Title

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The Role of Radiation Therapy in Addition to Lumpectomy and Hormone Therapy in Men 70 Years of Age and Older with Early Breast Cancer: A NCDB Analysis

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Abstract

Purpose: Current treatment guidelines for male breast cancer are guided by female-only trials despite data suggesting distinct clinicopathologic differences between sexes. We sought to evaluate if radiation therapy (RT) after lumpectomy was associated with equivalent survival among men ≥ 70 years of age with stage I, estrogen receptor (ER) positive tumors, as seen in women from the Cancer and Leukemia Group B (CALGB) 9343 trial.

Methods: We performed a retrospective analysis of 752 stage I, ER-positive male breast cancer patients ≥70 years who were treated with hormone therapy and surgery, with or without RT, from the National Cancer Database between 2004–2014. Patients were categorized based on surgery and RT (lumpectomy alone, lumpectomy with RT, and mastectomy alone). Multivariable Cox proportional hazards regression analysis was used to compare overall survival between treatment groups.

Results: Most patients underwent total mastectomy, with only 32.6% treated with lumpectomy. Of those who underwent lumpectomy, 72.7% received adjuvant RT. In multivariate analysis, there was no statistical difference in overall survival when comparing lumpectomy alone to lumpectomy with RT (aHR 0.72 [95%CI 0.38–1.37], p=0.31), or when comparing lumpectomy (alone or with RT) and mastectomy (aHR 1.28 [95%CI 0.88–1.87], p=0.20).

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Conflicts of interest: none

Conclusions: In this national sample of elderly men with ER-positive early-stage disease treated with endocrine therapy, there were no significant differences in overall survival when comparing lumpectomy alone to lumpectomy with RT, or lumpectomy (alone or with RT) to mastectomy. These results suggest that less aggressive treatment may be appropriate for a subset of male breast cancer patients.

Introduction

The Cancer and Leukemia Group B (CALGB) 9343 randomized clinical trial compared breast conserving therapy (i.e. lumpectomy and radiation therapy [RT]) to lumpectomy alone in in women ≥70 years of age with estrogen receptor (ER) positive, clinical stage I breast cancer who were all also treated with tamoxifen.[1,2] This landmark study showed that in a well-selected cohort of older female patients, lumpectomy alone was equivalent to breast conserving therapy with respect to time to distant metastases, breast cancer-specific survival, mastectomy free survival, and overall survival (OS). This study provided support that a specific population of older women with early-stage disease may safely choose to forego adjuvant radiation if treated with adjuvant hormonal therapy. However, an important limitation of the CALGB 9343 trial is that male patients were excluded, which decreases the universality of its conclusions.

With an estimated 2,670 new cases arising in the United States in 2019, male breast cancer remains a rare disease that compromises less than 1% of all new breast cancer diagnoses.[3] Despite its rarity, the incidence of male breast cancer has increased by approximately 26% in the past 30 years,[4] which leaves an increasingly larger population needing evidence-based treatment options. Due to the small number of patients, there are no prospective clinical trials to date comparing outcomes in male breast cancer and research in male breast cancer remains largely limited to retrospective cohort analyses.[5–14] As a result, current treatment guidelines for male patients are predominantly guided by female-only clinical trials.[15,16] However, male breast cancer has been shown to be biologically distinct from female breast cancer including differences in gene expression and prognosis.[17] Therefore, dedicated research in male breast cancer is imperative to determine if findings from landmark clinical trials in women may be equivalently applied to men.

Our study objective was to determine if there is a cohort of male patients with low-risk characteristics that would benefit from treatment de-escalation, similar to that seen in the CALGB 9343 study, which showed no difference in overall survival with the omission of radiation treatment following lumpectomy in combination with tamoxifen for Stage I, ER-positive tumors in women age 70 or older. Using the National Cancer Database (NCDB), we sought to evaluate if lumpectomy alone was associated with equivalent survival to lumpectomy with radiation. Secondarily, we sought to confirm equivalence of mastectomy alone in stage I, ER-positive male breast cancer patients who also received adjuvant hormone therapy. Mastectomy alone was included despite not being part of the CALGB 9343 trial as this is the most common operation performed, and by many still considered the gold standard, for male breast cancer.[13,18] We hypothesized that there is no difference in overall survival when comparing lumpectomy alone to lumpectomy plus RT based on the findings of the CALGB 9343 trial in women.

