Malignant Phyllodes Tumor of the Female Breast

Association of Primary Therapy With Cause-Specific Survival From the Surveillance, Epidemiology, and End Results (SEER) Program

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BACKGROUND. Malignant phyllodes tumor is a rare and potentially aggressive breast neoplasm. Little information is available regarding the optimal management of these lesions and rarer still are data regarding survival. The current study used a large population database to determine prognostic factors that predict cause-specific survival (CSS).

METHODS. Data were obtained from the Surveillance, Epidemiology, and End Results Program (SEER) for the years 1983–2002. Women receiving resection for primary nonmetastatic malignant phyllodes tumor of the breast were included ($n = 821$). Analyses of patient, pathologic, and treatment characteristics were performed using univariate and multivariate Cox regression analyses for the CSS endpoint.

RESULTS. With a median follow-up of 5.7 years, CSS was 91%, 89%, and 89%, at 5, 10, and 15 years, respectively. Mastectomy was performed in 428 women (52%) and wide excision or lumpectomy in 393 (48%). Women undergoing mastectomy were significantly older ($P = .004$) and had larger tumors ($P = .009$). Wide excision was associated with equivalent or improved CSS relative to mastectomy on univariate and multivariate analyses. Older age predicted for cause-specific mortality on multivariate analysis. Adjuvant radiotherapy (RT) predicted for worse CSS when implemented compared with surgery alone.

CONCLUSIONS. Mastectomy was not found to provide a benefit in CSS compared with wide excision in malignant phyllodes tumor of the breast. Women undergoing wide excision had at the minimum similar cancer-specific mortality compared with those who received mastectomy. The role of adjuvant RT is uncertain and requires further investigation. ***Cancer*** **2006;107:2127–33.** © *2006 American Cancer Society.*

KEYWORDS: phyllodes tumor, surgery, breast sarcoma, adjuvant therapy, malignant.

Phyllodes tumor (*cystosarcoma phyllodes*)[1] of the breast is a rare fibroepithelial lesion that accounts for less than 1% of all primary breast neoplasms.[2–4] Previously reported Surveillance, Epidemiology, and End Results (SEER) data estimate the average annual incidence of malignant phyllodes tumor to be 2.1 cases per million women.[5] The term phyllodes tumor[6] represents a broad range of fibroepithelial diseases spanning from benign, relatively indolent tumors to malignant neoplasms capable of rapid disease progression and distant spread. In 1981 the World Health Organization adopted the term phyllodes tumor and subclassified them histologically as benign, borderline, or malignant. The majority of phyllodes tumors have been described as benign (35% to 64%), with the remainder divided between the borderline and malignant subtypes.[7,8]

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Generally, phyllodes tumor presents as a rapidly growing and clinically benign breast lump in females within the fourth or fifth decade of life.[3,4]

Malignant phyllodes tumor of the breast, as opposed to its benign counterpart, can be characterized by an unusually aggressive course and has been reported to recur locally and have the capacity for distant metastasis.[3,9] A recent comprehensive review of the English literature found that the malignant subtype is found in approximately 25% of resected phyllodes tumors.[3] Mastectomy has been the standard surgical approach for treating phyllodes tumors,[10,11] but the current literature has suggested that wide excision with adequate negative surgical margins can be sufficient even in malignant disease.[2,4,7,8,12–18] The recent trend toward breast conservation has had a variable impact on the risk of local recurrence (reported as 20%–30% for malignant tumors),[3,8,16,17] without an apparent adverse effect on overall survival.[2–14,16,17]

The majority of reports within the contemporary literature contain series consisting of heterogeneous histologic subtypes with only a minority of malignant tumors included. In addition to being composed of small numbers of patients, these studies generally evaluate for predictors of local and distant disease recurrence and have not reported overall or cause-specific survival (CSS). As phyllodes tumor is a rare breast neoplasm and the malignant subtype accounts for an even smaller number of tumors, little information is available concerning overall and cancer-specific survival after diagnosis and primary management.

The current study utilizes a population database supported by the National Cancer Institute of the US to analyze a large series of women treated for malignant phyllodes tumor of the breast. The primary objective of this analysis was to identify clinical and pathologic factors that predict for cause-specific death, evaluate the role of adjuvant radiotherapy relative to the survival endpoint, and define a subgroup of women at greatest risk of cause-specific death for whom surgery alone may not be adequate initial therapy.

