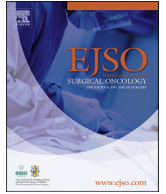




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Management of positive margins after initial lumpectomy in elderly women with breast cancer

Fernando A. Angarita^a, Sergio A. Acuna^a, David R. McCready^{a, b}, Jaime Escallon^{a, b, c, *}

^a Division of General Surgery, Department of Surgery, University of Toronto, Toronto, M5B 1W8, ON, Canada

^b Department of Surgical Oncology, Princess Margaret Cancer Centre, Toronto, M5G 2M9, ON, Canada

^c Marvella Koffler Breast Centre, Mount Sinai Hospital, Toronto, M5G 1X5, ON, Canada

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ABSTRACT

Introduction: It is unknown whether the treatment disparity observed between young and elderly women extends to the management of positive margins after initial lumpectomy. The primary aim was to evaluate the management of positive margins after initial lumpectomy in elderly women.

Methods: Women ≥ 50 y who underwent lumpectomy for stage I–III tumors were identified. Tumor and treatment characteristics were collected across two subgroups: young (50–69 y) and elderly (≥ 70 y). Univariate comparisons were done using chi-square and Wilcoxon Rank Sum test. A multivariable logistic regression was used to evaluate factors associated with reoperation. Incidence of overall recurrence was compared between young and elderly women by plotting the cumulative incidence function of overall recurrence and death without recurrence.

Results: Of 1670 women identified, 29.5% were elderly. Compared to young women, tumors in elderly patients were more frequently invasive lobular carcinoma, larger, low grade and lymphovascular negative. Positive margins were less common in elderly than young women (10.8% versus 16.2%, unadjusted OR 0.60, 95% CI 0.42–0.86). Compared to young women, elderly women were less likely to undergo reoperation (84.9% versus 100%, $p < 0.001$), adjuvant chemotherapy (5.7% versus 46.6%, $p < 0.0001$), and adjuvant radiation therapy (69.8% versus 83.9%, $p = 0.04$). Five-year disease free survival (DFS) was similar between age groups (86% versus 86%, $p = 0.8$).

Conclusions: Elderly women with positive margins after initial lumpectomy were treated differently than younger women as shown by a lower rate of reoperation and adjuvant radiation therapy. Despite these treatment variations there was no impact on overall recurrence and DFS.

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Introduction

Advanced age is a major risk factor for cancer [1]. Forty percent of breast cancers are diagnosed in elderly women [2]. In view of the aging population worldwide, the number of elderly patients with

breast cancer will present a challenge. In fact, by 2025 75% of breast cancers will be diagnosed in elderly women [3].

The recommended treatment for operable breast cancer is lumpectomy with adjuvant whole-breast radiation therapy (RT) or mastectomy followed by adjuvant RT in selected cases [4,5]. Lumpectomy remains a valid option in elderly women as body image is important for this age group [4,6]. In fact, lumpectomy has been proven to be the most common treatment in elderly breast cancer patients [7].

Elderly women are generally treated less aggressively than young patients [7]. Several factors influence this decision. These women have a reduced life expectancy and their risk of dying from other causes may exceed that of recurrence and breast cancer-related mortality [8]. The declining functional and mental status may limit their decision-making process thereby leading to

Abbreviations: 95% CI, 95% confidence interval; ASA, American Society of Anesthesiologists; DFS, disease free survival; ER, estrogen receptor; HR, hazard ratio; IQR, interquartile range; LN, lymph node; LVI, lymphovascular invasion; m, months; OBSP, Ontario Breast Screening Program; OR, odds ratio; OS, overall survival; PNI, perineural invasion; PR, progesterone receptor; RT, radiation therapy; TNBC, triple negative breast cancer; y, years old.

* Corresponding author. Marvella Koffler Breast Centre, Sinai Health System, Rm 1266, 600 University Avenue, Toronto, M5G 1X5, ON, Canada.

E-mail address: Jaime.Escallon@sinaihealthsystem.ca (J. Escallon).

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treatments that some would consider suboptimal. However, some of these actions are based on limited level I evidence to guide treatment decisions for this population [4,9]. Elderly women frequently do not undergo adjuvant RT after lumpectomy, lymph node staging procedures, or chemotherapy [7]. Depending on the study, “undertreating” elderly breast cancer patients has shown positive or negative effects on disease free (DFS) and overall (OS) survival [7,10–13].

It is unknown whether the disparity in treatment observed between young and elderly women also extend to the management of positive margins after initial lumpectomy. Given that margin status is the most important determinant of local recurrence [14], knowing the current state of positive margins in elderly women and how these are managed is critical. The primary aim of this study was to evaluate the management of positive margins after initial lumpectomy in elderly women. Secondary aims included determining factors that were associated with positive margins after initial lumpectomy and determining the effect of positive margins on tumor recurrence and DFS specifically for elderly women.