Methods

We performed a retrospective cohort analysis of early-stage, ER-positive male breast cancer patients from the NCDB diagnosed between 2004 and 2014. The NCDB is a hospital-based registry jointly sponsored by the American College of Surgeons and American Cancer Society. It is estimated that NCDB captures 70% of all new cancer diagnoses in the United States.[19–21] The patient data are de-identified; therefore, the study protocol was exempt from the University of California, Davis Institutional Review Board approval.

We abstracted data on males ≥70 years of age with stage I (T1 N0 M0), ER-positive invasive breast cancer who received surgery (lumpectomy or mastectomy) and adjuvant hormone therapy. Hormone therapy included aromatase inhibitors, estrogen inhibitors, or selective ER modulators and downregulators. Radiation therapy (RT) consisted of postoperative external beam RT to the breast and/or chest wall. A total of 18,984 male patients were identified in the NCDB. Exclusion criteria included multicentric/diffuse disease (n=2,611); Paget's disease (n=82); patients who did not undergo lumpectomy or mastectomy (n=675); brachytherapy, preoperative RT, or unknown RT status (n=428); unknown or missing survival data (n=1,291); age less than 70 (n=6,072); and/or unknown stage, T2-T4, and ≥N1 disease (n=6,338). Patients who underwent mastectomy with RT (n=31), had unknown ER expression (n=110), and did not receive adjuvant hormone therapy or had unknown adjuvant hormone therapy (n=571) data were also excluded. The final cohort consisted of 752 patients (Figure 1).

Patient demographic, clinicopathologic and treatment characteristics were abstracted from NCDB. Medical comorbidities were measured using the Charlson-Deyo comorbidity index (CDCI). Tumor histology was classified based on the international classification of disease oncology codes (ICD-O-3). Staging was determined based on AJCC TNM pathologic staging (6th and 7th edition); AJCC clinical staging was only utilized when pathologic staging information was missing. As described previously, sentinel lymph node biopsy (SLNB) was defined as the examination of 1–5 lymph nodes, while axillary lymph node dissection (ALND) was defined as the examination of ≥ 6 nodes.[5] Overall survival was determined based on patients' vital status and calculated as months from diagnosis to last contact and/or date of death. However, no data is collected on cause of death in the NCDB; therefore, no results of cancer specific survival can be determined.

Statistical Analysis

Patient demographic, clinicopathologic and treatment differences were compared between treatment groups (i.e. lumpectomy alone, lumpectomy plus RT, and mastectomy alone) using the Chi-squared test for categorical variables, the Kruskall Wallis test for non-normally distributed continuous variables (i.e. tumor size), and ANOVA for normally distributed continuous variables (i.e. age). Cox proportional hazards regression analyses were used to compare overall survival between groups. Multivariate Cox regression models accounted for select demographic and clinicopathologic differences between groups including age, race, CDCI score, tumor histology, grade and size, HER-2 status, nodal surgery, surgical margin status, and chemotherapy. We also performed an inverse probability of treatment weighted Cox proportional hazards model using propensity scores to compare overall survival between treatment groups controlling for demographic and clinicopathologic characteristics. As the results of the analysis were similar to the multivariable models, we selected to present the multivariable models as to present all variables associated with survival in this distinct population cohort. Statistical analyses were performed with SAS software (version 9.4, SAS Institute, Cary, NC). All tests were two-sided and p-values <0.05 were considered significant.

