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Outcomes of curative-intent treatment for breast cancer patients presenting with sternal or mediastinal involvement

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Abstract

Purpose: Optimal treatment of patients diagnosed with *de novo* metastatic breast cancer limited to the mediastinum or sternum has never been delineated. Herein the authors sought to determine the efficacy of multimodality treatment, including metastasis-directed radiotherapy (RT), in curing patients with this presentation.

Methods and Materials: This is a single institution retrospective cohort study of *de novo* metastatic breast cancer patients treated from 2005 – 2014, with a 50 month median follow up for the primary cohort.

The primary patient cohort had metastasis limited to the mediastinum/sternum treated with curative intent (n=35). We also included a cohort of patients with stage IIIC disease treated with curative intent (n=244). Additional groups included a mediastinal/sternal palliative cohort (treatment did not include metastasis-directed RT) (n=14), and all other patients with *de novo* stage IV disease/palliative cohort (n=1185). The primary study outcomes included local-regional recurrence-free, recurrence-free, and overall survival (LRRFS/RFS/OS), calculated using the Kaplan-Meier method. Cox multivariable models compared survival outcomes across treatment cohorts adjusted for molecular subtype, age, and race.

Results: For the mediastinal/sternal curative-intent cohort, five-year LRRFS was 85%, RFS was 52%, and OS was 63%.

After adjustment, there was no statistically significant difference in LRRFS (HR=0.39; 95% CI 0.13-1.13; P=0.08), RFS (HR=0.87; 95% CI 0.50-1.49; P=0.61), or OS (HR=0.79; 95% CI 0.44-1.43; P=0.44) between the stage IIIC cohort and the mediastinal/sternal curative-intent cohort (referent). In contrast, RFS was worse for the mediastinal/sternal palliative cohort (HR=2.29; 95% CI 1.05-5.00; P=0.04). Overall survival was worst for the *de novo* stage IV palliative cohort (HR=2.61; 95% CI 1.50-4.53; P<0.001).

Conclusions: For select patients presenting with breast cancer metastatic to the sternum and/or mediastinum, curative-intent treatment with chemotherapy, surgery, and radiation yields outcomes similar to stage IIIC disease and superior to *de novo* stage IV breast cancer treated with palliative intent.

Keywords

Breast cancer; oligometastasis; radiotherapy; sternum; mediastinum

Introduction

Approximately 6% of newly diagnosed breast cancer patients present with *de novo* stage IV disease¹. Of these, a subset present with oligometastatic disease, commonly defined as distant metastasis limited to 1-4, small volume sites^{2,3}. Five-year disease-free survival is approximately 30-40% among patients with oligometastatic disease undergoing curative-intent treatment^{2,4}. However, at present it is not possible to reliably identify which patients with oligometastatic disease are most likely to benefit from curative-intent therapy.

One unique subset of oligometastatic disease that may particularly benefit from curative-intent therapy are patients whose only site of distant metastasis is the sternum or mediastinal lymph nodes, anatomic locations which are in close proximity to the involved breast and nodal basins, particularly the internal mammary lymph nodes. Given their close proximity, it has been hypothesized that sternal or mediastinal disease may represent an extended form of local-regional disease and thus benefit from curative-intent local-regional management including radiation therapy⁵.

At present, data supporting the hypothesis that patients with *de novo* mediastinal/sternal disease benefit from curative-intent therapy are limited to small case series^{6,7}. Nevertheless, at The University of Texas MD Anderson Cancer Center, we have offered curative-intent therapy to such patients on an *ad hoc* basis. We therefore sought to characterize clinical outcomes for patients with *de novo* mediastinal/sternal disease treated with curative intent at our Institution. We also sought to assess the benefits of curative-intent treatment for these patients by comparing their outcomes to other groups of breast cancer patients, including an anatomic stage IIIC (by virtue of N3c disease) curative-intent cohort, a *de novo* mediastinal/sternal disease palliative-intent cohort, and a *de novo* stage IV palliative-intent cohort.

