Curr Oncol, Vol. 20, pp. e593-601; doi: http://dx.doi.org/10.3747/co.20.1543

ORIGINAL ARTICLE

Comparison of recurrence and survival rates after breast-conserving therapy and mastectomy in young women with breast cancer

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ABSTRACT

Multiple randomized trials have demonstrated that breast-conserving therapy with partial mastectomy and radiotherapy provides survival equivalent to that seen with mastectomy for patients with early-stage breast cancer. Breast-conserving therapy has been associated with better quality of life relative to mastectomy and has become the standard of care for patients with early-stage breast cancer. Young age has been identified as a risk factor for recurrence and death from breast cancer. Some studies have suggested that young women (less than 35 or 40 years of age) have inferior outcomes with breast-conserving therapy, implying that such women may be better served by mastectomy. On review of the available literature, there is no definitive evidence that mastectomy provides a consistent, unequivocal recurrence-free or overall survival benefit over breast-conserving therapy. However, available meta-analyses have not compared outcomes in young women specifically, and such analyses should be performed. In the interim, breast-conserving therapy is not contraindicated in young women (less than 40 years of age) and can be used cautiously; however, such women should be advised of the lack of unequivocal data proving that survival is equivalent to that with mastectomy in their age group.

KEY WORDS

Breast cancer, breast-conserving therapy, mastectomy, recurrence, survival, young women

1. INTRODUCTION

Young age at diagnosis of breast cancer in women is associated with more aggressive disease and worse clinical outcomes. However, there is no consensus on the exact age that defines "young" women, and numerous investigators have used cut-offs ranging from less than 35 years up to less than 50 years of age. Given the small numbers of young women in these studies, uncertainty persists about the optimal primary treatment for this higher-risk patient population.

The present article aims to provide an overview of the literature using a key word–indexed search strategy focused on recurrence and survival rates in younger women with early-stage breast cancer, comparing primary locoregional treatments with a particular question in mind: Should young women have mastectomies instead of breast-conserving therapy (BCT)?

2. METHODS

The literature indexed in PubMed, the journal search system at the U.S. National Library of Medicine, was searched using Medical Subject Headings (MeSH) to describe and retrieve citations. A search was built using the key words "breast cancer young women breast-conserving," which automatically generated MeSH terms ("breast neoplasms"[MeSH Terms] OR ("breast"[All Fields] AND "neoplasms"[All Fields]) OR "breast neoplasms"[All Fields] OR ("breast"[All Fields] AND "cancer"[All Fields]) OR "breast cancer"[All Fields]) AND young[All Fields] AND ("women"[MeSH Terms] OR "women"[All Fields] OR "female"[MeSH Terms] OR "female"[All Fields]) AND breast-conserving[All Fields]. The resulting 196 citations were compiled in a spreadsheet, and each abstract was reviewed for possible inclusion. Full manuscripts for eligible abstracts were then retrieved and reviewed in detail for possible discussion. Secondary literature searches were conducted using the reference lists in those primary resources.

3. RESULTS AND DISCUSSION

3.1 Randomized Controlled Trials of Breast-Conserving Therapy Compared with Mastectomy

Six well-known randomized controlled trials (RCTs) with long-term follow-up have demonstrated overall equivalence between BCT and mastectomy for

early-stage invasive breast cancer (summaries in Table I). However, whether a particular age subgroup has an inferior result with BCT is not clear from those trials. Two studies from the Institut Gustave-Roussy (IGR) and the National Cancer Institute of Milan included only patients with tumours less than 2 cm in size and clinically node-negative disease. A third study from the National Surgical Adjuvant Breast and Bowel Project expanded its eligibility criteria to include tumours up to 4 cm. Three subsequent trials from the U.S. National Cancer Institute, the European Organization for Research and Treatment of Cancer (EORTC), and the Danish Breast Cancer Cooperative Group (DBCG) also expanded their eligibility to include tumours up to 5 cm. These RCTs (described in the subsections that follow) varied in their surgical, radiotherapy, and systemic treatment details based on the different periods during which they were conducted and on individual institutional practice. Further, they used definitions of local recurrence (LR) that varied with respect to the distinction between true recurrences and second ipsilateral breast cancers, with patients experiencing the latter sometimes not being included.