Results

Of the 752 patients, there were 245 (32.6%) who were treated with lumpectomy (alone or with RT) and 507 (67.4%) who underwent total mastectomy. Among the lumpectomy patients, 178 (72.7%) received adjuvant RT, whereas 67 (27.3%) did not. As shown in Table 1, there were significant differences between groups with respect to age, histology, tumor size, grade, surgical margin status, nodal surgery, and chemotherapy (p<0.05). Patients who underwent lumpectomy alone were older than those who underwent lumpectomy with RT and mastectomy alone (78.9 years vs. 76.0 years & 76.9 years, p=0.004). When compared to the mastectomy group, lumpectomy patients (alone or with RT) had lower rates of ductal histology (77.6% & 71.4% vs. 85.4%, p<0.0001), smaller tumors (1.2 cm & 1.1 cm vs. 1.5 cm, p<0.0001), and lower rates of poorly differentiated tumors (11.9% & 12.4% vs. 19.9%, p<0.0001). Additionally, lumpectomy alone patients were more likely to forego nodal surgery (28.4% vs. 7.9% & 4.3%, p<0.0001) and less likely to receive chemotherapy (0% vs. 9.6% & 9.1%, p=0.003).

In univariate survival analysis of the lumpectomy cohorts (Figure 2a), lumpectomy with RT was associated with greater survival compared to lumpectomy alone (HR 0.48, [95%CI 0.28–0.83], p=0.01). However, after controlling for demographic, clinicopathologic and treatment differences between groups in multivariate analysis (Figure 2b), there was not a significant difference in survival between lumpectomy alone and lumpectomy with RT (aHR 0.72, [95%CI 0.38–1.37], p=0.31). When comparing lumpectomy patients (alone or with RT) to mastectomy in univariate and multivariable analysis (Figures 3a & 3b), there were no significant differences in survival between groups (univariable: HR 1.31, [95%CI 0.95–1.82], p=0.10; multivariable aHR 1.28, [95%CI 0.88–1.87], p=0.20).

Multivariable analyses of patients undergoing lumpectomy are shown in Table 2. The addition of radiation was not associated with improved overall survival (aHR 0.72, [95%CI 0.38–1.37], p=0.31). Older age (HR 1.11, [95%CI 1.04–1.18], p=0.0009), CDCI score ≥2 (HR 3.20, [95%CI 1.03–9.94], p=0.04), and poorly differentiated carcinoma (HR 2.63, [95%CI 1.05–6.60], p=0.04) were associated with poorer survival. Similar variables were associated with poorer survival in the multivariable analyses of all male patients with early stage (T1 N0) breast cancer, specifically showing no difference between surgical procedures (Table 3).

Discussion

In this NCDB analysis of male breast cancer patients ≥70 years of age with stage I, ER-positive breast cancer treated with hormone therapy, there was not a statistically significant difference in overall survival in men treated with lumpectomy alone compared to those who underwent lumpectomy with RT. Additionally, there was not a significant difference in survival when comparing lumpectomy (with or without RT) to mastectomy. We examined mastectomy despite its exclusion from the CALGB 9343 trial as this treatment for male breast cancer has been the gold standard, even though recent data has shown lumpectomy equivalence for male breast cancer.[5,14,16,18] Although retrospective, this is the first study to demonstrate these findings in a specific cohort of older male breast cancer patients.

Our analysis comparing lumpectomy alone to lumpectomy with RT complements the findings of the CALGB 9343 trial, which showed equivalent survival in women of the same demographic as our study population (exclusive of mastectomy).[1] Follow up data from CALGB 9343 has shown that adjuvant RT after lumpectomy does not greatly change 10-year overall survival (66% Tamoxifen, 67% Tamoxifen + RT) and suggests that comorbid conditions will ultimately dictate mortality in these patients.[2] Similarly, our study demonstrated that greater CDCI scores, a standardized measure of medical comorbidities, were associated with poorer overall survival and further supports that comorbidities may predominately influence survival in older patients, both male and female, with early-stage ER-positive breast cancer more than any tumor-related factor examined. A recent review cited that the omission of adjuvant RT, as in the CALGB 9343 trial, might be an appropriate consideration in comparable male patients, but acknowledged that dedicated research had not been conducted on this topic.[18] Our study helps fill that void in the literature and adds to the limited, but growing, body of research on male breast cancer.