MATERIALS AND METHODS

Data for these analyses were obtained from the National Cancer Institute's (NCI) SEER program using the SEER 11-Registries plus Alaska 1973–2002 dataset (November 2003 edition).[19] SEER is comprised of a set of geographically defined, population-based, central cancer registries in the US and is operated by local nonprofit organizations under contract with the NCI. The SEER database is a composite of cancer registry data from Connecticut, Iowa, Hawaii, New Mexico, Utah, metropolitan areas (Atlanta, Detroit, Los Angeles, Oakland, San Francisco, San Jose-Monterey, Seattle-Puget Sound), and Alaska Native populations. In general, the populations covered by SEER are known to be representative of the US as a whole regarding socioeconomic status and education level.[20]

The women deemed eligible for inclusion underwent resection for primary nonmetastatic malignant phyllodes tumor (ICD 9020/03) of the breast between 1983 and 2002. The behavior code "/03" refers to the malignant subtype and this identifier was verified to be present for all women included in this series. The following clinical and pathologic factors were collected from the database: age at diagnosis, race, year of diagnosis, ICD-0-3 code, behavior code, location of primary tumor within the breast, breast laterality (right or left breast), tumor size, primary surgical procedure (mastectomy or wide excision), and whether adjuvant external beam radiotherapy (RT) was delivered. Data on known prognostic variables including lymph node status and tumor hormone receptor status were collected but not included in the analysis owing to incomplete recording within the SEER program and are provided as information only. Vital status including cause of death and the duration of follow-up were recorded. Participants in the SEER program routinely link patient files with vital records (i.e., death certificates) in their respective areas of coverage to identify cancer patients that have died. Furthermore, the National Center for Health Statistics conducts routine reviews of death certificates to ensure quality of data.[20] The analyzed cohort consists of 821 women with a minimum of 1-year follow-up.

CSS was estimated using the Kaplan–Meier method and significance was determined by the log rank test.[21] Univariate and multivariate Cox proportional hazards regression analyses were conducted to study the association between the various prognostic factors and the CSS endpoint.[22] The rates of CSS were measured from the date of diagnosis to either the recorded date of death due to breast malignancy or the date of last contact. SEER StatVersion 6.1.4 was used to extract case level data from the SEER Cancer 11 Public-Use Database, 1973–2002, November 2003 submission. Statistical significance was declared for $P < .05$.

RESULTS

The median age at diagnosis of the 821 women was 50 years (range, 12–92 years). The median follow-up

