The Effect of Surgery Type on Survival and Recurrence in Very Young Women with Breast Cancer

May Lynn Quan, MD^{1,2}, Lawrence Frank Paszat, MD^{2,3,4}, Kimberly A. Fernandes², Rinku Sutradhar^{2,4}, David R. McCready, MD^{5,6}, Eileen Rakovitch, MD^{2,3}, Ellen Warner, MD³, Frances C. Wright, MD^{3,4,6}, Nicole Hodgson, MD⁷, Muriel Brackstone, MD⁸, Nancy N. Baxter, MD^{2,4,6,9},

¹University of Calgary, Foothills Medical Centre, 1403 29 Street NW, Calgary, AB T2N 2T9
Canada

²Institute for Clinical Evaluative Sciences, G1 06, 2075 Bayview Avenue, Toronto, ON M4N 3M5 Canada

³Sunnybrook Health Sciences Centre, 2075 Bayview Ave, Toronto, ON M4N 3M5 Canada

⁴Institute of Health Policy, Management and Evaluation, University of Toronto, 4th Floor, 155 College St, Toronto, ON M5T 3M6 Canada

⁵University Health Network-Princess Margaret Hospital, 610 University Ave, Toronto, ON M5G 2M9 Canada

⁶Department of Surgery, University of Toronto, 149 College Street, Toronto, ON, M5T 1P5
Canada

⁷Juravinski Cancer Centre, 699 Concession St, Hamilton, ON L8V 5C2 Canada

⁸London Health Sciences Centre, Victoria Hospital, 800 Commissioners Road East, London, ON N6A 5W9 Canada

⁹Department of Surgery, Li Ka Shing Knowledge Institute, St. Michael's Hospital, 30 Bond Street, Toronto, ON M5B 1W8 Canada

Corresponding Author: Dr. May Lynn Quan, MD, Foothills Medical Centre, 1403 29 Street NW, Calgary, AB T2N 2T9 Canada; Email: maylynn.quan@albertahealthservices.ca, Phone: (403) 944-0966

Running Head: Surgery Type and Survival Breast Cancer

Research Support: This study was funded by the Canadian Breast Cancer Foundation – Ontario Chapter.

Presented in part: Abstract at the ASCO Annual Meeting in Chicago (June 2013).

Synopsis: We sought to determine the effect of surgery type on risk of recurrence and survival in a population-based cohort of very young women with breast cancer. Outcomes after breast conserving surgery and mastectomy were similar for very young women.

Abstract

Background: The impact of surgical treatment on outcomes in breast cancer in very young women remains unclear. We sought to determine the effect of surgery type on risk of recurrence and survival in a population-based cohort.

Methods: All women diagnosed with breast cancer aged ≤ 35 (1994 to 2003) were identified from the Ontario Cancer Registry. Patient, tumour and treatment variables, including primary surgery, recurrences and death were abstracted from chart review. Cox regression models were fit to determine the effect of surgery type on recurrence and overall survival.

Results: We identified 1,381 patients with 11-year median follow-up of which 793 (57%) had BCS. Of the remaining mastectomy patients, 52% had post-mastectomy radiation. Overall, 41% of patients sustained a recurrence of any type and 31% died. Controlling for known confounders, there was no association between type of surgery and death from any cause (HR= 0.98, 95% CI= 0.78, 1.25) or first recurrence (HR= 0.93, 95% CI= 0.75, 1.14). Distant recurrence was most

common (13% in BCS; 25.3% in mastectomy) with local recurrence 12.4% after BCS and 7.5% after mastectomy.

Conclusion: In this cohort of very young women who were selected for treatment with BCS and mastectomy, we found similar oncologic outcomes.

Keywords: Breast cancer, very young women, surgery type, survival

Introduction

While randomized controlled trials have consistently demonstrated no difference between breast conserving surgery (BCS) and mastectomy in overall survival for early stage breast cancer, most women enrolled in these studies were 50 years of age or older at diagnosis [1,2]. Young women with breast cancer are known to have a higher risk of local recurrence and mortality, therefore these trial results may not be generalizable to this distinct patient sub-group [3-6]. Importantly, there is increasing evidence that local treatments do impact survival; a recent meta-analysis by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) evaluating the effects of radiation and extent of surgery on 15 year survival found that for every four local recurrences prevented by treatment, one death could be averted [7,8]. Because young women are at higher risk of local recurrence, more extensive surgery may result in better survival outcomes.