Methods

Patients

For this retrospective cohort study, patients were identified using a combination of the prospectively maintained Breast Medical Oncology patient database, the MD Anderson Cancer Center radiation oncology treatment record, and a natural language processing-based search of our institutional electronic medical record. The MD Anderson Institutional Review Board approved this study. Initial search criteria included both men and women, ages 18 years old, diagnosed with stage III and IV breast cancer from 2005 to 2014. Patients were

required to have received at least part of their initial treatment, including their curative-intent radiation therapy, at MD Anderson Cancer Center.

De novo mediastinal/sternal metastasis curative-intent cohort.—From the initial search, chart review identified patients presenting with newly diagnosed breast cancer with distant metastasis involving sternum and/or mediastinum. Patients were required to have received radiation therapy to these sites of metastasis with curative intent, defined as a minimum prescription dose of 50 Gy to the metastatic site. Patients also were required to have surgery to the primary site (breast and axilla), as well as chemotherapy (neo-adjuvant and/or adjuvant), in accordance with a curative approach. Patients were excluded if they presented with other concomitant sites of metastatic disease (with the exception of nodal cross-metastasis), experienced an early chest wall recurrence prior to initiation of radiation, were treated with pre-operative radiation, did not undergo surgery to the primary, or were initially treated with extended periods of chemotherapy (> 1 year) prior to local-regional therapy.

Stage IIIC (N3c) curative-intent cohort.—This group comprised patients with any T N3c (supraclavicular) M0 disease undergoing multimodality treatment including systemic chemotherapy, breast and axillary surgery, and curative-intent, post-operative radiation therapy at MD Anderson Cancer Center. Patients in this group typically received radiation to the low neck with a boost to initially involved disease to a prescription dose of 60-66 Gy.

De novo mediastinal/sternal metastasis palliative-intent cohort.—This cohort comprised all other patients with *de novo* mediastinal/sternal metastasis who did not receive curative-intent radiation therapy to the mediastinal and/or sternal metastasis. Of note, while not a formal exclusion criteria, there were no patients in this group whose disease progressed on frontline, standard of care systemic therapy. Supplementary table 1 provides patient-level detail as to treatment approach and potential reasons for exclusion of curative-intent radiation therapy in this patient group.

De novo stage IV palliative-intent cohort.—This cohort comprised patients with *de novo* stage IV disease identified in the Breast Medical Oncology database who did not meet criteria for the above cohorts. Patients in this cohort could have one or more sites of metastatic disease, and any volume of metastatic disease. None of these patients had disease only confined to the sternum or mediastinum. All patients in this cohort received systemic therapy (chemotherapy and/or monoclonal antibodies if indicated) and/or endocrine therapy.

Radiation Treatment

Patients were treated with standard techniques used at our center during the study interval; radiation treatment plans were subjected to peer review as per Departmental policy. Most commonly, patients were treated with three-dimensional conformal radiation techniques (3D-CRT) with lateral photon tangents matched to medial electron field(s). Some patients were treated with intensity modulated radiation therapy (IMRT) or proton therapy based on anatomic considerations and/or attending physician preference.

Outcomes

Survival outcomes included: (1) overall survival (OS) measured from diagnosis date to death; (2) recurrence-free survival (RFS) measured from diagnosis date to first documented recurrence (including local, regional, or distant); (3) local-regional recurrence-free survival (LRRFS) measured from diagnosis date to first documented local or regional recurrence including recurrence in the mediastinum or sternum; and (4) distant metastasis-free survival (DMFS) measured from diagnosis date to first distant metastasis. Patients were censored at loss to follow-up (all outcomes) and death (RFS, LRRFS, and DMFS). Toxicity outcomes included radiation-associated toxicities during and after treatment determined via chart review and coded using the National Cancer Institute Common Toxicity Criteria v4.0.