TABLE 1
Patient, Tumor, and Treatment Characteristics by Age Category

	Age < 50 y (n = 382) no. (%)	Age 50–59 y (n = 207) no. (%)	Age 60–69 y (n = 117) no. (%)	Age ≥70 y (n = 115) no. (%)	Total (n = 821) no. (%)
Ethnicity					
Black	46 (12)	18 (9)	11 (9)	7 (6)	82 (10)
Other	60 (16)	31 (15)	12 (10)	6 (5)	109 (13)
White	276 (72)	158 (76)	94 (81)	102 (89)	630 (77)
Year of diagnosis					
1980–1989	86 (23)	42 (20)	37 (32)	23 (20)	188 (23)
1990–1999	233 (61)	128 (62)	69 (59)	70 (61)	500 (61)
2000–2002	63 (16)	37 (18)	11 (9)	22 (19)	133 (16)
Site of primary tumor					
UOQ	95 (25)	65 (31)	34 (29)	33 (29)	227 (28)
UIQ	28 (7)	9 (4)	9 (8)	9 (8)	55 (7)
LOQ	23 (6)	14 (7)	7 (6)	6 (5)	50 (6)
LIQ	15 (4)	8 (4)	2 (2)	4 (3)	29 (3)
Overlap	193 (51)	97 (47)	53 (45)	54 (47)	397 (48)
Central	28 (7)	14 (7)	12 (10)	9 (8)	63 (8)
Laterality					
Left	196 (51)	115 (56)	63 (54)	63 (55)	437 (53)
Right	186 (49)	92 (44)	54 (46)	52 (45)	384 (47)
Size of primary tumor					
<5 cm	165 (43)	96 (46)	49 (42)	56 (49)	366 (44)
≥5 cm	124 (33)	64 (31)	33 (28)	31 (27)	252 (31)
Unknown	93 (24)	47 (23)	35 (30)	28 (24)	203 (25)
Estrogen receptor status (n = 107)*					
Positive	6 (15)	3 (9)	4 (27)	9 (45)	22 (21)*
Negative	33 (85)	30 (91)	11 (73)	11 (55)	85 (79)*
Lymph node status (n = 498)*					
N0	219 (57)	136 (66)	70 (59)	65 (57)	490 (60)
N1	3 (1)	1 (<1)	3 (3)	1 (<1)	8 (1)
Unknown	160 (42)	70 (34)	44 (38)	49 (43)	323 (39)
Surgery					
Wide excision	209 (55)	88 (43)	48 (41)	48 (42)	393 (48)
Mastectomy	173 (45)	119 (57)	69 (59)	67 (58)	428 (52)
Adjuvant therapy					
EBRT	33 (9)	23 (11)	12 (10)	8 (7)	76 (9)
None	349 (91)	184 (89)	105 (90)	107 (93)	745 (91)
Surgery ± adjuvant therapy					
Mastectomy	154 (40)	106 (51)	61 (52)	64 (56)	385 (47)
Mastectomy + EBRT	19 (5)	13 (6)	8 (7)	3 (3)	43 (5)
Wide excision	195 (51)	78 (38)	44 (38)	43 (37)	360 (44)
Wide excision + EBRT	14 (4)	10 (5)	4 (3)	5 (4)	33 (4)
Median follow-up					
Years	6.00	5.9	6.7	4	5.7
Range, y	1–20	1–20	1–19	1–19	1–20
Alive	341 (89)	176 (85)	90 (77)	57 (50)	664 (81)
Dead	41 (5)	31 (15)	27 (23)	58 (50)	157 (19)
Died of disease	24 (59)†	17 (55)†	12 (44)†	19 (33)†	72 (46)†

UOQ indicates upper outer quadrant; UIQ, upper inner quadrant; LOQ, lower outer quadrant; LIQ, lower inner quadrant; EBRT, external beam radiotherapy.

* Limited patient data available.

† Percentage of deaths due to disease compared with total deaths.

period was 5.7 years (range, 1–20 years). Table 1 details the patient, tumor, and treatment characteristics of the analyzed cohort by age. The majority of women were treated in the decade 1990–1999 (n = 500), with fewer treated in the period 1983–1989 (n = 188) and in the first few years of the current decade (2000–2002, n = 133). Mastectomy was performed on a total of 428 (52%) women, and wide excision or lumpectomy in 393 (48%). A significant increase in the use of wide excision or breast conservation com-

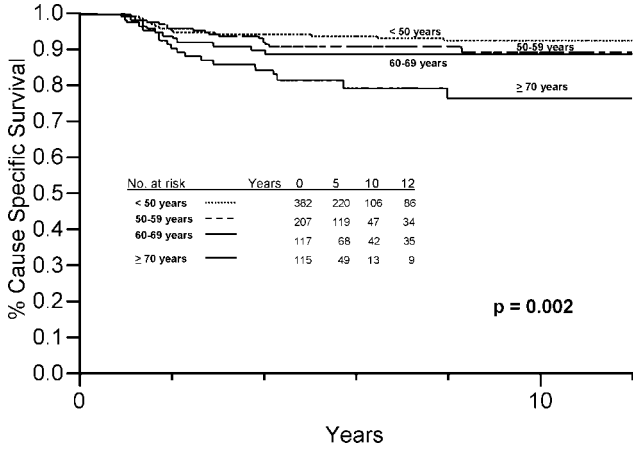

FIGURE 1. Estimated cause-specific survival adjusted for age category (<50, 50−59, 60−69, ≥70 years).

pared with mastectomy was observed for the current decade compared with the prior 2 (56% vs. 48% vs. 41%, for 2000–2002 vs. 1990–1999, vs. 1988–1989, respectively; $P = .02$ on chi-square analysis). Adjuvant RT was administered in 76 women (9%) and was more frequently used in the recent decades (12% vs. 11% vs. 4%, for 2000–2002 vs. 1990–1999, vs. 1988–1989, respectively; $P = .004$ on chi-square analysis).