Before the CALGB 9343 trial, several other trials questioned eliminating RT after lumpectomy in early stage breast cancer, but all failed to show non-inferiority. Fisher et. al performed a randomized trial to ascertain the impact of adjuvant therapies (tamoxifen alone, radiation alone, or both) on ipsilateral breast tumor recurrence (IBTR) in women of all ages with early stage breast cancer. They demonstrated significantly decreased IBTR rates when patients received radiation after lumpectomy (with or without tamoxifen) compared to tamoxifen alone.[22] In another randomized trial, Pötter et. al studied how adjuvant radiation influences local recurrence in postmenopausal women taking tamoxifen or anastrozole after lumpectomy. This study also strongly supported the use of adjuvant radiation as it demonstrated significantly reduced local and overall relapse rates in patients receiving breast irradiation after lumpectomy.[23] Finally, the British Association of Surgical Oncology II trial sought to identify a cohort with a low risk of local recurrence that could tolerate omission of adjuvant radiation after lumpectomy. The authors did not identify a subgroup who would not benefit from adjuvant radiation and similarly concluded that adjuvant radiation confers a significant risk reduction in local recurrence, especially when combined with tamoxifen.[24] Since CALGB 9343, the PRIME II trial studied 5-year IBTR in women ≥65 years of age with early stage disease who received breast-conserving treatment (BCT) and endocrine therapy. Participants randomized to adjuvant RT had a significant reduction in IBTR compared to women who did not receive adjuvant RT.[25] However, importantly, the aforementioned studies did not examine overall survival as their primary outcome and similar to the CALGB 9343, all were conducted with female patients.

While these trials advance our understanding of breast cancer and the importance of examining specific outcomes, they also highlight an important limitation in the management of male breast cancer in that current treatment guidelines are almost exclusively based on clinical trials comprised of female participants.[15,16] Investigating male-focused outcomes is valuable to provide individualized evidence-based surveillance and treatment recommendations because male breast cancer has distinct biologic, clinicopathologic, and prognostic differences from female breast cancer.[17,26–28] Our results build upon prior reports demonstrating that BCT may be an appropriate or better option for select male patients.[5,6,9,14,29] For example, a recent study comparing BCT to mastectomy in a large cohort of male breast cancer patients using the NCDB demonstrated that BCT was associated with improved survival compared to total mastectomy alone.[5]

This study does have some important limitations inherent to the analysis of administrative data. First, the data was retrospective, and patients were not randomized to treatment approaches. Despite multivariate analyses, our results may have been influenced by unmeasured confounders related to selection bias, as nuanced clinical, pathologic, or sociodemographic features may have affected patient or physician treatment decisions. Furthermore, as male breast cancer is rare, the population studied is a relatively small sample size, which increases our risk of Type II errors and underpowers our ability to detect small, but potentially important, differences in survival. However, our limited sample size obtained from a large national database underscores the importance of examining retrospective data for rare diseases when a prospective analysis may not be feasible. An additional limitation is that NDCB does not provide detailed data regarding the length of hormonal therapy treatment, which was an important metric outlined in CALGB 9343. Finally, Hughes et al. identified that women treated with Tamoxifen + RT versus Tamoxifen experienced a significantly longer time to locoregional recurrence,[2] and although we would have liked to study these endpoints, NCDB lacks data to evaluate locoregional recurrence or disease-specific survival, both of which represent important outcomes and areas for future research on this topic.

Conclusions

Ultimately, in this NCDB analysis of male breast cancer patients ≥ 70 years of age with stage I, ER-positive breast cancer treated with hormone therapy, there were non-significant differences in overall survival when comparing lumpectomy alone to lumpectomy with RT, and also when comparing lumpectomy (alone or with RT) to mastectomy. Our retrospective results complement the findings of the CALGB 9343 trial conducted in women and prompt additional questions about treatment de-escalation for certain male patients.

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Synopsis

This retrospective review examined if radiation therapy after lumpectomy was associated with equivalent survival among older men with early stage hormone positive breast cancer, as seen in women from the Cancer and Leukemia Group B 9343 trial.

