristics. It would be more appropriate to determine the baseline risk for a particular outcome and then compare that to each local intervention. ***Only single institution study: had equal exposure, or quality of intervention. Since everything done according hospital protocol (admin of XRT, etc.). Although protocols changed during different time periods.
QUALITY RATING OF STUDY: GOOD, FAIR, POOR	
Selection of cohorts	+
Adjustment for Confounding	+
Measurement	++
Statistical analysis	+
Internal validity	++
External validity/Generalizability	++
STUDY QUALITY SCORE	Fair/Poor
STRENGTH/GRADE OF EVIDENCE: HIGH, MODERATE, LOW	
Study Design	+
Study Quality	+
Consistency	++
Directness	+
Precision	+
STRENGTH OF EVIDENCE (GRADE)	Low

Table 3. Bantema-Joppe, et al.

STUDY INFOMRATION	
Study Citation	Bantema-Joppe EJ, De Munck L, Visser O, et al. Early-stage young breast cancer patients: Impact of local treatment on survival. Int J Radiaton Oncol Bio Phys. 2011; 81(4):e553-9.
Funding	No COI statement
Country of Origin	The Netherlands
STUDY QUESTION	
QUESTION	Does difference in local control translate into inferior survival after BCT in young breast cancer patients?
POPULATION	Young (<40) Dutch women diagnosed with early stage (up to 2A) invasive breast cancer treated with BCT or M (+/-XRT) between 1/89-1/05)
Inclusion criteria	
Age	<40
Stage	Stage I to IIA
T	pT1a-c (≤ 2 cm)
N	pN0-1 (≤ 3 +LN)
Histologic Subtypes	Not specified
Exclusion criteria	Distant metastases, previous history of invasive cancer (except non-melanoma skin cancer), and patients treated with neoadjuvant chemotherapy.
INTERVENTION	BCT
COMPARISON	Mastectomy
OUTCOME	Overall survival (OS)
TIMING	
Years of diagnosis	January 1989-January 2005
Stratified?	Yes 1989-1994 (38.9%) 1995-2000 (29.1%) 2001-2004 (33.1%)
TIME FORWARD	10 years Median time to outcome: 9.6 years (IQR 5.9-14.3)
STUDY DESIGN	Retrospective cohort study
SELECTION OF COHORTS	Patient data obtained from 2 Dutch population based cancer registries (cover 40% of pop) Young women <40 years old at the time of diagnosis with invasive early stage breast cancer who were “ideal candidates for BCT”
POPULATION CHARACTERISTICS	
N	1,453 (M=504; BCT= 909)
Age	<40 Median: 36.5 (IQR 33.8-38.4) Stratified: yes <35 (34%) 35-39 (66%)
Race	Not reported/controlled for
SES	Not reported/controlled for
HR status assessed	Not routinely tested for at the beginning of the study period so it was not included in the analysis.
Hormone therapy	Yes
Chemotherapy	Yes

POTENTIAL FOR SELECTION BIAS? (+, ++, +++) (Based on appropriate selection of cases or cohorts and controls, descriptive demographics, eligibility criteria (and how chosen), and initial comparability of groups)	+
OUTCOME MEASUREMENT	
Definition of outcome	OS defined as interval from date of pathologic diagnosis to the date of death from any outcome
Method of Outcome Assessment **How often?** **Equal, valid, reliable?**	Data on mortality from municipal personal records database last linkage Feb 2009.
Length of follow-up time	**+++**
POTENTIAL FOR MEASUREMENT BIAS? (+, ++, +++)	**+**
CONFOUNDING	
Quality of intervention	Unknown
Confounders and how each was addressed	M +XRT=(23%)-> could make mastectomy outcomes seem better than they are. Didn't control for grade, histologic subtype, receptor type (unless they assume all ER+ patients got ERB or ovarian suppression)
POTENTIAL FOR CONFOUNDING? (+, ++, +++)	+/++
STATISTICAL ANALYSIS	
Statistical Analysis	Multivariate cox regression survival analysis for 10 year OS
Powered to show difference?	Not stated a-priori
Variables controlled for in regression model	Age at diagnosis Period of diagnosis (year categories above) Pathological T stage Adjuvant chemo Adjuvant hormone therapy Stratified by Nodal status N0 vs. N1
RESULTS	
OS	
Results	**<u>Overall:</u>** <u>Actuarial10 year survival rate</u> M: 78% BCT: 83% Log-rank test (p=0.007) HR= 1.37 (CI:1.09-1.72) for M vs. BCT (HR=1) <u>Multivariate regression (adjusted)</u> Not reported **<u>N0:</u>** <u>Actuarial 10 year survival rate</u> M: 81% BCT: 84% Log-rank test (p=0.26) No diff. after M (HR=1.18; CI:0.88-1.57) vs. BCT