The estimated 5-, 10-, and 15-year rates of CSS for all women were 91%, 89%, and 89%, respectively. The median CSS has not yet been reached. The rates of overall survival for the same time periods were 84%, 77%, and 73%, respectively. A total of 157 deaths occurred at a median 2.7 years (range, 1–19 years) from diagnosis. Death due to recurrent or progressive breast disease was recorded in 72 (46%) women at a median 1.8 years (range, 1–8 years) from diagnosis. Nineteen (12%) deaths occurred because of nonbreast malignancies. CSS adjusted for age at diagnosis is presented in Figure 1.

The results of the univariate analysis are presented in Table 2. Factors that were significantly associated with improved CSS on univariate analysis included younger age, tumor size <5 cm, and wide excision without adjuvant RT. On multivariate analysis, predictors for improved CSS (Table 2) included younger age ($P = .01$) and wide excision alone compared with wide excision plus RT and mastectomy with or without RT ($P = .0001$).

Analysis of the subset of women undergoing mastectomy compared with wide excision was performed to analyze the patterns of care for these patient subgroups. Women who received mastectomy were significantly more likely to have larger tumors—56% had a tumor >5 cm compared with 32% in the wide excision group ($P = .009$, by chi-square analysis). In addition, these women were relatively older—32% were ≥60 years old compared with 24% in the wide excision group ($P = .004$). Kaplan–Meier plots of tumor size adjusted for surgical procedure are presented in Figure 2. Wide excision significantly associated with improved CSS for tumor size <5 cm and >5 cm compared with other treatment approaches.

TABLE 2
Unadjusted and Adjusted Hazard Ratio (HR) for Cause-Specific Survival in 821 Women

			Univariate analysis		Multivariate analysis	
Variable	No.	No. (%) CSD*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age, y						
<50	382	24 (6)	Reference		Reference	
50–59	207	17 (8)	0.84 (0.5–1.2)	.007	0.7 (0.4–1.1)	.01
60–69	117	12 (10)	0.99 (0.6–1.5)		1.0 (0.5–1.7)	
>70	115	19 (17)	1.9 (1.3–2.8)		2.2 (1.3–3.4)	
Race						
White	630	58 (9)	Reference		Reference	
Black	82	9 (11)	1.5 (0.8–2.5)	.17	1.7 (0.9–3.1)	.19
Other	109	5 (5)	0.6 (0.3–1.0)		0.6 (.3–1.1)	
Year of diagnosis						
2000–2002	133	6 (5)	Reference		Reference	
1990–1999	500	43 (9)	0.9 (0.6–1.3)	.68	0.9 (0.6–1.4)	.81
1983–1989	188	23 (12)	1.1 (0.7–1.7)		1.1 (0.6–2.0)	
Tumor location						
UOQ	227	24 (11)	Reference		NA	
UIQ	55	2 (4)	0.5 (0.1–1.5)	.52		
LOQ	50	3 (6)	0.9 (0.3–2.3)			
LIQ	29	2 (7)	1.0 (0.2–2.9)			
Overlap	398	37 (9)	1.4 (0.9–2.4)			
Central	63	4 (6)	0.9 (0.3–2.1)			
Size of primary tumor						
<5 cm	366	24 (7)	Reference		Reference	
≥5 cm	252	27 (11)	1.8 (1.1–3.1)	.04	1.5 (0.8–2.7)	.18
Surgery ± adjuvant therapy						
Mastectomy	385	43 (11)	Reference		Reference	
Mastectomy + EBRT	43	12 (28)	2.8 (1.6–4.6)	<.0001	2.7 (1.5–4.8)	<.0001
Wide excision	360	13 (4)	0.3 (0.2–0.5)		0.3 (0.1–0.5)	
Wide excision + EBRT	33	4 (12)	1.2 (0.5–2.4)		1.6 (0.6–3.3)	

CI indicates confidence interval; CSD, cause-specific death; NA, not analyzed; UOQ, upper outer quadrant; UIQ, upper inner quadrant; LOQ, lower outer quadrant; LIQ, lower inner quadrant; EBRT, external beam radiotherapy.