Currently, BCS is an accepted standard of care for women with breast cancer who meet established criteria [9-10] and is generally preferred by women given the psychological consequences of mastectomy [11]. However, in 2005, the National Comprehensive Cancer

Network (NCCN) guidelines on breast cancer treatment recommended that age <35 be an indication for mastectomy [12]. Although these recommendations have been subsequently moderated, the fear of inferior outcomes for younger women has undoubtedly influenced surgical treatment in these patients. Younger age has consistently been associated with high use of mastectomy, but this may be unwarranted, driven by fear of under treatment by clinicians and the hope that more aggressive surgery will confer a survival advantage [13-15]. If BCS carries no higher risk of poor outcomes than mastectomy in young women, then it should be promoted as a standard option. Unfortunately, there are few rigorous studies of BCS and mastectomy in young women with breast cancer. Most data come from a few retrospective single institution studies, limited by possible selection bias and small numbers [16-19]. In two population based analyses of premenopausal women including those under age 35, one from the British Columbia Breast Cancer Outcomes Unit [20] and the other from the Danish Breast Cancer Cooperative Group [21], higher rates of local and distant recurrence, as well as shortened survival were found in women under 40 and 50 years of age, respectively. However, in these studies, there was no significant difference in locoregional failure or breast cancer specific survival in those treated with mastectomy compared to BCS even in the subgroup of women under 35 [21,22]. Like all studies including women under 35, both had small numbers and limited power.

The equivalence of BCS and mastectomy in young women remains unclear. We therefore sought to determine the effect of surgery type on the risk of recurrence and survival in a large, population-based cohort of very young women diagnosed with breast cancer aged 35 or younger.

Methods

The Research Ethics Board (REB) at Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada as well as the REBs or equivalent at each participating hospital approved this study.

Study Design and Data Sources

We designed a population-based retrospective cohort study using administrative data and primary chart review. Patients for the study were identified from the Ontario Cancer Registry (OCR), a provincial cancer registry that records all patients with incident cancers diagnosed in the province of Ontario since 1964. Reporting cancer cases to the OCR is provincially mandated and estimated to be 95% complete [23]. All women diagnosed with invasive breast cancer (ICD-9 174) aged 35 or younger in Ontario between 1994 and 2003 were identified through the OCR. Patients with a previous diagnosis of a non-cutaneous malignancy, who did not have any surgery for their breast cancer or who had evidence of stage IV disease within 6 months of diagnosis were excluded.

For each woman meeting our study criteria, we identified the primary surgical treatment location using the Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DADs) which captures all inpatient surgical procedures and the National Ambulatory Care and Reporting System (NACRS) which contains data for all hospital and community based ambulatory care including day surgeries. At these hospitals, trained data abstractors performed a primary chart review to identify patient, tumour and treatment variables, as well as locoregional, distant recurrences and death until November 15, 2011 (Appendix 1). These datasets were linked using unique, encoded identifiers and analyzed at the Institute for Clinical Evaluative Sciences (ICES).

We reviewed patient charts to confirm invasive diagnosis and age. Other abstracted variables included diagnostic modality, biopsy type (core/open), all surgeries associated with breast cancer diagnosis (BCS, mastectomy, axillary surgery, reconstruction), primary tumour characteristics (tumor size (0-<20mm, 20-<50mm, 50+ mm), primary histologic type (ductal, lobular, mixed, other), grade (I, II, or III), presence of lymphovascular invasion (LVI) (yes / no), total number of nodes positive (0, 1-3, 4+), presence of extranodal deposits (yes / no), ER status (negative / positive), PR status (negative / positive), HER2 status when available (negative / positive), size of the closest margin, (0mm, >0-2mm, >2mm), multicentric tumor (yes / no) and multifocal tumor (yes / no)), all systemic therapy (chemotherapy adjuvant/neoadjuvant/none, Herceptin (yes/no)) as well as radiation therapy (yes/no), as previously described [24]. In addition, we determined if there was a recurrence of any type, categorized as local (in breast for BCS or chest wall for those having total mastectomy), regional (axillary nodal) or distant (diagnostic imaging or pathologic evidence of metastases). Neighbourhood income quintile (1-5 from lowest to highest) was determined through linkage to Statistics Canada census data.

We categorized primary surgical management as either BCS or mastectomy, based on definitive surgery occurring within a year of the first surgery. Thus, patients who had BCS followed by mastectomy within the first year were categorized as having a mastectomy. For mortality, in addition to chart review, we also referenced vital status from the Registered Persons Database, which contains date of death from provincial administrative datasets.

Statistical Analysis

Descriptive statistics were calculated for the entire cohort and stratified by primary surgical management. Continuous variables were analyzed using the Wilcoxon Rank Sum Test and categorical variables using the chi-square test.