Statistical Analysis

Survival outcomes were estimated using the Kaplan-Meier method. Because patients in the *de novo* Stage IV palliative-intent cohort typically were never rendered free of disease, only OS was evaluated for this cohort. For the other three cohorts, OS, RFS, LRRFS, and DMFS were measured. Survival outcomes across cohorts were compared using the log-rank test.

Within the *de novo* mediastinal/sternal metastasis curative-intent cohort, predictors of survival outcomes were identified using Cox proportional hazards (PH) multivariable models for each outcome using a backward elimination method to retain variables with p-values less than 0.1. Descriptive statistics summarized radiation-associated toxicity for this cohort as well.

To characterize differences in survival outcomes across cohorts, separate Cox PH models were implemented for each survival outcome, including cohort as the key independent variable. The proportionality assumption was evaluated by visual inspection of the log(-log) plots. Due to limited overlap of variables across these disparate cohorts, we opted to force age (< 50, ≥50), race (white, black, Hispanic, other), estrogen status [ER] (negative, positive), and human epidermal growth factor receptor 2 [HER2] status (negative, positive) into each model.

Statistical analyses were carried out using SAS Version 9.3 (Cary, NC). P-values less than 0.05 were considered statistically significant; all tests were two-sided.

Results

In total, we identified 35 patients in the *de novo* mediastinal/sternal metastasis curative-intent cohort, 244 patients in the stage III (N3c) curative-intent cohort, 14 patients in the *de novo* mediastinal/sternal palliative-intent cohort, and 1185 patients in the *de novo* stage IV palliative-intent cohort. Details regarding demographics, clinical, and treatment characteristics of these cohorts are described in Table 1. Differences were noted in distribution of race, molecular subtype, and local therapy.

De novo mediastinal/sternal metastases curative-intent cohort.

In this cohort, 23 of 35 patients (66%) were treated exclusively with 3D-CRT and 12 of 35 (34%) were treated with advanced radiation modalities such as IMRT or proton therapy. The

median radiation dose to the metastatic site was 60 Gy (range: 50 – 71 Gy). The maximum prescribed radiation dose was 66 Gy for 3D-CRT, 71 Gy for IMRT, and 66 Gy proton therapy. For patients treated with advanced techniques, the majority (83%, n=10/12) were treated with tangent fields to the breast or chest wall, with IMRT or proton therapy used to boost the central metastatic site. All patients received systemic therapy with adjuvant endocrine therapy as indicated. Thirty patients were treated with neoadjuvant chemotherapy, and 5 patients (14%) were treated with adjuvant chemotherapy alone. No patients progressed clinically during neoadjuvant chemotherapy. Only 3 patients (9%) underwent surgery to remove the site of sternal metastasis. No patients underwent surgery to remove mediastinal lymph nodes. Two-thirds of patients (n=23) had internal mammary adenopathy found during staging work-up. Six patients (17%) presented with concomitant cross-metastasis to contralateral nodal basins including the supraclavicular (n=5), internal mammary (n=2), and/or axilla regions (n=1). All patients with involvement of the contralateral axilla underwent axillary dissection. All patients with cross-metastasis received radiation to the involved contralateral nodal basins to a minimum dose of 50 Gy, as part of the curative aim of radiation.

With a median follow up of 50 months (range: 14 – 123 months), 22 patients were alive (63%). The 5-year OS, RFS, LRRFS, and DMFS, were 63%, 52%, 85% and 55%, respectively. In multivariable analyses, type of radiation modality was significantly associated with RFS. Patients treated with IMRT or proton therapy to the metastatic site experienced a 5-year RFS of 74% compared to 41% for those treated with 3D techniques (HR=0.27, 95% CI 0.08-0.99; P=0.048). Additionally, patients without contralateral nodal cross-metastasis experienced 5-year RFS of 60% compared to 17% for those with cross-metastasis (HR=0.22, 95% CI 0.07–0.66; P=0.007). There were no significant patient or treatment characteristics associated with differences in OS, LRRFS, or DMFS, including whether disease was present in the sternum, mediastinum, or both or whether disease extended to the internal mammary lymph nodes. Of note, surgery to remove the site of sternal metastasis did not appear to improve disease control, with 5-year LRRFS of 100% in all patients with sternal disease, regardless of surgical intervention.