3.1.1 Institut Gustave–Roussy

From 1972 to 1979, the IGR conducted a randomized trial of 179 patients with cT1N0 breast cancers, comparing wide lumpectomy and breast irradiation with modified radical mastectomy (MRM)[4]. Based on available published data, it appears that 7 patients (4%) were under 35 years of age, and approximately 32 patients (18%) were under 40 years of age at enrolment. With a mean follow-up of 22 years, the risk of LR in the BCT cohort during the first 5 years was one fifth that in the MRM group [risk ratio (RR): 0.2], but it was higher by a factor of 12 after 5 years (RR: 12.4; $p = 0.0001$).

Considering the small sample size, Arriagada *et al.* performed a separate IGR database analysis in the same paper. That analysis considered 1847 patients from 1954 to 1983, excluding the trial patients, and assessed time-dependent treatment effects. In patients 40 years of age and younger ($n = 224$), a major difference was observed in the 15-year LR rates for BCT and MRM (36% vs. 12% respectively). The authors also noted that in this younger patient subgroup, the risk of LR after 5 years follow-up was higher by a factor of 12 in the BCT group than in the MRM group ($p = 0.000001$). Yet, despite this "excess risk" of late LR, no difference in the risk of either death or metastasis was observed between the BCT group and the MRM group, with the 10-year overall survival (OS) rates being 65% and 67% respectively ($p = 0.16$).

Notably, in a separate analysis and publication, the IGR Breast Cancer Group also reviewed a large series of patients ($n = 757$) from a time period (1970–1982) similar to that of the original RCT and assessed the clinical and pathologic factors that might identify patients at increased risk of LR[7]. Multivariate analysis revealed that only age younger than 40 years (RR: 2.5; $p < 0.02$) or inadequate surgical excision (RR: 2.34; $p < 0.02$) were significant risk factors. Patients less than 40 years of age had a 10-year local relapse rate that was twice that in women 40 years of age and older (14% vs. 7%).

3.1.2 National Cancer Institute of Milan

From 1973 to 1980, the National Cancer Institute of Milan recruited 701 patients with cT1N0 breast cancers into a randomized study comparing quadrantectomy (a type of BCT) with Halsted radical mastectomy (RM). Notably, a distinction was made between "recurrent tumour in the same breast" in the quadrantectomy group, which could be subdivided into true recurrences and second ipsilateral carcinomas, and "local recurrence" in the RM group, although all were considered local events. With a median follow-up of 20 years, the probability of LR was significantly higher in the BCT group than the RM group (30 of 352 vs. 8 of 349, $p < 0.001$), corresponding to mean crude cumulative incidence rates of 8.8% and 2.3% respectively. In the BCT group, the average event rate was higher than that in the RM group by a factor of approximately 4, and the rate varied with age. The recurrence rate was highest among women 45 years of age or younger at baseline, reported as 1.05 per 100 patient–years of observation, compared with 0.34 and 0.54 for the groups that were 46–60 and more than 60 years of age. However, the long-term rates of breast cancer–specific survival (26.1% vs. 24.3%, $p = 0.8$) and OS (41.7% vs. 41.2%, $p = 1.0$) were similar in both groups[3].

3.1.3 National Surgical Adjuvant Breast and Bowel Project B-06

The B-06 study was the largest of the six trials, and it convincingly confirmed the role of radiotherapy in breast-conserving surgery by including a treatment arm with lumpectomy alone (initially called "segmental mastectomy" and distinctly differing from the Milan quadrantectomy), which was compared with lumpectomy followed by breast irradiation and with total mastectomy. From 1976 to 1984, the National Surgical Adjuvant Breast and Bowel Project randomly assigned 2163 women with tumours up to 4 cm and either negative or positive axillary nodes to one of the three treatments. Despite 40% of women being younger than 50, a subset analysis was not performed. With a mean follow-up of more than 20 years, the cumulative incidence rate of recurrence in the ipsilateral breast was 39.2% in the lumpectomy-alone group and 14.3% in the group that underwent irradiation after lumpectomy ($p < 0.001$). Of particular note, a first recurrence of tumour in the chest wall or surgical scar, but not in the ipsilateral breast, was classified as a LR. Occurrence of a tumour in the ipsilateral breast post-lumpectomy was instead

TABLE I Summary of randomized control trials comparing breast-conserving therapy with mastectomy