We implemented regression models to determine the relationship between the main exposure (primary surgical management) and the outcomes of time to death and time to recurrence, separately. Variables considered for inclusion in the multivariable models were based on known clinical predictors; using univariate hypothesis testing, we included potential confounding variables (those that were associated with both the main exposure and the outcome). Up front variables considered were tumour and treatment factors as listed above. When modeling time to recurrence, the need to control for death without recurrence as a competing risk was assessed by comparing cumulative incidence curves between time to first recurrence and time to death without recurrence. We ultimately examined time to death and time to recurrence using standard survival analysis (Kaplan-Meier curves and Cox proportional hazards regression) [25]. Time to death and time to first recurrence were defined as the interval from primary surgical management until the death date and first recurrence date, respectively. When examining time to death, patients were followed until the minimum of their death date or March 31, 2012 (the last date where death information was available at the time of analysis). When examining time to first recurrence, patients were followed until the minimum of the first recurrence date, death date, or November 15, 2011 (the last date recurrence information was recorded from chart abstraction). Power calculations based on a log-rank test demonstrated that a hazard ratio of 1.47 or higher would be required to detect a difference between the mastectomy and BCS patients in our study, based on 80% power and an alpha of 0.05.

Due to the inherent differences between patients having mastectomy and those having BCS, we also used a propensity score adjustment in the multivariable model as a sensitivity analysis among the subset of patients with no missing data (n=870). For this study, the propensity score was the probability of being assigned to receive a mastectomy vs BCS,

conditional on measured baseline covariates. Conditioning on the propensity score allows for unbiased (with respect to the observed confounders included in the score) comparisons between the BCS and mastectomy groups since, conditional on the propensity score, assignment to mastectomy *vs* BCS is independent of measured baseline covariates [26]. The propensity of undergoing mastectomy *vs* BCS was predicted *via* logistic regression. We then incorporated the propensity score *via* covariate adjustment into the Cox regressions models.

Two-sided p-values less than 0·05 were considered statistically significant. All statistical analyses were conducted using SAS 9·2 (Cary, NC).

Role of the Funding Source

This study was supported by the Institute for Clinical Evaluative Sciences, which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care. No endorsement by the Institute for Clinical Evaluative Sciences or the Ontario Ministry of Health and Long-Term Care is intended or should be inferred. The funding sources played no role in design, conduct, or reporting of this study. The opinions, results and conclusions reported in this paper are those of the authors and are independent from the funding sources.

Results

From January 1, 1994 through December 31, 2003, there were 1,566 women aged ≤ 35 years diagnosed with breast cancer in Ontario. Of those, 141 were excluded because they had no surgical treatment (n=103) or had Stage IV disease within 6 months of diagnosis (n=35) (Figure 1), leaving 1,381 patients in the final study group. The primary surgical treatment was BCS in 793 women (57%), of whom the majority (88·9%) had adjuvant radiotherapy. Of the 588 women

(43%) who had mastectomy, 52% had post-mastectomy radiotherapy. The median follow-up time was 11 years. There were differences in the tumour characteristics between the BCS and mastectomy groups (Table 1); in particular, the mastectomy group had larger tumours and more nodal involvement. The use of chemotherapy was similar between groups.

Based on the cumulative incidence curves for time to first recurrence and time to death without recurrence, we found that death without a recurrence was not a concerning competing risk (the probability of this event was very low at 3%) (Appendix 2). Overall, 41% of patients sustained a recurrence of any type and 31.1% had died by the end of study follow up. First recurrence was most frequently at a distant site alone, with no evidence of concurrent local or regional disease, occurring in 18.2% of the cohort at a median of 2.7 years (Table 2). After 11 years follow up, local recurrence alone occurred in 5.4% of the cohort (7.6% of those having BCT, 2.6% of those having mastectomy– defined as a chest wall recurrence). Isolated regional recurrences were uncommon in both groups (0.6% of those having BCS, 2.6% of those having TM). The overall risk of subsequent contralateral breast cancer was 3.3%.

The cumulative probability of 5-year recurrence free survival was 77% (n=610) in the BCS group, vs 57% (n=335) in the mastectomy group and at 10 years, 68% (n=443) in the BCS vs 50% (n=205) in the mastectomy group (Figure 2a). Cumulative 5-year overall survival was 87% (n=690) in the BCS group, compared to 73% (n=429) in the mastectomy group (Figure 2b).

Univariate hypothesis tests of known clinical predictors identified use of radiation therapy, presence of LVI, total number of nodes positive, tumour size, use of neo-adjuvant and adjuvant chemotherapy, grade, multicentricity, and multifocality as confounders. After controlling for these variables in our multivariable models, there was no association between the receipt of mastectomy and hazard of death among the entire cohort (n=1,381) [Hazard Ratio

(HR) = 0.98, 95% Confidence Interval (CI): 0.78 to 1.25] or with propensity adjustment (n=870) (HR=0.90, 95% CI: 0.69 to 1.19). Similarly, there was no association between receipt of mastectomy and hazard of recurrence among the entire cohort based on multivariable adjustment (HR=0.93, 95% CI: 0.75 to 1.14) or propensity adjustment (HR=0.90, 95% CI: 0.69 to 1.17) (Table 3).