* Percentage refers to the ratio of women dying because of disease to total women in that subcategory.

DISCUSSION

Malignant phyllodes tumor of the breast is an unpredictable disease entity that remains enigmatic owing to its relative rarity. This analysis of 821 women from

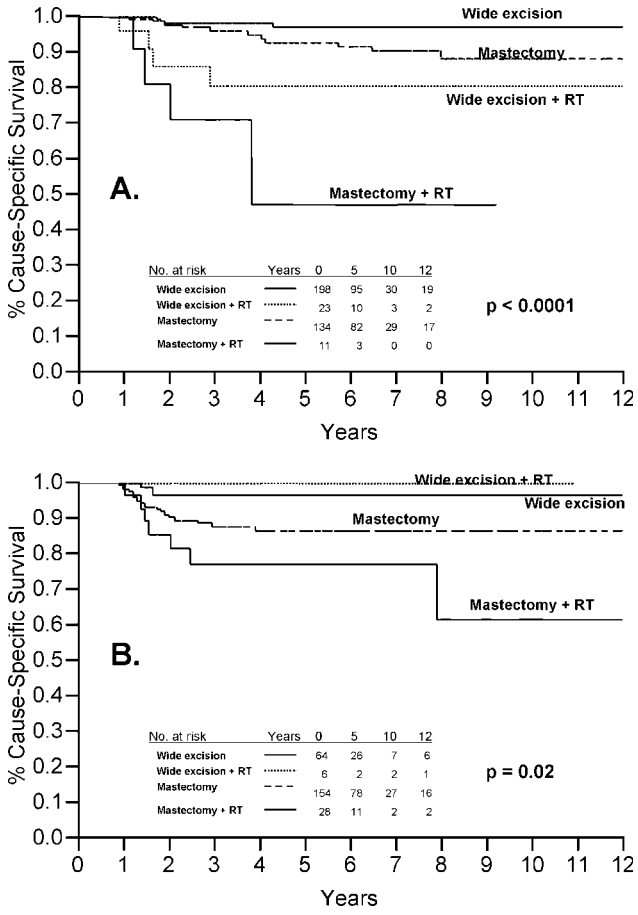

FIGURE 2. Estimated cause-specific survival by tumor size adjusted for treatment approach. (A) Tumor $<$ 5 cm. (B) Tumor $\geq$ 5 cm.

a large observational database maintained by the NCI represents the largest reported series to date of this rare breast malignancy. Despite the potential for locally aggressive growth and distant disease spread, this analysis reveals that women with malignant phyllodes tumor of the breast can enjoy a relatively optimistic prognosis regarding cause-specific and overall survival after initial surgical management. This analysis did not find a significant detriment in cause-specific death for breast conservation (wide excision) compared with mastectomy. Based on the SEER data, physicians within the US advocated mastectomy more in prior decades and in older women with larger or locally aggressive tumors. Adjuvant RT was determined to associate with poorer disease outcomes, although only a minority of women in this series received additional therapy after primary surgery.

Malignant phyllodes tumor, although referenced by the misnomer "sarcoma," is not a particularly lethal neoplasm relative to other malignant breast and true sarcomatous tumors. An earlier epidemiologic review of cystosarcoma phyllodes of the breast estimated a 5-year survival rate of 80% after surgery.[9] Our results are consistent with the former report; we report a 5-year overall survival rate of 84% and CSS of 91%. In this series there is little decrement in those rates at 10 years—overall survival is 77% with 89% CSS. A recent report from the M. D. Anderson Cancer Center on a subset of 30 women with the malignant histological subtype (of a total 101 woman) estimated 5- and 10-year survival rates of 79% and 42%, respectively.[4] The variation between these reports may be because of the finding that overall survival alone was estimated in their report, an endpoint that is potentially confounded by comorbidities and patient characteristics that are considered and adjusted for when evaluating cause-specific death.