	(HR=1) <u>Multivariate regression (adjusted)</u> M: 1.19 (0.89-1.58) BCT: 1 Log-rank test (p= 0.25) **<u>N1:</u>** <u>Actuarial 10 year survival rate</u> M: 71% BCT: 79% Log-rank test (p=0.014) M (HR=1.62; CI:1.10-2.40) is inferior to BCT (HR=1) <u>Multivariate regression (adjusted)</u> M: 1.91 (CI: 0.89-1.58) BCT: 1 Log-rank test (p=0.001)
Magnitude	8%
Direction	BCT superior to M
Statistically significant?	Yes
Clinically relevant?	Yes
CONCLUSIONS/COMMENTS	
Overall conclusions/interpretation (include consistency with other studies; biologic plausibility; conflicts of interest; selective endpoint reporting; costs; potential harms; patient decision making preferences)	Hormone therapy improves survival (HR= 0.34 vs. 1); p=0.001 M group more likely to take hormone therapy: Overall 18.4% vs. 13.0% p=0.005 N2 group: 35.3% vs. 25.9% p=0.00 Goes back to attributable benefit. How much is local therapy making/not making a difference? Don't know which races were included in study but most likely white European females, not applicable to US pop. Overall: favors BCT* N0: No difference in 10yr OS for BCT N1: BCT> M 10 yr OS (p=0.014) Even after adjusting for other characteristics HR for OS in M= 1.91 vs. BCT= 1 (p=0.001)
QUALITY RATING OF STUDY: GOOD, FAIR, POOR	
Selection of cohorts	++
Adjustment for Confounding	+
Measurement	+
Statistical analysis	+
Internal validity	
External validity/Generalizability	+
STUDY QUALITY SCORE	Poor
STRENGTH/GRADE OF EVIDENCE: HIGH, MODERATE, LOW	
Study Design	+
Study Quality	+
Consistency	++
Directness	+
Precision	++
STRENGTH OF EVIDENCE (GRADE)	Low

Table 4. Van Der Sangen, et al.

STUDY INFOMRATION	
Study Citation	Van der Sangen MJC, van de Wiel, FNM, Poortmans, PMP. Are breast conservation and mastectomy equally effective in the treatment of young women with early breast cancer? Long-term results of a population-based cohort of 1,451 patients aged ≤ 40 years. Breast Cancer Res Treat. 2011;(127):207-215.
Funding	No COI reported
Country of Origin	The Netherlands
STUDY QUESTION	
QUESTION	Long term outcomes: Local recurrence (LR), Distant recurrence-free survival (DRFS), and Overall survival (OS) in young breast cancer patients with early stage breast cancer.
POPULATION	Young women diagnosed with breast cancer (<40 years old) from the Netherlands
Inclusion criteria	
Age	<40 years old
Stage	Stage I-IIB
T	T: pT1-2
N	N: 0-2
Histologic Subtypes	Ductal lobular/mixed other
Exclusion criteria	Missing or incomplete data Stage III or IV Neoadjuvant chemo Synchronous bilateral breast cancer Lumpectomy without XRT DCIS
INTERVENTION	BCT
COMPARISON	Mastectomy
OUTCOME	LR DRFS OS
TIMING	
Years of diagnosis	1988-2005
Stratified?	Yes 1988-1993 1994-1999 2000-2005
TIME FORWARD	15 year follow up Different follow-up durations for BCT and mastectomy. Mastectomy: Data censored on Jan 1, 2007 Median follow-up: 7.4 years BCT: Data censored on Jan 1, 2008 Median follow-up 9.5 years
STUDY DESIGN	Retrospective cohort study using registry and hospital data
SELECTION OF COHORTS	Eindhoven Cancer Registry (2.4 mill in south of Netherlands. Data compared to data derived from 2 radiotherapy departments in the region. Records of patients that did not