Reference (study)	*Period*	*Pts (n)*	*Follow-up (years)*	*Treatment*		*Age (years)*	*Local recurrence (%)*	*Overall survival by age*	*Subset analysis*
				Type	*Pts (n)*				
van Dongen *et al.,* 2000[1] (EORTC 10801)	1980–1986	868	13.4 (median)	BCT	448	Not stated 41%<50[a] 12%<40[a] 4.5%<35[a]	LRR: 19.7 at 10 years	65.2% at 10 years	Yes
				MRM	420	Not stated 41%<50[a] 12%<40[a] 4.5%<35[a]	LRR: 12.2 at 10 years (p=0.0097)	66.1% at 10 years (p=0.11)	
Fisher *et al.,* 2002[2] (NSABP B-06)	1976–1984	1851	20 (mean)	BCT	628	Not stated 44%<50y 15%<40[a,b]	2.7%[c]	46% at 20 years	No
				TM	589	Not stated 41.2%<50 14%<40	10.2%[c]	47% at 20 years (p=0.57)	
Veronesi *et al.,* 2002[3] (National Cancer Institute of Milan)	1973–1980	701	20 (median)	BCT	352	Mean: 50 7%<35[a,d] 23%<40[a,d]	8.8% at 20 years	41.7% at 20 years	Yes
				RM	349	Mean: 51 7%<35[a,d] 23%<40[a,d]	2.3% at 20 years (p<0.001)	41.2% at 20 years (p=1.0)	
Arriagada *et al.,* 2003[4] (Institut Gustave–Roussy)	1972–1979	179	22 (mean)	BCT	88	Mean: 51.8 4%<35[a] 18%<40[a]	Not stated, reported as RR	65% at 10 years	No
				MRM	91	Mean: 51.4 4%<35[a] 18%<40[a]	Not stated, reported as RR	67% at 10 years (p=0.16)	
Poggi *et al.,* 2003[5] (U.S. National Cancer Institute)	1979–1987	237	18.4 (median)	BCT	121	Median: 50 23%<40	22% at 20 years	54% at 20 years	No
				MRM	116	Median: 50 21%<40	0% at 20 years	58% at 20 years (p=0.67)	
Blichert–Toft *et al.,* 2008[6] (DBCG-82TM)	1983–1989	731	19.6 (median)	BCT	367	Mean: 50.9 4%<35 14%<40	4.5% at 10 years	57.8% at 20 years	Yes
				MRM	364	Mean: 51.4 3.5%<35 12%<40	6.9% at 10 years (p=0.16)	50.6% at 20 years (p=0.20)	

[a] Estimate based on data available in the publication.
[b] Estimate used published numbers for women 49 years of age and under, and assumed that one third would be less than 40 years of age.
[c] Tumours in the ipsilateral breast after lumpectomy were not considered recurrences, and women in the lumpectomy groups who had such tumours were classified as being event-free.
[d] Estimate used pooled data from the National Cancer Institute of Milan that included patients in the trial and other patients. The same distribution of age was assumed.

Pts = patients; EORTC = European Organisation for Research and Treatment of Cancer; BCT = breast-conserving therapy; LRR = locoregional recurrence; MRM = modified radical mastectomy; NSABP = National Surgical Adjuvant Breast and Bowel Project; TM = total mastectomy; RM = radical mastectomy; RR = risk ratio; DBCG = Danish Breast Cancer Cooperative Group.

considered to be a cosmetic failure. At 8.8% in the lumpectomy-alone arm and 10.2% in the total mastectomy arm, the reported first LR rates were similar, but much higher than the 2.7% in the lumpectomy-plus-irradiation group. Nonetheless, no differences were observed between the three arms with respect to disease-free survival ($p = 0.26$), distant disease-free survival ($p = 0.34$), and OS ($p = 0.57$)[2].

3.1.4 U.S. National Cancer Institute

From 1979 to 1987, the U.S. National Cancer Institute compared BCT with a "Patey modified mastectomy" in 237 patients with cT1–2 N0–1 invasive breast carcinoma. The study included 50 women, 21% of whom were less than 40 years of age at enrolment. Patients were stratified by age (<50 years vs. ≥50 years), and in contrast with the three RCTs already discussed, microscopically negative surgical margins on pathology examination were not required nor frequently obtained even though re-excisions were permitted. With respect to the index breast carcinoma, a LR had to be confined to the chest wall or ipsilateral breast. In the 121 patients of the BCT group, isolated ipsilateral in-breast events occurred in 27 patients (22%) after primary surgery, and in the 116 patients of the MRM group, no isolated chest wall events occurred. With a median follow-up of 18.4 years and 237 evaluable patients, no difference in disease-free survival ($p = 0.64$), distant disease-free survival ($p = 0.82$), or OS ($p = 0.67$) was observed. Although 23% of the BCT patients and 19% of the MRM patients were less than 40 years of age, a subset analysis was not performed[5].