Discussion

In our population-based cohort we found that over half of very young women with breast cancer in Ontario were treated with BCS during the study period. These women had lower risk disease (based on standard predictors of recurrence and survival) than women undergoing mastectomy as primary surgical management as surgeons likely performed surgery based on both known and unknown variables. After controlling for the common, known predictors of cancer outcomes using both propensity and multivariable statistical techniques, we found primary surgical management had no effect on time to death or time to first recurrence, indicating that for many very young women, BCS does not have a negative impact on cancer outcomes. Site of first failure was most frequently at a distant site, irrespective of primary surgical treatment.

Our findings are consistent with other studies evaluating age and breast cancer outcomes. Subset analyses of younger women in three randomized controlled trials have failed to demonstrate differences in outcomes between treatment with BCS and mastectomy, even though younger age consistently predicted poorer outcomes. The Milan trial randomized women with T1N0 tumors to quadrantectomy versus radical mastectomy and found almost 4 times the rate of local recurrence in women <45 compared to women >46 in the quadrantectomy group, but this did not translate into a difference in breast cancer specific survival (26.1% vs 24.3%, $p = 0.8$) or

overall survival (41.7% vs 41.2%, $p = 1.0$) between the surgical groups after 20 years of follow up [1]. Younger age was also significantly associated with local recurrence in the quadrantectomy arm compared to those aged 46-60 and >60, however the number of patients under 35 in this study is not reported. A study combining data analysis with data from the European Organization for Research and Treatment of Cancer (EORTC) 10801 and Danish Breast Cancer Cooperative Group (DBCG) 82 trials similarly found women <35 had 9.24 times the risk of local recurrence compared to women >60, but no difference in local recurrence free or overall survival at 10 years follow up [4]. Only 65 women included in these two trials were under age 35, less than 4% of those enrolled.

Generalization from other large cohort studies comparing BCS to mastectomy with respect to survival is challenging as these cohorts include only small numbers of young women and lack of consistency in the definition of “young”. Most studies do not explicitly state the breakdown of women by age quintile. Women <35 comprise less than 2% of all women with breast cancer in the United States, and account for only a minority of those studied, making it difficult to draw conclusions in this very young age group. As a result, outcomes in the very young patient are not well described. Given the small proportion of women under 35, studies often extend the definition of “young” considerably, by including women <40, those <50 or those who are “premenopausal”. In spite of these and other limitations, other large population or registry-based series have been published and have not found significant differences in breast cancer specific or overall survival by surgery type (Table 4). This finding persisted in a recent meta-analysis of over 22000 women aged 40 or less with early stage breast cancer by Vila et al. They evaluated 5 population-based cohorts and the pooled analysis from the EORTC/DBCG randomized control trial of BCS vs mastectomy in women <35, concluding that mastectomy was not associated with

an improved OS or DDFS compared to BCS. Similar to our findings, the authors acknowledge the probability of selection bias in patient selection for surgery type in the majority of their analyzed patients from retrospective studies like the current study.

Our study adds to the body of evidence finding no survival advantage to mastectomy over BCS in very young breast cancer patients. Importantly, our series includes the largest sample size of women strictly ≤ 35 years of age with detailed pathology and treatment data obtained through primary chart review (data not generally available from large registry and population-based datasets) increasing the importance and relevance of our findings. We found the rate of loco-regional recurrences were 8.2% post BCS and 5.2% post TM, with no difference overall survival. This suggests that for every 100 women treated with mastectomy vs BCS, 3 loco-regional recurrences would be prevented, with no difference in deaths. Importantly, distant metastatic disease represented the most common site of first failure for all women in the study, irrespective of the surgical approach and occurred in 252 (18.2%) of the overall cohort. This high rate of distant metastases may reflect an inherent biologic difference in young women with breast cancer compared to their older counterparts. Certainly the pathologic characteristics of our patients indicated more aggressive disease, for example a high proportion of women had hormone receptor negative tumours, a characteristic associated with worse prognosis [4,7,8]. However, the poor outcomes suffered by many women in our study were not mitigated by more aggressive local management; our study does not support the premise that more extensive surgery results in improved survival.

Our study has limitations. Firstly, it is non-randomized - women were clearly selected for primary surgical therapy by their treating surgeons. Our study is however large and population-based including only very young women ≤ 35 treated over a 10-year period. Our study

demonstrates that irrespective of treating institution, a diverse group of clinicians were able to select women for BCS without a negative impact on cancer outcomes. The study is retrospective in design - while we were unable to control for unmeasured confounders, an extensive number of factors known to impact on our primary outcomes were considered. Because HER2/neu testing in pathology specimens became mainstream only in the final years of our cohort, we do not know the HER2 status of most (75.5%) of our patients. However, HER2 status does not influence surgical decision-making and thus would not be expected to significantly impact choice of primary surgical therapy. Finally, we acknowledge that treatments given to the women in this cohort predate the widespread use of targeted therapy such as trastuzumab, neoadjuvant chemotherapy, broader indications for regional nodal irradiation and more readily available adjuncts such as genetic testing which may impact not only outcomes but patient decision making.