	have XRT were obtained from surgical departments of the 10 regional hospitals.
POPULATION CHARACTERISTICS	
N	1451 (M= 562; BCT= 889)
Age	≤ 40 Median in M: 37.2 Median in BCT: 37.4 Stratified: yes Stratification: ≤ 30 31-35 36-40
Race	Not reported/controlled for
SES	Not reported/controlled for
HR status assessed	Just looked at ER+/-, but did not control for receptor status
Hormone therapy	Yes
Chemotherapy	Yes
POTENTIAL FOR SELECTION BIAS? (+, ++, +++) **(Based on appropriate selection of cases or cohorts and controls, descriptive demographics, eligibility criteria (and how chosen), and initial comparability of groups)**	+++ comparison groups not comparable on clinical characteristics including: age, period of dx, tumor size, nodal status, tumor type, grade, microscopic completeness of tumor excision, radiotherapy, adjuvant systemic treatment.
OUTCOME MEASUREMENT	
Definition of outcome	**Measured survival from time of primary treatment instead of time of diagnosis.** LR- recurrence in the ipsilateral breast, overlying skin or chest wall. DRFS- OS- death from any cause
Method of Outcome Assessment **How often?**	
Equal, valid, reliable?	BIAS-> different follow-up times based on surgical procedure
Length of follow-up time	+; not consistent
POTENTIAL FOR MEASUREMENT BIAS? (+, ++, +++)	+++
CONFOUNDING	
Quality of intervention	Not known
Confounders and how each was addressed	Different follow-up durations for BCT and mastectomy. Just looked at ER+/-, but did not control for receptor status in multivariate analysis. 101 records missing in M group, no records missing in BCT group. Could alter results. Did not state whether this data was missing at random.
POTENTIAL FOR CONFOUNDING? (+, ++, +++)	+++
STATISTICAL ANALYSIS	
Statistical Analysis	Violated proportional hazards assumption because in the first 7 years after treatment distant recurrence was significantly lower for BCT group (p=0.009), but patients who survived without DM until 7th year, risk of developing DM after year 7 lower in M group (p=0,044). Actuarial analysis for LR (5, 10,15 year), DRFS (10 year) and

	Overall survival (10 year) Multivariate cox proportional hazards model to assess DRFS ONLY! Didn't state how they addressed survival analysis since KM actuarial curves violated PH assumption.
Powered to show difference?	Not stated a-priori
Variables controlled for in regression model	Only adjusted for age at dx, period of dx, tumor size, axillary nodal status, use of adjuvant systemic treatment.
RESULTS	
LR	
Results	**Actuarial LR rates** **M:** 5 year: (4.4% CI: 2.4-6.4) 10year: (6.0% CI: 3.5-8.5) 15 year: (6.0% CI: 3.5-8.5) -> risk plateaued at 6 years **BCT:** 5 year: 8.3% (CI: 6.3-10.5) 10 year: 18.3% (CI: 14.9-21.7) 15 year: 27.9% (CI: 22.9-32.9) Actuarial differences between M and BCT were significant (p<0.0001)
Magnitude	3.9%, 12.4%, 22.2% respectively
Direction	Favored M
Statistically significant?	Yes
Clinically relevant?	Yes, actuarial LR is higher in BCT
DRFS	
Results	**Actuarial 10 year DRFS rates** M: 67.0% (CI:62.4-71.6) BCT: 71.0% (67.6-74.4) p= 0.0831 **Actuarial 10 year HRs** <u>Treatment- year 7:</u> M: HR=1 (standard) BCT: HR= 0.75 (CI:0.61-0.93) p=0.009 <u>Year 7 onwards:</u> M: HR=1 (standard) BCT: HR=1.96 (CI: 1.02-3.76) p=0.044 **Multivariate** M: HR=1 BCT: HR=0.97 (0.78-1.20) p=0.771
Magnitude	4%
Direction	Favors BCT for tx-7 year, then favors M after 7 years.
Statistically significant?	No
Clinically relevant?	Might be, would like to see trend at 5 and 15 years too
OS	
Results	**Actuarial 10-year OS** M: 71.20% (CI:62.4-71.6) BCT: 74.9% (CI:71.7-78.1) p=0.215
Magnitude	3.7% difference