3.1.5 EORTC 10801

From 1980 to 1986, the EORTC conducted a multicentre trial comparing BCT with MRM for patients with tumours up to 5 cm. Of the 868 eligible patients, 696 (80.2%) had clinical tumour sizes between 2.1 cm and 5.0 cm, although a pathologic T-stage migration might have occurred after surgery, because only 422 (48.6%) were confirmed with pT2 disease. The study did not have a lower age limit for eligibility; 39 patients (4.5%) were younger than 35, and 356 (41%) were younger than 50. Based on a pooled publication with the Danish series, it appears that approximately 106 patients (12%) were less than 40 years of age[8]. Compared with the MRM group at a median follow-up of 13.4 years, the BCT group experienced a statistically significant difference in the rate of locoregional recurrence (LRR) happening before or at the same time as, but not after, distant metastasis (19.7% for BCT vs. 12.2% for MRM, $p = 0.0097$). All relapses within the treated area—including the breast, chest wall, or axilla—were considered LRRs, although a distinction was not reported between the local and regional relapse rates. When considering hazard ratios (HRs) in subgroups based on age, the LRR rates actually appeared higher in the BCT cohort for patients 50 years of age and older. However, at 10 years, there was no difference between the groups in terms of distant disease-free survival ($p = 0.24$) or OS ($p = 0.11$), even after adjusting for size, nodes, and age[1].

3.1.6 DBCG 82-TM

From 1983 to 1989, the DBCG conducted a trial comparing the long-term efficacy of breast-conserving surgery (BCS) and MRM. The study recruited 1154 patients with primary operable breast carcinoma of any tumour size, 1133 of which were protocol-eligible. The most recently published analysis—at a median follow-up of 20 years—focuses on a corrected randomized group comprising 793 of the protocol-eligible patients with "specification of recurrence as a first event confined to the subset composed of randomized evaluable patients ($n = 731$)." At 10 years' observation, the local tumour control rates in the BCS and MRM groups were equal (4.5% vs. 6.9% respectively, $p = 0.16$). Regardless of whether the analysis used the 731 evaluable patients, the 793 randomized patients, or the 1133 protocol-eligible patients, the 10-year recurrence-free survival and the 20-year OS were not significantly different between the BCS and MRM groups. Of the patients randomized, 27 (3.4%) were younger than 35, and 94 (11.8%) were younger than 40[6]. Although a subset analysis in younger women was not performed, a pooled analysis with the EORTC was later published.

3.2 Combined Analysis and Meta-analyses

3.2.1 EORTC and DBCG

Data from the EORTC and DBCG trials were pooled to increase the statistical power for an analysis of risk factors for LR. By combining the two datasets, 1772 patients were eligible for the analysis at a median follow-up of 9.8 years. After BCT, LR was defined as any tumour growth in the preserved breast or overlying skin; LRs more than 3 months after distant metastasis, which are considered less important clinically and are often histologically unconfirmed, were excluded. Cox analysis by treatment actually given demonstrated that, compared with patients more than 60 years of age, patients no more than 35 years of age at BCS had a higher risk of developing LR (by a factor of 9.24); the same risk did not exist in the MRM cohort. For patients 35 years of age or younger, the 10-year actuarial rate of LR was 35% after BCT and 7% after MRM. The authors questioned whether LR might be a source of distant spread in some patients younger than 35. They suggested that further studies were needed to rule out the possibility of worse survival outcomes in the population of young patients treated with breast conservation[9].

3.2.2 EORTC

The EORTC subsequently combined three of its early-stage breast cancer RCTs to evaluate prognostic factors for isolated LRR. Of the 4395 patients enrolled in

EORTC trials 10801 (1980–1986), 10854 (1986–1991), and 10902 (1991–1999), 3602 were included in the combined analysis. Of those 3602 patients, 1996 underwent BCT (55.4%) and 1606 underwent mastectomy (44.6%). Only 176 of 3602 patients (4.9%) were 35 years of age or younger, and median follow-up varied from 5.3 to 11.9 years. Multivariate analysis showed that younger age and breast conservation were risk factors for isolated LRR (age ≤35 vs. >50 years, HR: 2.80; age 35–50 vs. >50 years, HR: 1.72; breast conservation, HR: 1.82)[10].