In summary, we have evaluated a large, population-based sample of very young women ≤ 35 years of age with breast cancer, to determine if mastectomy provides a survival advantage over BCS in this group. The population-based nature of this study provides a real world understanding of treatment patterns, estimates of recurrence and breast cancer specific survival on a large scale in this unique group of women. We failed to find a statistically significant effect of surgery type on recurrence or survival this cohort of women who had their surgery type selected, but confirmed that the most frequent site of failure for the entire cohort was distant metastases. Clearly, a better understanding of the biologic drivers of poorer outcomes in young women is needed. Given that our study finds no survival advantage for mastectomy, the decision to pursue mastectomy as primary surgical management should not be mandated by young age alone.

Acknowledgements: We would like to thank Corinne Daly for her assistance in preparation of this manuscript.

Compliance with Ethical Standards

Funding: This study was funded by the Canadian Breast Cancer Foundation – Ontario Chapter.

Conflict of Interest: All authors declare they have no conflicts of interest.

Ethical approval: All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

References

1. 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**(16): 1227-32.
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**(16): 1233-41.
3. Winchester DP, Osteen RT, Menck HR. The National Cancer Data Base report on breast carcinoma characteristics and outcome in relation to age. *Cancer* 1996; **78**(8): 1838-43.
4. 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**(6): 1688-97.
5. de la Rochefordiere A, Asselain B, Campana F, et al. Age as prognostic factor in premenopausal breast carcinoma. *Lancet* 1993; **341**(8852): 1039-43.
 6. Bartelink H, Horiot JC, Poortmans PM, et al. Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-year results of the randomized boost versus no boost EORTC 22881-10882 trial. *J Clin Oncol* 2007; **25**(22): 3259-65.
 7. Clarke M, Collins R, Darby S, et al. 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): 2087-106.
 8. Punglia RS, Morrow M, Winer EP, Harris JR. Local therapy and survival in breast cancer. *N Engl J Med* 2007; **356**(23): 2399-405.
 9. Scarth H, Cantin J, Levine M. Clinical practice guidelines for the care and treatment of breast cancer: mastectomy or lumpectomy? The choice of operation for clinical stages I and II breast cancer (summary of the 2002 update). *Cmaj* 2002; **167**(2): 154-5.
 10. Whelan T, Olivotto I, Levine M. Clinical practice guidelines for the care and treatment of breast cancer: breast radiotherapy after breast-conserving surgery (summary of the 2003 update). *Cmaj* 2003; **168**(4): 437-9.
 11. Rosenberg SM, Tamimi RM, Gelber S, et al. Body image in recently diagnosed young women with early breast cancer. *Psychooncology* 2013; **22**(8): 1849-55.
 12. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: Breast cancer V2.2007. 2014.

http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf (accessed August 2014).

13. Narod A S. Breast Cancer in young Women. *Nature Reviews Clinical Oncology* 2012; **9**: 460-70.
14. Cancer TCPA. Breast Cancer Control in Canada: A system Performance Special Focus Report. Toronto, Ontario: The Canadian Partnership Against Cancer, 2012.
15. Sariego J. Breast cancer in the young patient. *Am Surg* 2010; **76**(12): 1397-400.
16. Han W, Kim SW, Park IA, et al. Young age: an independent risk factor for disease-free survival in women with operable breast cancer. *BMC Cancer* 2004; **4**: 82.
17. 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): 1-8.
18. Bollet MA, Sigal-Zafrani B, Mazeau V, et al. Age remains the first prognostic factor for loco-regional breast cancer recurrence in young (<40 years) women treated with breast conserving surgery first. *Radiother Oncol* 2007; **82**(3): 272-80.
19. Gajdos C, Tartter PI, Bleiweiss IJ, Bodian C, Brower ST. Stage 0 to stage III breast cancer in young women. *J Am Coll Surg* 2000; **190**(5): 523-9.
20. Cao JQ, Truong PT, Olivotto IA, et al. Should women younger than 40 years of age with invasive breast cancer have a mastectomy?: 15-year outcomes in a population-based cohort. *Int J Radiat Oncol Biol Phys* 2014; **90**(3): 509-17.
21. 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**(4): 688-93.

22. 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**(5): 1282-90.
23. Robles SC, Marrett LD, Clarke EA, Risch HA. An application of capture-recapture methods to the estimation of completeness of cancer registration. *J Clin Epidemiol* 1988; **41**(5): 495-501.
24. Quan ML, Osman F, McCready D, Fernandes K, Sutradhar R, Paszat L. Postmastectomy radiation and recurrence patterns in breast cancer patients younger than age 35 years: a population-based cohort. *Ann Surg Oncol* 2014; **21**(2): 395-400.
25. Wolbers M, Koller MT, Witteman JC, Steyerberg EW. Prognostic models with competing risks: methods and application to coronary risk prediction. *Epidemiology* 2009; **20**(4): 555-61.
26. Austin PC. Goodness-of-fit diagnostics for the propensity score model when estimating treatment effects using covariate adjustment with the propensity score. *Pharmacoepidemiol Drug Saf* 2008; **17**(12): 1202-17.
27. 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**(5): 1387-93.
28. van Laar C, van der Sangen MJ, Poortmans PM, et al. Local recurrence following breast-conserving treatment in women aged 40 years or younger: trends in risk and the impact on prognosis in a population-based cohort of 1143 patients. *Eur J Cancer* 2013; **49**(15): 3093-101.