Direction	Favors BCT
Statistically significant?	No
Clinically relevant?	Might be, would like to see trend at 5 and 15 years too
CONCLUSIONS/COMMENTS	
Overall conclusions/interpretation (include consistency with other studies; biologic plausibility; conflicts of interest; selective endpoint reporting; costs; potential harms; patient decision making preferences)	101 records missing in M group, no records missing in BCT group. Could alter results. Did not state whether this data was missing at random. Differential follow-up time for comparison groups Distant recurrence was significantly lower for BCT group but patients who survived without distant mets until 7th year, risk of developing distant mets after year 7 lower in M group Would be helpful to see the attributable benefit of surgical treatment after subtracting baseline risk of having each outcome.
QUALITY RATING OF STUDY: GOOD, FAIR, POOR	
Selection of cohorts	+
Adjustment for Confounding	+
Measurement	+
Statistical analysis	+
Internal validity	+
External validity/Generalizability	+
STUDY QUALITY SCORE	Poor
STRENGTH/GRADE OF EVIDENCE: HIGH, MODERATE, LOW	
Study Design	+
Study Quality	+
Consistency	++
Directness	+
Precision	+
STRENGTH OF EVIDENCE (GRADE)	Low

Table 5. Mahmood, et al.

STUDY INFOMRATION	
Study Citation	Mahmood U, Morris C, Neuner G, et al. Similar Survival with breast conservation therapy or mastectomy in the management of young women with early-stage breast cancer. Int J Radiaton Oncol Bio Phys. 2012;83(5):1387-1393.
Funding	No COI statement
Country of Origin	USA
STUDY QUESTION	
QUESTION	Cause specific survival (CSS) and overall survival (OS) outcomes after BCT vs. Mastectomy in young women (<40) with invasive breast cancer.
POPULATION	SEER data derived from US population
Inclusion criteria	
Age	20-39 years old
Stage	Stage I-IIB
T	T1-2 (≤5 cm)
N	N0-1 (≤ 3 +LN)
Histologic Subtypes	Invasive Ductal Carcinoma (IDC 0-3: 8500, 8521, 8523) Invasive Lobular Carcinoma (ILC: 8520, 8524) Both (8522)
Exclusion criteria	previous history of malignancy missing info on extent of surgery or XRT lumpectomy without XRT died within 6 months of diagnosis
INTERVENTION	BCT
COMPARISON	Mastectomy (+/-) XRT
OUTCOME	OS Survival CSS Survival
TIMING	
Years of diagnosis	1990-2007
Stratified?	No
TIME FORWARD	5, 10, 15 years in matched-pair. Not clear what time forward was in pooled, BCT and M analyses 5.7 years (0.5-17.9) 5 year: 56% of sample had 5 years of follow up time 10 year: 23% 15 year: 7%
STUDY DESIGN	Retrospective cohort study and matched pair analysis using SEER registry data (covers 26% of US pop).
SELECTION OF COHORTS	US females dx with invasive early stage breast cancer between 20-39 years old and candidates for BCT, ideal?
POPULATION CHARACTERISTICS	
N	14, 764 (M=8124; BCT=6640)
Age	Range: 20-39 Stratified: yes Stratification: ≤ 33

	34-36 37-38 39
Race	White: 64% Black: 11% Hispanic: 11% Asian: 11% Other/unknown: 1%
SES	Not reported/controlled for
HR status assessed	ER, PR only
Hormone therapy	Unknown
Chemotherapy	Unknown, made assumption
POTENTIAL FOR SELECTION BIAS? (+, ++, +++) **(Based on appropriate selection of cases or cohorts and controls, descriptive demographics, eligibility criteria (and how chosen), and initial comparability of groups)**	+
OUTCOME MEASUREMENT	
Definition of outcome	Survival defined as interval from date of diagnosis to date of death or last visit.
Method of Outcome Assessment	Used national cancer database.
How often?	Contains info up until 2007.
Equal, valid, reliable?	Follow-up is generally less frequent in patients undergoing M since they do not need surveillance of remaining breast tissue, however we don't have info since data was not collected prospectively and frequency of follow-up in not available through SEER.
Length of follow-up time	**++;** 23% had 10 year follow up
POTENTIAL FOR MEASUREMENT BIAS? (+, ++, +++)	**++**
CONFOUNDING	
Quality of intervention	Unknown, but likely represents academic institutions with higher patient volume, cancer care coordination, resources etc. Requires a cancer registrar to submit information.
Confounders and how each was addressed	Chemotherapy-> assume that most women got chemo. HR status-> controlled for hormone receptor status and assume that ER+ females got tamoxifen. No info on her-2 neu which is associated with poor outcomes prior to trastuzmab. Patients with poor prognostic factors such as her-2 positivity or triple negative status are more likely to undergo more aggressive treatment (mastectomy) giving this study arm a poorer baseline prognosis that is not accounted for.
POTENTIAL FOR CONFOUNDING? (+, ++, +++)	++ Matched pair analysis may help alleviate confounding, however without info about chemo +/- hormone treatment, there may be inherent bias. (e.g. studies show that BCT+ chemo has decreased rate of LRR, any benefit or non-difference between BCT and M could be due to synergistic benefit with additional therapies.
STATISTICAL ANALYSIS	