3.2.3 DBCG

The DBCG also used a combined analysis of their nationwide prospective studies to investigate the effect of BCT compared with MRM on prognosis for young women. A cohort of 9285 patients with breast cancer diagnosed when they were younger than 50 years of age was identified from the population-based Danish breast carcinoma database, which included DBCG trials 82 (1982–1989) and 89 (1989–1998). In total, 2120 patients (22.8%) underwent BCT and 7165 patients (77.2%) underwent MRM. More than half the patients were younger than 40 (1483 were diagnosed at 35–39 years of age, and 719, at less than 35 years of age). Median follow-up was 7.1 years. Compared with women older than 35 at diagnosis, women less than 35 years of age were more likely to have tumours greater than 2 cm in size ($p = 0.007$) and node-positive disease ($p = 0.002$). Interestingly, younger patients were more likely to undergo BCT ($p < 0.001$). A multivariate analysis with patients divided into 5-year age groups revealed that, among patients who underwent BCT, the incidence of LR in the breast within 5 years was greater by a factor of 5.2 among women less than 35 years of age than among women 45–49 years of age (15.4% vs. 3%). However, the authors observed no increased risk of death between the two treatments, regardless of age at diagnosis[11].

3.2.4 EBCTCG

Most recently, the Early Breast Cancer Trialists' Collaborative Group updated their collaborative meta-analysis with further follow-up, subsequently increasing the total number of women analyzed by about 50% to 10,801 individual patients with a median follow-up of 9.5 years[12]. However, the main emphasis of their analysis was any first recurrence, whether it was locoregional or distant. (They had previously focused on time to locoregional recurrence.)

The 10-year risk of any first recurrence was reduced from 35.0% in women with BCT only to 19.3% in women allocated to radiotherapy, corresponding to an absolute risk reduction of 15.7% ($2p < 0.00001$). The analysis was also stratified by age, either in 5 groups (<40, 40–49, 50–59, 60–69, and 70+ years), or when data were subdivided by other factors, in 2 groups (<50 and 50+ years). The characteristics that were independently predictive of the absolute risk of recurrence or of the absolute risk reduction with radiotherapy were included in a model to show how 10-year recurrence risks with and without radiotherapy in the trials depended on age, grade, estrogen receptor status, tamoxifen, and extent of surgery. Compared with older women and women with low-grade tumours, younger women and those with high-grade tumours had substantially larger absolute recurrence risks without radiotherapy and substantially larger absolute risk reductions with radiotherapy. Furthermore, women less than 40 years of age treated with BCT plus radiotherapy had a higher relapse rate at any site: 36% at 10 years compared with 21% for women in their 40s. Even with boost doses, as described in the EORTC boost study, the 10-year relapse rate was 13% in women less than 40 years of age compared with 4.9% in women in their 50s[13].

Unfortunately, the Early Breast Cancer Trialists' Collaborative Group has not reported a subgroup analysis that addresses whether younger women experience better outcomes with mastectomy than with BCT. Based on the available published data from the randomized trials, we estimated that there would be approximately 620 patients less than 40 years of age and 200 patients less than 35 years of age in the trials. The 10- to 20-year survival rates reported in the trials are in the range of 50%–60%. With 300 patients in each group, it would be possible to confidently detect an absolute survival difference in the range of 10%–12%. However, a survival difference between mastectomy and BCT for young women on the order 5% would still be meaningful in terms of patient decision-making. To be statistically confident (80% power and 5% alpha error) that a survival improvement from 55% to 60% is real, 3000 patients would be required. It is therefore unlikely that a meta-analysis of the available data focusing on women less than 40 years of age would be definitive even if performed.

3.3 Population-Based and Retrospective Studies in Young Women

Numerous retrospective reviews have evaluated the outcomes of young breast cancer patients (ranging in age from <35 years to <50 years) receiving BCT. Table II presents selected studies in this area. Although the studies provide a range for the LR rates in younger women, they do not provide information about the advantages, if any, of mastectomy relative to BCT. We therefore focus on studies in which a direct comparison was made between the two treatments (summarized in Table III).

To examine whether outcomes were improved with MRM compared with BCT in young women, Coulombe *et al.*[27] retrospectively analyzed the BC Cancer Agency's prospectively assembled Breast Cancer Outcomes Unit database. Age less than 40 years was used to define "young" based on a previous Breast Cancer Outcomes Unit study identifying worse prognosis in

TABLE II Selected retrospective studies of breast-conserving therapy in young women