29. Vila J, Gandini S, Gentilini O. Overall survival according to type of surgery in young (≤ 40 years) early breast cancer patients: A systematic meta-analysis comparing breast-conserving surgery versus mastectomy. *The Breast* 2015; 24(3):175 -181.

Figure Captions

Figure 1. Young women with primary surgical treatment between 1994 and 2003 meeting study inclusion criteria.

Table 1. Patient and tumour characteristics for very young women with breast cancer, by surgery type.

Table 2. Patterns of recurrence and mortality among all patients included in study (n=1,381), by surgery type.

Figure 2. a) Recurrence-free probability and b) survival probability for young women with breast cancer treated with lumpectomy versus mastectomy.

Table 3. Results of multivariable Cox models for time to death and time to first recurrence between breast conserving surgery and mastectomy as primary surgical treatment.

Table 4. Major studies evaluating effect of primary surgical treatment on recurrence and survival among young women with breast cancer.

Appendix 1. Patient, tumour, treatment and recurrence variables collected through primary chart review at participating Ontario hospitals for the current study.

Table 1. Patient and tumour characteristics for very young women with breast cancer, by surgery type.

Characteristic	Total n = 1,381	Primary Surgical Management		<i>p-value</i>
		BCS n = 793	Mastectomy [†] n = 588	
Age at Diagnosis (y)				
Mean $\pm$ SD	32.15 $\pm$ 2.83	32.19 $\pm$ 2.86	32.11 $\pm$ 2.78	0.606
Median (IQR)	33 (31-34)	33(31-34)	33 (31-34)	0.394
Range	18-35	18-35	22-35	
Tumour size (mm)				
Mean $\pm$ SD	28.30 $\pm$ 20.70	23.36 $\pm$ 14.30	35.20 $\pm$ 25.70	<.001
Median (IQR)	23 (16-35)	20 (15-29)	30 (18-45)	<.001
Range	1-230	1-230	2-200	
0 - < 20	440 (31.9)	297 (37.5)	143 (24.3)	<.001
20 - < 50	713 (51.6)	433 (54.6)	280 (47.6)	
50+	150 (10.9)	29 (3.7)	121 (20.6)	
Missing	78 (5.6)	34 (4.3)	44 (7.5)	
Size of closest margin (mm), n (%)				
0	147 (10.6)	90 (11.3)	57 (9.7)	0.035
>0 and $\leq$ 2	246 (17.8)	158 (19.9)	88 (15.0)	
>2	488 (35.3)	277 (34.9)	211 (35.9)	
Not reported	500 (36.2)	268 (33.8)	232 (39.5)	
Number of nodes positive, n (%)				
0	494 (35.8)	324 (40.9)	170 (28.9)	<.001
1 to 3	344 (24.9)	181 (22.8)	163 (27.7)	
4+	257 (18.6)	79 (10.0)	178 (30.3)	
No lymph node biopsy performed	264 (19.1)	199 (25.1)	65 (11.1)	
Missing	22 (1.6)	10 (1.3)	12 (2.0)	
Primary Histology, n (%)				
Ductal	664 (48.1)	447 (56.4)	217 (36.9)	<.001
Lobular	23 (1.7)	11 (1.4)	12 (2.0)	
Mixed	30 (2.2)	261 (32.9)	301 (51.2)	
Other	562 (40.7)	59 (7.4)	43 (7.3)	
Missing	102 (7.4)	15 (1.9)	15 (2.6)	
Grade, n (%)				0.002
I	92 (6.7)	65 (8.2)	27 (4.6)	
II	379 (27.4)	219 (27.6)	160 (27.2)	
III	791 (57.3)	277 (34.9)	211 (35.9)	
Not reported	500 (36.2)	268 (33.8)	232 (39.5)	
LVI Present, n (%)				
Positive	547 (39.6)	241 (30.4)	306 (52.0)	<.001
Negative	590 (42.7)	406 (51.2)	184 (31.3)	
Not reported	244 (17.7)	146 (18.4)	98 (16.7)	
ER Status, n (%)				
Positive	638 (46.2)	363 (45.8)	275 (46.8)	0.828
Negative	616 (44.6)	359 (45.3)	257 (43.7)	
Not reported	127 (9.2)	71 (9.0)	56 (9.5)	
PR Status, n (%)				
Positive	593 (42.9)	335 (42.2)	258 (43.9)	0.831
Negative	637 (46.1)	370 (46.7)	267 (45.4)	
Not reported	151 (10.9)	88 (11.1)	63 (10.7)	
HER2 Status, n (%)				
Positive	104 (7.5)	43 (5.4)	61 (10.4)	<.001
Negative	235 (17.0)	127 (16.0)	108 (18.4)	
Not reported	1,042 (75.5)	623 (78.6)	419 (71.3)	
Multicentric tumour, n (%)				
Yes	1,327 (96.1)	12 (1.5)	42 (7.1)	<.001
No	54 (3.9)	781 (98.5)	546 (92.9)	
Multifocal tumour, n (%)				
Yes	1,030 (74.6)	140 (17.7)	211 (35.9)	<.001
No	351 (25.4)	653 (82.3)	377 (64.1)	