Historically, some have espoused the need for extensive surgery for more aggressive or larger tumors,[2,8,23,24] although recent reports indicate no significant difference in survival outcomes with wide excision compared with mastectomy[3,4,7–9,12,16–18,25] in the primary treatment setting. Higher local recurrence rates have been reported with conservative excision compared with mastectomy, but thus far the increase in local recurrence has not appeared to translate into a decrement in survival.[7–9,12,13,16,18] Optimal surgical therapy aims at complete excision of tumor with margin. This objective is achieved with either mastectomy or lumpectomy and depends on the size of the tumor and surrounding breast parenchyma. The favorable rates of CSS demonstrated in this series of women with wide excision alone substantiates the available literature and serves to solidify the observational evidence that complete removal of the breast tissue for malignant phyllodes tumor is not necessary if a woman meets the criteria for breast conservation. Extensive surgery, or mastectomy, for women with large tumors or poorer disease characteristics who are still candidates for breast conservation should be reconsidered and prospectively studied in light of this growing body of evidence. Unfortunately, this series is unable to provide information regarding the risk of local recurrence after wide excision because of the limitations of the SEER database.

Interestingly, this analysis revealed a significant benefit in CSS favoring women undergoing more conservative surgery in the unadjusted and adjusted Cox regression analyses. Additionally, evaluation of primary surgery with or without adjuvant RT when grouped by tumor size revealed significantly improved CSS among those who underwent breast conservation, suggesting that at the minimum, wide

excision is equivalent to mastectomy as they relate to CSS. Thus, larger tumors can be effectively removed with wide excision (assuming all other criteria for breast conservation are met) without jeopardizing a women's risk of cancer-specific death.

We recognize that this analysis is observational in nature and is subject to the biases inherent in retrospective data collection, including initial physician bias, recording bias, and selection bias. Furthermore, SEER reports a 97.5% ascertainment at all the participating sites, and the composite of these represent approximately 10% of the US population. In addition, important clinical and pathologic data that have previously been reported to have prognostic significance, including the presence of stromal overgrowth, tumor necrosis, margin status, lymph node status, histologic subtype, hormone receptor status, and specifics of the surgical and radiotherapy procedures, are not available or are incomplete within the SEER record. Tumor grade was not included; eligible women were identified by the behavior code representing malignant disease. The clinical reasoning for mastectomy versus wide excision is also not available. SEER does not contain data on local or distant failures, information that would be necessary to determine event-free survival or for conclusions regarding patterns of failure. Despite these shortcomings, these results suggest that treatment recommendations should be tailored to the individual patient insofar as CSS outcomes are equivalent regardless of the extent of primary surgery.

Various reports in the literature have suggested that stromal overgrowth, surgical margin status, tumor necrosis, and histologic subtype predict for local or distant recurrence after primary surgery.[4,7,13,14,26] Multivariate analysis in this series of women revealed that older age predicted for poorer CSS in addition to the treatment approach. To our knowledge, this is the first analysis to identify independent predictors of cancer-specific death in women with malignant phyllodes tumor of the breast.

The use of adjuvant RT appears to be increasing in recent years based on the SEER program, but its efficacy is debatable. Only a few reports have suggested a benefit from additional therapy after surgery,[15,24,27,28] a benefit that is reported as a decrease in local recurrence.[15,28] Our study was unable to evaluate the effect of RT on local recurrence due to the lack of this information within the SEER program. Adjuvant RT was an independent predictor for worse CSS on unadjusted and adjusted analyses, but few women in this series received adjuvant RT, which dramatically underpowers this analysis. Furthermore, definitive conclusions regarding RT should be guarded because the specifics of therapy are unavailable and information regarding the adequacy and quality of RT are indeterminate. A current, prospective Phase II study of adjuvant RT after resection in patients with borderline or malignant phyllodes tumors of the breast has been ongoing since 1998 and is designed to analyze recurrence rates and survival for women who receive breast conservation surgery followed by RT.

Malignant phyllodes tumor of the breast is an unpredictable and sometimes aggressive neoplasm. Complete surgical removal of the involved breast was not determined to be necessary and did not confer a benefit in CSS in this large population-based series of women relative to wide excision. Older age and the primary therapeutic approach were found to independently predict for CSS. As the largest population-based analysis to date, these results question the role of mastectomy in women who are candidates for breast conservation. Adjuvant therapies, including the role of RT, should be more carefully investigated so that treatment approaches can be tailored to the individual patient.

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