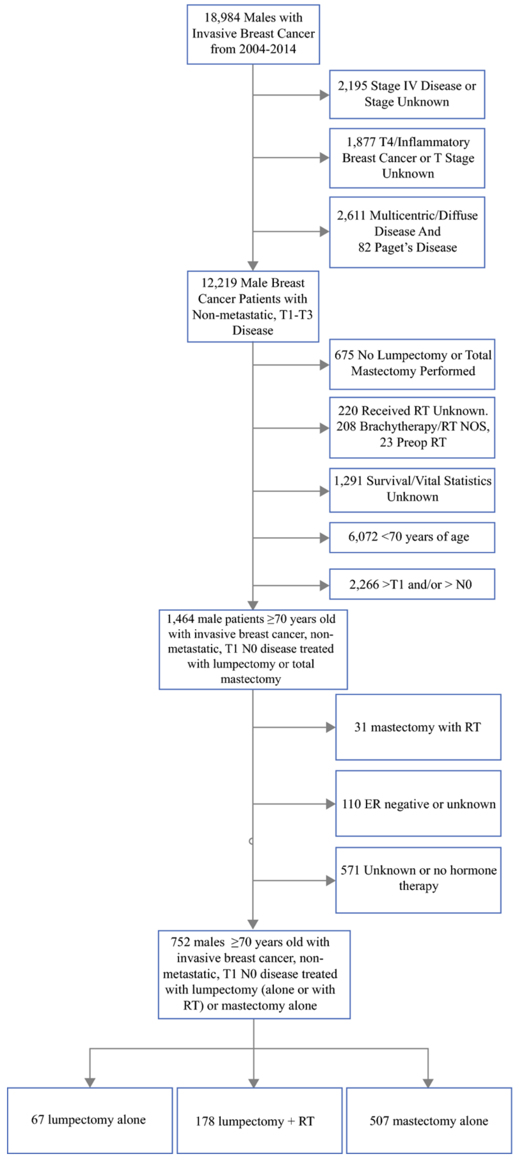

Fig. 1.
CONSORT diagram

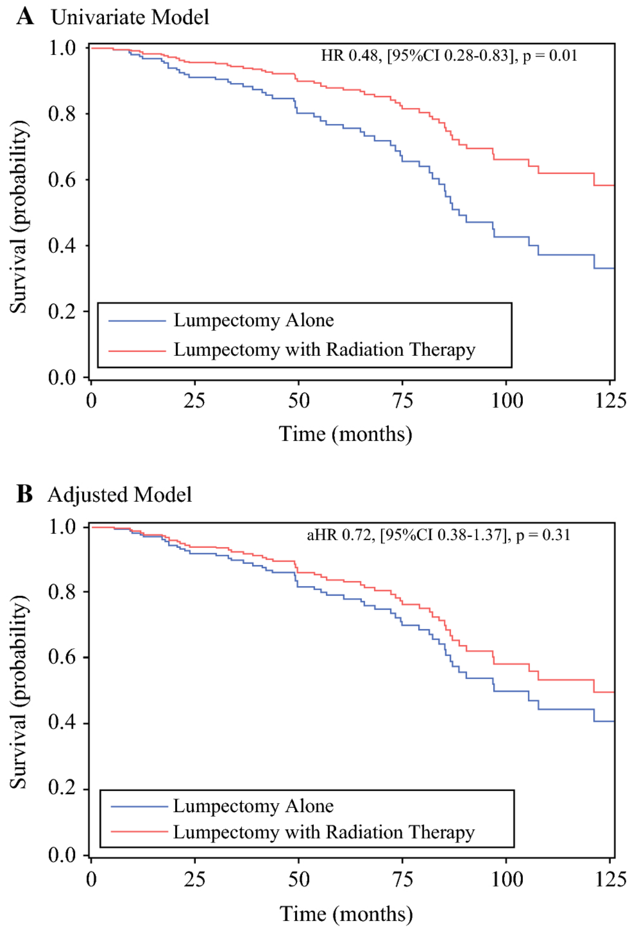

Fig. 2a-b.