Reference	*Time period*	*Total patients* (n)	*Age (years)*	*Subset patients* (n)	*Follow-up (years)*	*Local recurrence (%)*
Kurtz *et al.,* 1988[8]	1963–1981	1382	<40	210	11	19
Recht *et al.,* 1988[14]	Not stated	597	<35	47	5.3	26
Kurtz *et al.,* 1990[15]	Not stated	496	<40	62	5.9	21
Fowble *et al.,* 1994[16]	1981–1991	980	<35	64	4.6	14
			36–50	363		7
Nixon *et al.,* 1994[17]	1968–1985	1398	<35	107	8.3	Not stated
Elkhuizen *et al.,* 1998[18]	1980–1994	1393	<35	77	4.3	28
			35–44	300		16
			45–54	407		14
Kim *et al.,* 1998[19]	1984–1993	290	<35	87	8.0	LRR: 30
Jobsen *et al.,* 2003[20]	1983–1999	1697	<40	143	6.5	15
			41–50	432		
Vrieling *et al.,* 2003[21]	1989–1996	5569	<35	156	5.1	18
			36–40	314		15
			41–50	1407		8
Cabioglu *et al.,* 2005[22]	1970–1996	1355	<35	116	Not stated	11
			35–50	494		6
Oh *et al.,* 2006[23]	1987–2000	196	<35	71	5.3	12
			35–40	125		8
van der Leest *et al.,* 2007[24]	1988–2002	758	<30	57	8.5	7
			31–35	213		15
			36–40	488		12
Zhou *et al.,* 2007[25]	1993–1999	130	≤34	50	7.8	14
			35–40	80		10
Gentilini *et al.,* 2010[26]	1997–2004	201	<35	201	6.0	9

LRR = locoregional recurrence.

that age group than in older patients. The 540 women 20–39 years of age with early-stage breast cancer (pT1–2 pN0–1) diagnosed between 1989 and 1998 had a median follow-up of 9.0 years. Comparing BCT (n = 356) with MRM (n = 184), no difference was observed in the 10-year rates of local relapse-free survival (86% vs. 83.8%, p = 0.34) and of locoregional relapse-free survival (82.6% vs. 80.9%, p = 0.41). Similarly, the use of BCT did not translate into worse breast cancer–specific survival or OS, suggesting that young age alone is not a contraindication to BCT.

Beadle *et al.*[28] retrospectively analyzed LRR rates for 652 patients 35 years of age or younger treated at the University of Texas MD Anderson Cancer Center from 1973 to 2006, with median follow-up of 9.5 years. The authors compared the impact of three different locoregional treatment strategies: BCT (n = 196), mastectomy alone (n = 237), or mastectomy with adjuvant radiation (PMRT, n = 234). Ten-year actuarial rates of LR differed by treatment strategy: 15.8% for BCT, 12.5% for mastectomy, and 7.0% for PMRT (p = 0.04). For the 101 patients with stage I disease, a direct comparison was made between BCT (n = 53) and mastectomy alone (n = 42); the 6 patients treated with PMRT were excluded from the analysis. Based on locoregional treatment, no difference was observed in the 10-year actuarial LRR rates (18.0% vs. 19.8%, p = 0.56) or in the distant metastasis rates or OS.

Most recently, two very large population-based database studies[29,30] compared the effectiveness of BCT and mastectomy in women 40 years of age or younger diagnosed with early-stage breast cancer.

Van der Sangen *et al.*[29] obtained data for 1988 through 2005 from the population-based Eindhoven Cancer Registry of the Netherlands. Only patients 40 years of age or younger with stage I or II breast cancer (pT1–2 N0–2 M0) were eligible. After exclusions, 1451 patients were available for analysis, of whom 889 (61.3%) received BCT and 562 received mastectomy (38.7%). In the mastectomy group, 37% of patients received PMRT. At a median follow-up of 7.4 years, the LR risk for mastectomy patients was 4.4% at 5 years; the rate then plateaued at 6.0% after 6 years. At a median of 9.5 years of follow-up in the BCT cohort, the 5-, 10-, and 15-year LR risks were 8.3%, 18.4%, and 28.2% respectively (p < 0.0001). No significant associations were found between the risk of LR and age group (<30, 30–35, and 35–40 years).

TABLE III Published studies comparing breast-conserving therapy and mastectomy in young women (≤40 years of age)

Reference	*Study type*	*Time period*	*Follow-up (years)*	*Treatment*	*Pts (n)*	*Local recurrence (% at 10 years)*
Coulombe *et al.,* 2007[27]	Population-based registry	1989–1998	9.0	BCT	356	14
				MRM	184	16.2 (p=0.34)
Beadle *et al.,* 2009[28]	Retrospective, single-institution	1973–2006	9.5	BCT	197	19.8
				M	237	24.1
				MXRT	234	15.1 (p=0.05)
Van der Sangen *et al.,* 2011[29]	Population-based registry	1988–2005	7.4	BCT	889	18.3
				MRM	562	6.0
Mahmood *et al.,* 2012[30]	Population-based registry	1990–2007	5.7	BCT	~6644	Not stated[a]
				MRM	~8120	

[a] Lack of local recurrence data in the Surveillance, Epidemiology and End Results database precluded analysis.
Pts = patients; BCT = breast-conserving therapy; MRM = modified radical mastectomy; M = mastectomy; MXRT = mastectomy with adjuvant radiation therapy.