Material and methods

Study design

After ethics board approval, a retrospective cohort study was conducted including all female breast cancer patients ≥ 50 years old (y) at time of cancer diagnosis between January 1, 2014 and December 31, 2011. Cases were identified and data extracted from the eClinical Breast Database, a prospectively collected database of patients treated at Mount Sinai Hospital and Princess Margaret Cancer Centre. Both hospitals are large-volume academic cancer centers in Toronto, Ontario, Canada. Inclusion criteria were first time diagnosis of breast cancer, biopsy proven invasive cancer, stage I–III tumors, and lumpectomy at one of our institutions. We excluded patients with non-breast primary tumor, in situ tumor, phyllodes tumor, lymphoma, sarcoma, or Paget's disease.

Clinical practice

In Ontario, breast cancer screening is provided through the Ontario Breast Screening Program (OBSP), a province-wide, organized screening program that provides high-quality breast cancer screening for women. The OBSP provides screening for average risk women ages 50 to 74. Women over age 74 can be screened within the program, but they are encouraged to make a personal decision in consultation with their physician. To undergo surgical consultation at Mount Sinai Hospital or Princess Margaret Cancer Centre, a physician must make a referral to one of the breast surgeons. Cases are eligible for discussion at the weekly breast cancer multidisciplinary tumor board held to develop treatment recommendations. Both hospitals do not have specific policies regarding the treatment of elderly women with breast cancer. All treatment plans are proposed taking into consideration the benefits and risks of each treatment modality, patient preference, comorbidities, and functional status.

Data collection

Extracted data encompassed features relating to patient and tumor characteristics, surgery, surgical pathology, non-surgical treatments, and surveillance. Details regarding comorbidities, American Society of Anesthesiologists (ASA) score, performance status score, factors influencing acceptance or rejection of clinical treatment decision, details about chemotherapy and RT (dose,

number of sessions, and response to treatment), and cause of death were unavailable from the database.

Definitions

Young and elderly were defined as age 50–69 y and ≥ 70 y, respectively. Positive margins were defined as invasive tumor on ink. For clarity throughout the paper the term positive margin will refer to margins from the initial lumpectomy, unless otherwise noted. Reoperation was defined as re-excision in a separate operation and/or completion mastectomy. DFS was defined as time elapsed from date of initial surgery to date of recurrence or death from any cause. Types of recurrence were defined as follows: local if they involved the same breast or surgical scar as the primary tumor, regional if it involved nearby lymph nodes, and distant if it involved other parts of the body. Tumor recurrence was assessed using overall recurrence, which was defined as local, regional, and/or distant recurrence.

Statistics

Continuous data are presented as medians with interquartile range (IQR). Univariate comparisons were done using chi-square and Wilcoxon Rank Sum test. A multivariable logistic regression model was used to evaluate factors associated with positive margins post-lumpectomy and factors associated with reoperation after positive margins. Variables were selected *a priori*. DFS probabilities were estimated using the Kaplan–Meier method, and log-rank test was used to determine the level of significance between survival curves. A Cox proportional hazard regression model was used to assess the association between age groups and DFS and to obtain hazard ratios (HR) for age group adjusting by pathologic lymph node status, RT, and reoperation. To address competing risks in the time to recurrence, we modeled time to recurrence and time to death without recurrence, and plotted the cumulative incidence of both events and groups were compared using Gray's test. Cause-specific hazard models were used to estimate the unadjusted HR. We tested the assumptions of proportionality in our Cox models by plotting $\log[-\log(\text{survival})]$ versus $\log(\text{time})$ and assessing parallelism. SAS 9.4 (SAS Institute Inc., Cary, NC, USA) was used for data management and statistical analyses. Statistical significance was set at p -value < 0.05 .

Results

A total of 1670 women met the inclusion criteria; 1177 (70.5%) were young and 493 (29.5%) were elderly. The age distribution of elderly women was as follows: 70–79 y [$n = 379$ (76.9%)], 80–89 y [$n = 107$ (21.7%)], and > 90 y [$n = 7$ (1.4%)]. Table 1 summarizes tumor features for both age groups. Compared to young women, tumors in elderly patients were more frequently invasive lobular carcinoma, larger, low grade and lymphovascular invasion (LVI) negative. Tumors in elderly women were more frequently hormone receptor positive whereas in young women they had a greater proportion of HER2 positive and triple negative breast cancer (TNBC). Lymph nodes were more frequently positive in young women on pathology. Sixteen percent of elderly women had unknown lymph node status because they lacked lymph node staging. Neoadjuvant chemotherapy (NAC) was rarely provided to the elderly as compared to young women (0.2% versus 2.6%, $p = 0.0009$). Young women more frequently underwent adjuvant chemotherapy (41.2% versus 4.7%, $p < 0.0001$) and RT (81% versus 71%, $p < 0.0001$) than elderly women.

A total of 244 (14.6%) women had positive margins after their initial lumpectomy. A logistic regression model was used to evaluate factors associated with positive margins after initial

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