Regarding radiation-associated toxicity, there was one grade 3 moist desquamation extending beyond skin folds, 3% (n=1). Grade 2 toxicities were as follows: moist desquamation, 31% (n=11); esophagitis, 14% (n=5); pneumonitis, 6% (n=2); and one emergency room visit due to dehydration, 3% (n=1). There were no grade 4 or 5 toxicities.

Comparison of de novo mediastinal/sternal metastasis curative-intent cohort to other cohorts.

Median follow up was 42 months for the stage IIIC (N3c) curative-intent cohort, 40 months for the *de novo* mediastinal/sternal metastasis palliative-intent cohort, and 26 months for the *de novo* stage IV palliative cohort. In unadjusted analysis, OS, RFS, LRRFS, and DMFS were similar between the stage IIIC (N3c) curative-intent and mediastinal/sternal metastasis curative-intent cohorts and generally worse for patients in the *de novo* mediastinal/sternal palliative-intent and stage IV palliative-intent cohorts (Table 2 and Figure 1).

After adjusting for age, race, ER status, and HER2 status, outcomes for the stage IIIC (N3c) cohort were similar to the mediastinal/sternal curative-intent cohort (referent), as follows: OS (HR=0.79; 95% CI 0.44-1.43; P=0.44), RFS (HR=0.87; 95% CI 0.50-1.49; P=0.61), LRRFS (HR=0.39; 95% CI 0.13-1.13; P=0.08) and DMFS (HR=0.95; 95% CI 0.54-1.68; P=0.87). In contrast, for the mediastinal/sternal palliative-intent cohort compared to the mediastinal/sternal curative-intent cohort (referent), RFS was worse (HR=2.29; 95% CI 1.05-5.00; P=0.04) and LRRFS trended toward worse (HR=3.52; 95% CI 0.97-12.73; P=0.06); there was no significant difference in OS (HR=1.05; 95% CI 0.40-2.78; P=0.92) or DMFS (HR 1.16; 95% CI 0.46-2.89; P=0.76). Overall survival was worst for the *de novo* stage IV palliative cohort (HR=2.61; 95% CI 1.50-4.53; P<0.001) compared to the mediastinal/sternal curative-intent cohort. Results are shown in Table 3.

Discussion

While patients with isolated mediastinal/sternal disease comprise only a small subset of all patients with *de novo* metastatic breast cancer (4% of our stage IV study population), our findings suggest this group is unique with regard to disease natural history when treated aggressively with trimodality therapy including breast/axillary surgery, systemic therapy, and curative-intent radiation. Specifically, the unadjusted five-year recurrence-free survival was 60% for those patients with isolated mediastinal/sternal disease (without nodal cross-metastasis) treated with curative-intent. This outcome is similar to 5-year recurrence-free survival among patients with stage IIIC (N3c) disease (55%) and substantially better than patients with mediastinal/sternal disease not treated with curative intent (14%). Similarly, 5-year overall survival of 63% among the mediastinal/sternal curative-intent cohort was considerably better than patients with *de novo* stage IV disease in both our study (33%) and other published case series⁸⁻¹⁰ and better than a recent series from our institution of patients undergoing curative intent treatment for sternal recurrence (39.5%)¹¹.