The 10-year OS rates did not differ significantly between patients undergoing BCT and those undergoing mastectomy (74.9% vs. 71.2%, p = 0.215).

Mahmood *et al.*[30] used the U.S. Surveillance, Epidemiology and End Results database to obtain information for all women 20–39 years of age diagnosed with pT1–2 N0–1 M0 breast cancer between 1990 and 2007 who underwent BCT or mastectomy. Of the 14,764 women identified, most had tumours 2.0 cm or smaller in size (58.5%) or N0 disease (64.0%) or both. In this cohort, 6640 patients received BCT (45.0%), and 8124 received mastectomy (55.0%). In the mastectomy group, 17% received PMRT. Median follow-up was 5.7 years. For analysis, age was divided into four quartiles: 33 years or younger, 34–36 years, 37–38 years, and 39 years. The proportion of BCT patients increased with age quartile: 43%, 44%, 46%, and 47% respectively. Multivariate analysis for the entire cohort revealed age to be an independent predictor of cause-specific survival and OS, an association that remained significant in a separate analysis by treatment type. Compared with all other groups, the youngest quartile (≤33 years) experienced inferior cause-specific survival (HR: 1.26) and OS (HR: 1.17). Matched-pair analysis of 4644 patients confirmed no difference in the 5-, 10-, and 15-year rates of cause-specific survival (p = 0.88) and OS (p = 0.99). Subset analyses confirmed that there were no differences in outcome for local treatment when stratified by age quartile. Although the Surveillance, Epidemiology and End Results database does not contain information about LR, the multivariable and matched-pair analyses on such a large number of patients provide reassurance about the comparable survival outcomes with BCT and mastectomy.

4. CONCLUSIONS

The proportion of women diagnosed with breast cancer at a young age is relatively low. Considering the relatively low incidence and prevalence of breast cancer in young women, it is difficult to know if evidence from the randomized controlled trials showing equivalency between BCT and mastectomy are applicable to the young patient population. No definitive meta-analyses have specifically compared mastectomy with BCT plus radiation in young women. Ideally, meta-analyses using pooled individual patient data should be conducted to compare survival outcomes for BCT and mastectomy. However, given the currently available trials, such an analysis may be underpowered to rule out a meaningful survival difference. The available population-based—and institutional—data comparing mastectomy with BCT in young women are potentially biased and have reported somewhat conflicting results with respect to locoregional relapse; however, none has reported inferior survival in young women treated with BCT. Breast-conserving therapy is not contraindicated in young women (<40 years of age) and can be used cautiously; however, those women should be advised about the lack of unequivocal data proving that survival is equivalent to mastectomy in their age group.

5. CONFLICT OF INTEREST DISCLOSURES

RAO's protected research time is supported by the University of British Columbia's Northern Medical Program. SKT is supported by a scholar award from the Michael Smith Foundation for Health Research.

The authors have no financial conflicts of interest to declare.