Table 2. Patterns of recurrence and mortality among all patients included in study (n=1,381), by surgery type.

	Total n = 1,381	Primary Surgical Management		<i>p-value</i>
		BCS n = 793	Mastectomy [†] n = 588	
Recurrence ¹				
No	785 (56·8)	504 (63·6)	281 (47·8)	<·001
Yes	528 (38·2)	254 (18·4)	274 (46·6)	
Died Without Recurrence	68 (4·9)	35 (4·4)	33 (5·6)	
Site of First Recurrence				
Local	142 (10·2)	98 (12·3)	44 (7·5)	<·001
Regional	75 (5·4)	19 (2·4)	56 (9·5)	
Contralateral	57 (4·1)	33 (4·2)	24 (4·1)	
Distant	252 (18·2)	103 (13·0)	149 (25·3)	
Site of any recurrence ²	596 (41)	270 (34)	299 (38)	0·002
Isolated local	75 (5·4)	60 (7·6)	15 (2·6)	
Regional	20 (2·6)	5 (0·6)	15 (2·6)	
Distant +/- other	362 (26·2)	140 (17·8)	221 (27·6)	
Contralateral	46 (3·3)	29 (3·7)	17 (2·9)	
Multiple non-distant sites	23 (1·7)	17 (2·1)	6 (1·0)	
Unknown	43 (3·1)	18 (2·3)	25 (4·2)	
Death ³				
No	951 (68·9)	608 (76·7)	343 (58·3)	<·001
Yes	430 (31·1)	185 (23·3)	245 (41·7)	

Abbreviations: BCS, breast conserving surgery.

[†]Mastectomy group includes those with BCS and mastectomy performed or mastectomy alone.

¹Recurrence as of November 15, 2011.

²Recurrences collapsed according to most severe location. An individual could have any multiple combination of recurrences over the entire follow-up period. 125 patients had multiple sites of recurrence overall, 45 in the lumpectomy group and 80 in the mastectomy group

³Died from any cause as of March 31, 2012

Table 3. Results of multivariable Cox models for time to death and time to first recurrence between breast conserving surgery and mastectomy as primary surgical treatment.