The five-year recurrence-free survival of 60% among the curative-intent mediastinal/sternal cohort (without nodal cross-metastasis) in our study compares favorably to other series of patients with oligometastatic stage IV breast cancer treated with curative intent. For example, a modern study from the University of Rochester prospectively enrolled 40 patients with oligometastatic breast cancer (≤ 5 metastatic sites) treated with curative intent systemic therapy, surgery when indicated, and stereotactic body radiation (SBRT)⁴. The most common sites of disease were liver, lung and bone and 71% of patients had 1 – 2 sites. Among this cohort, 5-year progression-free survival was 38%. A more heterogeneous series of 75 patients with oligometastatic breast cancer from Jikei University in Tokyo, Japan reported a five-year relapse-free survival of approximately 45% following treatment with systemic chemotherapy and consolidative surgery and/or radiotherapy among responders³. The numerically superior five-year recurrence-free survival in our cohort of patients with oligometastasis limited to the sternum and/or mediastinum suggests that this unique presentation of oligometastatic breast cancer may confer a better prognosis.

To account for this empiric observation, we hypothesize that sternal and mediastinal metastases typically arise from direct tumor seeding via lymphatic channels connected to an involved internal mammary nodal basin^{5,12}. This hypothesis is supported by the observation

that 66% of the patients in the *de novo* mediastinal/sternal metastases curative-intent cohort had radiographic evidence of internal mammary nodal involvement, much higher than the overall prevalence of internal mammary involvement in node-positive breast cancer. The implication of this hypothesis is twofold. First, patients with lymphogenous rather than hematogenous metastasis would be expected to experience a lower risk of hematogenous distant metastasis elsewhere in the body. And second, such patients would be more likely to benefit from extended local therapy to eradicate all sites of disease. From a practical standpoint, the proximity of these disease sites allows for relatively straightforward inclusion of the areas in radiation post-operative volumes, with very little in the way of added toxicities.

Two decades ago, a paradigm shift emerged with regard to classification and treatment of ipsilateral supraclavicular disease. In the American Joint Committee on Cancer (AJCC) 5th edition staging manual, ipsilateral supraclavicular nodal disease was classified as M1 disease ¹³. However, a study of 70 patients from MD Anderson Cancer Center reported that patients with ipsilateral supraclavicular disease treated with curative-intent including radiation therapy experienced survival similar to stage IIIB patients ¹⁴. Based on these findings, the AJCC staging system reclassified ipsilateral supraclavicular nodal metastases from M1 to N3c disease in the 6th edition ¹⁵. The aggressive treatment of these patients (and their improved disease outcomes) has undoubtedly led to long-term survival of many patients who at one point were deemed incurable.

Regarding sternal metastases specifically, the available published literature addressing local treatment is mostly surgical in nature ^{7,16}. Surgical resection of the sternum requires expert technical skill, reconstruction, and prolonged recovery versus radiation to the sternum, which confers less morbidity ^{16,17}. A small retrospective study of 8 patients with sternal metastases from breast cancer included one patient who remained disease free for 7 years following systemic therapy and definitive radiation ⁶. Our case series extends this anecdotal data, revealing that definitive sternal radiation conferred 100% sternal control, regardless of the incorporation of surgical resection.

Our finding of superior RFS for patients treated with IMRT or proton therapy was unexpected. Generally, these patients were treated more recently in our experience, and thus could have benefitted from potential confounders such as growing expertise in our practice and improvements in imaging and target delineation. Supporting this hypothesis is the trend toward improved LRRFS for patients treated with IMRT or proton therapy versus 3D, as the LRRFS was 100% vs. 78%, respectively ($p = 0.25$). An alternative explanation is that the higher degree of conformality facilitated by IMRT or proton therapy may have facilitated modest dose escalation, which may be beneficial when treating sternal or mediastinal disease. Further research will be needed to elucidate this finding.