Crude (a) and adjusted (b) overall survival for all male breast cancer patients treated with lumpectomy alone versus lumpectomy with radiation therapy

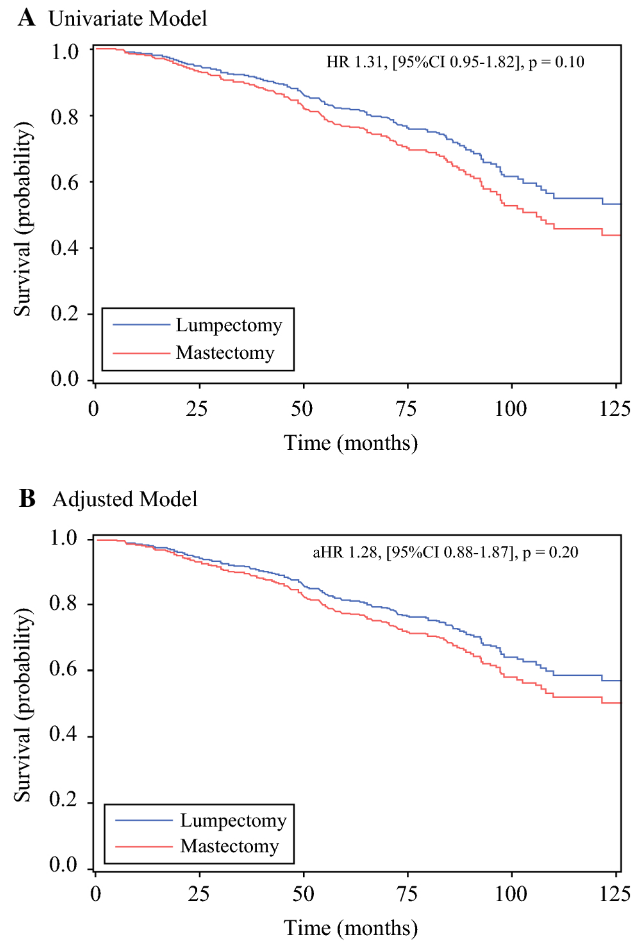

Fig. 3a-b.

Crude (a) and adjusted (b) overall survival for male breast cancer patients treated with lumpectomy (alone or with radiation therapy) versus mastectomy

TABLE 1

Patient demographics and clinicopathologic characteristics by treatment approach

	Lumpectomy Alone N=67	Lumpectomy with RT[1] N=178	Mastectomy Alone N=507	P-value
Age	78.9 (±5.7)	76.0 (± 4.4)	76.9 (± 5.2)	0.004
Race				0.34
Caucasian	59 (88.1%)	160 (89.9%)	466 (91.9%)	
African American	6 (9.0%)	16 (9.0%)	28 (5.5%)	
Other	2 (3.0%)	2 (1.1%)	13 (2.6%)	
Charlson Comorbidity Index				0.18
0	50 (74.6%)	143 (80.3%)	359 (70.8%)	
1	13 (19.4%)	28 (15.7%)	117 (23.1%)	
2+	4 (6.0%)	7 (3.9%)	31 (6.1%)	
Facility Type				0.28
Comprehensive Community Cancer Center	31 (46.3%)	84 (47.2%)	234 (46.2%)	
Academic/Research Center	18 (26.9%)	44 (24.7%)	156 (30.8%)	
Community Cancer Center	13 (19.4%)	23 (12.9%)	65 (12.8%)	
Other	5 (7.5%)	27 (15.2%)	52 (10.3%)	
Histology				<0.0001
Ductal Carcinoma	52 (77.6%)	127 (71.4%)	433 (85.4%)	
Lobular Carcinoma	5 (7.5%)	28 (15.7%)	13 (2.6%)	
Other	10 (14.9%)	23 (12.9%)	61 (12.0%)	
Tumor Size, median, IQR[2]	1.2 (0.8–1.5)	1.1 (0.8–1.4)	1.5 (1.1–1.7)	<0.0001
Grade				<0.0001
Well differentiated	22 (32.8%)	71 (39.9%)	99 (19.5%)	
Moderately Differentiated	33 (49.3%)	77 (43.3%)	292 (57.6%)	
Poorly Differentiated	8 (11.9%)	22 (12.4%)	101 (19.9%)	
Unknown	4 (6.0%)	8 (4.5%)	15 (3.0%)	
HER-2 Positive	6 (9.0%)	10 (5.6%)	39 (7.7%)	0.35
Negative Surgical Margins	64 (95.5%)	169 (94.9%)	501 (98.8%)	0.002
Nodal Surgery				<0.0001
None	19 (28.4%)	14 (7.9%)	22 (4.3%)	
SLNB[3]	42 (62.7%)	134 (75.3%)	329 (64.9%)	
ALND[4]	6 (9.0%)	29 (16.3%)	152 (30.0%)	
Chemotherapy[*]	0 (0.0%)	17 (9.6%)	46 (9.1%)	0.003