6. REFERENCES

1. 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;92:1143–50.
2. 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;347:1233–41.
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;347:1227–32.
4. Arriagada R, Le MG, Guinebretiere JM, Dunant A, Rochard F, Tursz T. Late local recurrences in a randomised trial comparing conservative treatment with total mastectomy in early breast cancer patients. *Ann Oncol* 2003;14:1617–22.
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. Blichert–Toft M, Nielsen M, During M, *et al.* Long-term results of breast conserving surgery vs. mastectomy for early stage invasive breast cancer: 20-year follow-up of the Danish randomized DBCG-82TM protocol. *Acta Oncol* 2008;47:672–81.
7. Dewar JA, Arriagada R, Benhamou S, *et al.* Local relapse and contralateral tumor rates in patients with breast cancer treated with conservative surgery and radiotherapy (Institut Gustave Roussy 1970–1982). IGR Breast Cancer Group. *Cancer* 1995;76:2260–5.
8. Kurtz JM, Spitalier JM, Amalric R, *et al.* Mammary recurrences in women younger than forty. *Int J Radiat Oncol Biol Phys* 1988;15:271–6.
9. Voogd AC, Nielsen M, Peterse JL, *et al.* Differences in risk factors for local and distant recurrence after breast-conserving therapy or mastectomy for stage I and II breast cancer: pooled results of two large European randomized trials. *J Clin Oncol* 2001;19:1688–97.
10. de Bock GH, van der Hage JA, Putter H, Bonnema J, Bartelink H, van de Velde CJ. Isolated loco-regional recurrence of breast cancer is more common in young patients and following breast conserving therapy: long-term results of European Organisation for Research and Treatment of Cancer studies. *Eur J Cancer* 2006;42:351–6.
11. Kroman N, Holtveg H, Wohlfahrt J, *et al.* Effect of breast-conserving therapy versus radical mastectomy on prognosis for young women with breast carcinoma. *Cancer* 2004;100:688–93.
12. Darby S, McGale P, Correa C, *et al.* on behalf of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet* 2011;378:1707–16.
13. Antonini N, Jones H, Horiot JC, *et al.* Effect of age and radiation dose on local control after breast conserving treatment: EORTC trial 22881–10882. *Radiother Oncol* 2007;82:265–71.
14. Recht A, Connolly JL, Schnitt SJ, *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* 1988;14:3–10.
15. Kurtz JM, Jacquemier J, Amalric R, *et al.* Why are local recurrences after breast-conserving therapy more frequent in younger patients? *J Clin Oncol* 1990;8:591–8.
16. Fowble BL, Schultz DJ, Overmoyer B, *et al.* The influence of young age on outcome in early stage breast cancer. *Int J Radiat Oncol Biol Phys* 1994;30:23–33.
17. Nixon AJ, Neuberg D, Hayes DF, *et al.* Relationship of patient age to pathologic features of the tumor and prognosis for patients with stage I or II breast cancer. *J Clin Oncol* 1994;12:888–94.
18. Kim SH, Simkovich–Heerdt A, Tran KN, Maclean B, Borgen PI. Women 35 years of age or younger have higher locoregional relapse rates after undergoing breast conservation therapy. *J Am Coll Surg* 1998;187:1–8.
19. Elkhuizen PH, van de Vijver MJ, Hermans J, Zonderland HM, van de Velde CJ, Leer JW. Local recurrence after breast-conserving therapy for invasive breast cancer: high incidence in young patients and association with poor survival. *Int J Radiat Oncol Biol Phys* 1998;40:859–67.
20. Jobsen JJ, van der Palen J, Ong F, Meerwaldt JH. The value of a positive margin for invasive carcinoma in breast-conservative treatment in relation to local recurrence is limited to young women only. *Int J Radiat Oncol Biol Phys* 2003;57:724–31.
21. Vrieling C, Collette L, Fourquet A, *et al.* Can patient-, treatment- and pathology-related characteristics explain the high local recurrence rate following breast-conserving therapy in young patients? *Eur J Cancer* 2003;39:932–44.
22. Cabioglu N, Hunt KK, Buchholz TA, *et al.* Improving local control with breast-conserving therapy: a 27-year single-institution experience. *Cancer* 2005;104:20–9.
23. Oh JL, Bonnen M, Outlaw ED, *et al.* The impact of young age on locoregional recurrence after doxorubicin-based breast conservation therapy in patients 40 years old or younger: how young is "young"? *Int J Radiat Oncol Biol Phys* 2006;65:1345–52.
24. van der Leest M, Evers L, van der Sangen MJ, *et al.* The safety of breast-conserving therapy in patients with breast cancer aged < or = 40 years. *Cancer* 2007;109:1957–64.
25. Zhou P, Gautam S, Recht A. Factors affecting outcome for young women with early stage invasive breast cancer treated with breast-conserving therapy. *Breast Cancer Res Treat* 2007;101:51–7.
26. Gentilini O, Botteri E, Rotmensz N, *et al.* Breast-conserving surgery in 201 very young patients (< 35 years). *Breast* 2010;19:55–8.
27. Coulombe G, Tyldesley S, Speers C, *et al.* Is mastectomy superior to breast-conserving treatment for young women? *Int J Radiat Oncol Biol Phys* 2007;67:1282–90.
28. Beadle BM, Woodward WA, Tucker SL, *et al.* Ten-year recurrence rates in young women with breast cancer by locoregional treatment approach. *Int J Radiat Oncol Biol Phys* 2009;73:734–44.
29. van der Sangen MJ, van de Wiel FM, Poortmans PM, *et al.* 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;127:207–15.

30. 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 Radiat Oncol Biol Phys* 2012;83:1387–93.

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