Our study has several limitations. Most significant, selection bias could have influenced the decision for curative vs. palliative treatment of patients with mediastinal/sternal disease and biased outcomes in favor of the curative-intent group. While we cannot exclude this possibility, it is worth noting that 10 of 14 patients in the *de novo* mediastinal/sternal metastasis palliative-intent cohort were actually offered curative-intent surgery, suggesting

that extent of disease, or lack of response to systemic therapy, was not the primary motivating factor for a palliative approach. Further, because 71% (35/49) of patients with mediastinal/sternal disease in our cohort did receive curative treatment, findings of benefit of curative-intent therapy should be generally applicable to most patients with this disease presentation. Another limitation is the small sample size, reflecting that isolated mediastinal or sternal involvement is a rare presentation of breast cancer. This small sample size limited statistical power to measure certain differences between cohorts. Nevertheless, we were still able identify statistically significant differences in outcomes between cohorts, and providing this data is crucially important for those patients afflicted with this unusual presentation. Further, to the best of our knowledge, this is the largest case series of patients presenting with *de novo* sternal or mediastinal disease treated with curative intent.

In our current practice, we offer curative-intent combined modality therapy to patients presenting with *de novo* sternal and/or mediastinal disease who do not demonstrate progressive clinical or radiographic disease after neoadjuvant chemotherapy. Most commonly, patients undergo appropriate breast surgery (lumpectomy or mastectomy) and appropriate axillary surgery (most commonly axillary lymph node dissection) followed by comprehensive radiation therapy with a dose of 50 Gy in 25 fractions to the breast/chest and the following nodal basins: undissected axilla, infraclavicular, supraclavicular, and internal mammary (most commonly the first three interspaces). For those with mediastinal involvement, the radiographically abnormal nodes are included. All targeted nodal basins receive a minimum dose of 45 Gy in 25 fractions. For patients with sternal disease, the gross tumor volume is also treated, typically with a 2 cm in-bone expansion to define the clinical target volume to receive 50 Gy. A boost is then delivered to all nodal/bone areas that are unresected. Boost doses are 10 Gy in 5 fractions for areas demonstrating a radiographic complete response and 16 Gy in 8 fractions for areas demonstrating a radiographic partial response. A variety of treatment techniques are evaluated, including partially wide tangents, electron-photon technique, proton therapy, and IMRT/VMAT. The technique that offers optimal lung and heart sparing is chosen, with a goal of keeping the mean heart dose less than 5 Gy and the ipsilateral lung V20 less than 35% on the composite plan.

In summary, our data suggest that patients with mediastinal or sternal disease treated with curative-intent, trimodality therapy experience 5-year recurrence-free survival approaching that of patients with stage IIIC (N3c) disease and better than patients presenting with *de novo* stage IV disease. We strongly advocate for curative-intent therapy in such patients, provided they are treated by radiation oncologists who can safely deliver radiotherapy to all sites of involved disease. We recommend that AJCC staging nomenclature (i.e. re-formatting to “Stage IV M/S”) and tumor registry extent of disease codes be updated to capture this unusual and unique presentation of breast cancer, which would allow future studies to evaluate such patient’s outcomes and validate the findings presented herein.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Summary:

Optimal treatment for patients with *de novo* metastatic breast cancer limited to the mediastinum/sternum has not been defined. We examine a cohort of patients treated with curative intent using chemotherapy, breast/axillary surgery, and metastasis directed radiotherapy, and compare these outcomes to other patient groups (including stage III and other *de novo* stage IV patients). Trimodality treatment, including metastasis-directed radiation, may be curative in *de novo* metastatic breast cancer involving the sternum/mediastinum.

Figure 1: Oncologic outcomes for the four cohorts

Overall survival curves for all four cohorts included in the study. Distant metastasis free survival, local regional recurrence free survival, and relapse free survival curves shown for mediastinal/sternal curative intent, mediastinal/sternal palliative intent, and stage IIIc cohorts.

Abbreviations: M/S, Mediastinal/Sternal.