Author Manuscript

Variable	Time to Death						Time to First Recurrence					
	without propensity adjustment			with propensity adjustment			without propensity adjustment			with propensity adjustment		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Primary Surgical Management												
BCS	1·00	Referent	0·88	1·00	Referent	0·45	1·00	Referent	0·47	1·00	Referent	0·44
Mastectomy [†]	0·98	(0·78, 1·25)		0·90	(0·69, 1·19)		0·93	(0·75, 1·14)		0·90	(0·69, 1·17)	
Adjuvant Radiation												
No	1·00	Referent	<·0001	1·00	Referent	<·0001	1·00	Referent	<·0001	1·00	Referent	0·0003
Yes	0·57	(0·45, 0·72)		0·52	(0·39, 0·68)		0·55	(0·44, 0·67)		0·44	(0·28, 0·69)	
Lymphovascular Invasion												
No	1·00	Referent	0·0002	1·00	Referent	0·004	1·00	Referent	0·004	1·00	Referent	0·01
Yes	1·55	(1·21, 1·99)		1·52	(1·15, 2·01)		1·43	(1·15, 1·77)		1·38	(1·08, 1·76)	
Not reported	0·86	(0·60, 1·23)			N/A		1·08	(0·81, 1·44)			N/A	
Number of positive lymph nodes												
0	1·00	Referent	<·0001	1·00	Referent	<·0001	1·00	Referent	<·0001	1·00	Referent	<·0001
1 to 3	1·64	(1·24, 2·17)		1·58	(1·15, 2·17)		1·45	(1·15, 1·84)		1·46	(1·10, 1·94)	
4 +	3·11	(2·32, 4·18)		3·24	(2·32, 4·52)		2·57	(1·99, 3·33)		3·01	(2·10, 4·32)	
No biopsy performed	0·99	(0·71, 1·38)			N/A		1·08	(0·82, 1·41)			N/A	
Tumour Size (mm)*												
0 - <20	1·00	Referent	0·001	1·00	Referent	0·17	1·00	Referent	0·000	1·00	Referent	0·01
20 - <50	1·27	(0·99, 1·63)		1·18	(0·88, 1·57)		1·25	(1·02, 1·54)		1·18	(0·92, 1·53)	
50 +	1·65	(1·19, 2·29)		1·43	(0·99, 2·08)		1·86	(1·40, 2·48)		1·85	(1·24, 2·76)	
Not reported	2·13	(1·35, 3·45)			N/A		1·49	(0·98, 2·27)			N/A	
Neoadjuvant Therapy												
No	1·00	Referent	<·0001	1·00	Referent	<·0001	1·00	Referent	<·0001	1·00	Referent	0·0002
Yes	2·19	(1·64, 2·91)		2·29	(1·62, 3·24)		2·05	(1·58, 2·65)		2·16	(1·44, 3·24)	
Grade												
I	1·00	Referent	0·02	1·00	Referent	0·001	1·00	Referent	0·260	1·00	Referent	0·09
II	2·14	(1·11, 4·10)		2·42	(1·05, 5·59)		1·33	(0·86, 2·05)		1·52	(0·84, 2·78)	
III	2·54	(1·34, 4·82)		3·40	(1·49, 7·77)		1·43	(0·94, 2·18)		1·77	(0·98, 3·18)	
Not reported	2·68	(1·27, 5·62)			N/A		1·64	(0·96, 2·81)			N/A	
Multicentric												
No	1·00	Referent	0·7	1·00	Referent	0·71	1·00	Referent	0·390	1·00	Referent	0·73
Yes	1·09	(0·71, 1·66)		0·92	(0·57, 1·48)		1·18	(0·81, 1·72)		1·08	(0·70, 1·66)	
Multifocal												
No	1·00	Referent	0·81	1·00	Referent	0·82	1·00	Referent	0·880	1·00	Referent	0·42
Yes	1·03	(0·83, 1·28)		1·03	(0·80, 1·32)		1·01	(0·84, 1·23)		1·10	(0·87, 1·40)	

[†]Mastectomy group includes those with BCS and mastectomy performed or mastectomy alone.

*At time of primary surgery

Propensity adjustment was the probability of being assigned treatment with mastectomy based on covariates in the subset of the overall cohort with no missing variables in any category (n=870).

Abbreviations: BCS, breast conserving surgery; HR, hazard ratio; CI, confidence interval; N/A, not applicable.

Table 4. Major studies evaluating effect of primary surgical treatment on recurrence and survival among young women with breast cancer.

Study	n	Age (years)	Outcomes
Surveillance, Epidemiology and End Results (SEER) Registry_ENREF_27 [27]	14,800	All: <40 <36 years: 56%	Younger age predictor of cause-specific survival. Matched-pair subset analysis of 4,644 patients confirmed no difference in 5-, 10-, 15-year rates of cause-specific survival ($p=0.88$) and overall survival ($p = 0.99$) between patients undergoing mastectomy and BCS
Danish Breast Cancer Cooperative Group (DBCG) [21]	9,000	All: <50 <35 years: 7%	Patients receiving BCT indicated a 5.2-fold greater incidence (15.4% vs 3.0%) of local recurrence in the breast within 5 years of diagnosis among women age < 35 years compared with women ages 45–49 years.
British Columbia Breast Cancer Unit Outcomes (BCOU) [20]	935	All: <40 <35: 30% (293)	No difference in 15-year rates of local relapse-free survival (86.2% vs 84.2%, $p=0.50$) , breast cancer specific survival (86.1% vs 82.9%, $p=0.57$), or overall survival (82.6% vs 82.9%, $p=0.89$) between patients treated with BCS versus mastectomy
Eindhoven Cancer Registry of the Netherlands [28]	1,143	All: <40 <35: 27%	10-year overall survival rates did not differ significantly between patients undergoing BCT and those undergoing mastectomy (74.9% vs 71.2%, $p = 0.215$).

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Quan, ML;Paszat, LF;Fernandes, KA;Sutradhar, R;McCready, DR;Rakovitch, E;Warner, E;Wright, FC;Hodgson, N;Brackstone, M;Baxter, NN

Title:

The Effect of Surgery Type on Survival and Recurrence in Very Young Women With Breast Cancer

Date:

2017-02-01

Citation:

Quan, M. L., Paszat, L. F., Fernandes, K. A., Sutradhar, R., McCready, D. R., Rakovitch, E., Warner, E., Wright, F. C., Hodgson, N., Brackstone, M. & Baxter, N. N. (2017). The Effect of Surgery Type on Survival and Recurrence in Very Young Women With Breast Cancer. JOURNAL OF SURGICAL ONCOLOGY, 115 (2), pp.122-130. <https://doi.org/10.1002/jso.24489>.

Persistent Link:

<http://hdl.handle.net/11343/292305>