Statistical Analysis	1. Multivariable analyses (proportional hazards regression) to determine which variables were independent "predictors" of OS and CSS using entire cohort (pooled). 2. Multivariable analyses (proportional hazards regression) to determine which variables were independent "predictors" of OS and CSS for BCT patients and then M patients separately. 3. Matched pair analysis of BCT vs. M (n=4,644). Matched on age at dx, year of dx, grade, tumor size, # of positive LN, # of evaluated LN, ER and PR. KM curves generated for OS and CSS, statistical sig. evaluated using log-rank tests. 4. Subset analyses for OS and CSS of the matched pair cohort in each age quartile.
Powered to show difference?	Not stated a-priori
Variables controlled for in regression model	Year of diagnosis Age at diagnosis (converted into categorical var) Race histology Grade Area of involvement within the breast Tumor size (converted into categorical var) # positive LN (converted into categorical var) # nodes evaluated (categorized) ER PR
RESULTS	
OS	
Results	Pooled analysis: HR for OS: M=1.00; BCT= 0.93 (0.83-1.04) p=0.16 Matched-pair analysis: 5 year: M=91.9%; BCT= 92.5% 10 year: M= 83.6%; BCT= 83.5% 15 year: M= 79.1%; BCT = 77.0% p= 0.99
Magnitude	Small
Direction	Favors BCT
Statistically significant?	No

Clinically relevant?	No
CSS	
Results	Pooled analysis: HR for CSS: M=1.00; BCT= 0.93 (0.83-1.05) p=0.26 Matched-pair analysis: 5 year: M= 92.5% (died or censored= 604); BCT= 93.3% (died or censored= 445) 10year: M= 85.5% (died or censored= 1178); BCT= 85.5% (died or censored= 963) 15 year: M=81.9% (died or censored= 1470); BCT= 79.9% (died or censored= 1633) p= 0.88 **Repeated these analyses and stratified by age quartile, no differences.**
Magnitude	Small
Direction	Favors BCT
Statistically significant?	No
Clinically relevant?	No
CONCLUSIONS/COMMENTS	
Overall conclusions/interpretation (include consistency with other studies; biologic plausibility; conflicts of interest; selective endpoint reporting; costs; potential harms; patient decision making preferences)	Chemo: assume they all got chemo but data not available in SEER, had to make a lot of assumptions. Some important data missing. Her status, hormone therapy, chemotherapy regimens are known to affect These could all confound the data. Also it would be helpful to include triple negative status as a separate variable to control for. Pooled analysis: Year of diagnosis, age, race, grade, PR status, tumor size, # of +LN, and # of examined LN predictors of OS AND CSS Youngest quartile ≤33 had inferior OS and CSS than all other women. ER status (CSS) Subgroup analyses: year of dx, race, grade, tumor size, and number of + LN were predictors of OS and CSS for **BOTH** BCT and M groups Other predictors in BCT group: ER status (CSS) Other predictors in M group # of examined LN (OS and CSS) age and PR status (CSS only)
QUALITY RATING OF STUDY: GOOD, FAIR, POOR	
Selection of cohorts	+
Adjustment for Confounding	+

Measurement	+
Statistical analysis	++
Internal validity	++
External validity/Generalizability	++
STUDY QUALITY SCORE	Fair/poor
STRENGTH/GRADE OF EVIDENCE: HIGH, MODERATE, LOW	
Study Design	++
Study Quality	+
Consistency	++
Directness	+
Precision	++
STRENGTH OF EVIDENCE (GRADE)	Moderate/Low