Table 1:

Baseline Demographic, Clinical, and Treatment Characteristics

	M/S Curative Intent [n=35]	M/S Palliative [n=14]	Stage IIIC (N3c) [n=244]	Stage IV Palliative [n=1185]	p
	N (%)	N (%)	N (%)	N (%)	
Age					
< 50	18 (51)	3 (21)	105 (43)	433 (36)	0.05
≥ 50	17 (49)	11 (79)	139 (57)	752 (64)	
Race					
White	24 (67)	9 (65)	148 (61)	828 (70)	0.04
Black	4 (11)	2 (14)	36 (15)	170 (14)	
Hispanic	3 (9)	1 (7)	40 (16)	134 (11)	
Other	4 (11)	2 (14)	20 (8)	53 (5)	
cT Category					
T0-2	13 (37)	4 (29)	102 (42)	454 (38)	0.95
T3	5 (14)	2 (13)	36 (15)	161 (14)	
T4a,b,c	7 (20)	4 (29)	54 (22)	228 (19)	
T4d	10 (28)	4 (29)	46 (19)	208 (18)	
Unknown [†]	-	-	6 (2)	134 (11)	
Subtype					
ER/PR positive, HER2 negative	16 (46)	10 (72)	66 (27)	443 (37)	<0.001
HER2 positive	13 (37)	1 (7)	82 (34)	272 (23)	
Triple negative	6 (17)	3 (21)	29 (12)	116 (10)	
Unknown [†]	-	-	57 (23)	354 (30)	
Surgery					
BCS	7 (20)	1 (7)	47 (19)	126 (10)	0.02
Mastectomy	28 (80)	6 (43)	194 (80)	292 (25)	
None	0	7 (50)	-	-	
Unknown [†]	-	-	3 (1)	767 (65)	
Metastectomy					
Yes	3 (9)	0	NA	NA	0.55
No	32 (91)	14 (100)			
Radiation Technique (to metastatic site)					
3D	23 (66)	NA	NA	NA	NA
IMRT	6 (17)				
Proton	6 (17)				

Abbreviations: BCS, breast conserving surgery; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; IMRT, intensity modulated radiation therapy.

[†]“Unknown” variables were not included in chi-squared analysis.

Table 2:

Unadjusted 5-year OS, RFS, DMFS, and LRRFS estimates

	5 year estimate (95% CI)				P
	M/S Curative [n=35]	M/S Palliative [n=14]	Stage IIIC (N3c) [n=244]	Stage IV Palliative [n=1185]	
OS	63 (44 – 77)	51 (21 – 75)	66 (58 – 72)	33 (29 – 36)	<0.001
RFS	52 (34 – 68)	14 (2 – 37)	55 (47 – 62)	NA	<0.001
LRRFS	85 (68 – 93)	52 (23 – 75)	93 (88 – 96)	NA	<0.001
DMFS	55 (36 – 70)	40 (12 – 67)	57 (50 – 64)	NA	0.81

Abbreviations: NA, not applicable; OS, overall survival; RFS, recurrence free survival; DMFS, distant metastasis free survival; LRRFS, local-regional recurrence-free survival

Table 3:

Adjusted Cox Proportional Hazards Models for OS, RFS, DMFS, LRRFS for all cohorts.

	Hazard Ratio (95% CI)							
	OS		RFS		LRRFS		DMFS	
		p		p		p		p
M/S curative intent	1		1		1		1	
M/S palliative intent	1.05 (0.40 – 2.78)	0.92	2.29 (1.05 – 5.00)	0.04	3.52 (0.97 – 12.73)	0.06	1.16 (0.46 – 2.89)	0.76
Stage IIIc / N3c	0.79 (0.44 – 1.43)	0.44	0.87 (0.50 – 1.49)	0.61	0.39 (0.13 – 1.13)	0.08	0.95 (0.54 – 1.68)	0.87
De novo stage IV palliative	2.61 (1.50 – 4.53)	<0.001	NA		NA		NA	

Abbreviations: M/S, Mediastinal/Sternal.

Adjusted for age, race, ER status, and HER2 status