[1]RT=radiation therapy;

[2]IQR=interquartile range;

[3]SLNB=sentinel lymph node biopsy;

[4]ALND=axillary lymph node dissection

[*]Chemotherapy includes Traztuzumab therapy

TABLE 2

Multivariate analysis of overall survival in patients undergoing lumpectomy

Variable	aHR[4]	95% CI[5]	P-value
Primary Site Therapy			
Lumpectomy Alone	Reference		
Lumpectomy with RT[1]	0.72	0.38–1.37	0.31
Age	1.11	1.04–1.18	0.0009
Race			
Caucasian	Reference		
African American	0.86	0.28–2.64	0.80
Other	0.72	0.09–5.82	0.75
Charlson Comorbidity Index Score			
0	Reference		
1	1.51	0.72–3.15	0.27
2+	3.20	1.03–9.94	0.04
Histology			
Ductal Carcinoma	Reference		
Lobular Carcinoma	0.52	0.18–1.46	0.21
Grade			
Well Differentiated	Reference		
Moderately Differentiated	0.94	0.46–1.92	0.87
Poorly Differentiated	2.63	1.05–6.60	0.04
Tumor size	1.19	0.62–2.31	0.60
HER-2 Positive	2.90	0.74–11.4	0.13
Positive Surgical Margins	0.61	0.08–4.75	0.63
Nodal Surgery			
None	Reference		
SLNB[2]	0.64	0.31–1.31	0.22
ALND[3]	0.96	0.36–2.60	0.94
Chemotherapy*	1.27	0.31–5.27	0.74

[1]RT=radiation therapy;

[2]SLNB=sentinel lymph node biopsy;

[3]ALND=axillary lymph node dissection;

[4]aHR=adjusted hazard ratio;

[5]CI=confidence interval

*Chemotherapy includes traztuzumab therapy

TABLE 3

Multivariate analysis of overall survival in all Stage I (T1 N0) male breast cancer patients

Variable	aHR[4]	95% CI[5]	P-value
Primary Site Therapy			
All lumpectomy (alone or with RT[1])	Reference		
Mastectomy	1.28	0.88–1.87	0.20
Age	1.10	1.07–1.13	<0.0001
Race			
Caucasian	Reference		
African American	0.93	0.47–1.84	0.84
Other	0.57	0.21–1.56	0.27
Charlson Comorbidity Index Score			
0	Reference		
1	1.89	1.33–2.67	0.0004
2+	3.36	1.98–5.68	<0.0001
Histology			
Ductal Carcinoma	Reference		
Lobular Carcinoma	0.78	0.39–1.54	0.47
Grade			
Well Differentiated	Reference		
Moderately Differentiated	1.27	0.86–1.89	0.23
Poorly Differentiated	1.53	0.92–2.53	0.10
Tumor size	1.16	0.81–1.66	0.41
HER-2 Positive	1.11	0.49–2.53	0.80
Positive Surgical Margins	1.01	0.24–4.21	0.99
Nodal Surgery			
None	Reference		
SLNB[2]	0.59	0.37–0.95	0.03
ALND[3]	0.62	0.36–1.05	0.08
Chemotherapy[*]	1.16	0.62–2.17	0.64

[1]RT=radiation therapy;

[2]SLNB=sentinel lymph node biopsy;

[3]ALND=axillary lymph node dissection;

[4]aHR=adjusted hazard ratio;

[5]CI=confidence interval

[*]Chemotherapy includes traztuzumab therapy