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A Prospective, Multi-Institutional Study of Adjuvant Radiotherapy After Resection of Malignant Phyllodes Tumors

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Abstract

Background—Malignant phyllodes tumors of the breast are unusual neoplasms, with an incidence of approximately 500 cases annually in the United States. Published local recurrence rates after margin-negative breast-conserving resections of borderline malignant and malignant phyllodes tumors are unacceptably high, at 24 and 20%, respectively. It is uncertain whether radiotherapy after resection of phyllodes tumors is beneficial.

Methods—We prospectively enrolled patients who were treated with a margin-negative breast-conserving resection of borderline malignant or malignant phyllodes tumors to adjuvant radiotherapy. The primary endpoint was local recurrence.

Results—Forty-six women were treated at 30 different institutions. The mean patient age was 49 years (range, 18–76 years). Thirty patients (65%) had malignant phyllodes tumors; the rest were borderline malignant. The mean tumor diameter was 3.7 cm (range, .8–11 cm). Eighteen patients had a negative margin on the first excision. The median size of the negative margin was .35 cm (range, <.1–2 cm). Twenty-eight patients underwent a re-excision because of positive margins in the initial resection. Two patients died of metastatic phyllodes tumor. During a median follow-up of 56 months (range, 12–129 months), none of the 46 patients developed a local recurrence (local recurrence rate, 0%; 95% confidence interval, 0–8).

Conclusions—Margin-negative resection combined with adjuvant radiotherapy is very effective therapy for local control of borderline and malignant phyllodes tumors. The local recurrence rate with adjuvant radiotherapy was significantly less than that observed in reported patients treated with margin-negative resection alone.

According to the Surveillance, Epidemiology, and End Results Program (SEER) 17 data registry from 2000 to 2004, approximately 500 women are diagnosed annually in the United States with a malignant phyllodes tumor of the breast.¹ These tumors manifest in young women (median age, 45 years), tend to be large in size (4–5 cm), and metastasize in 10–30% of patients.^{2–5} Mastectomy is commonly performed (and is sometimes required for very

large tumors), obtaining local control in 90% of patients.⁶ In recent years, SEER data indicate that approximately 50% of women with malignant phyllodes tumors are being treated with breast-conserving surgery.^{1,5} However, in 1998, at the time the current study was initiated, we performed a review of the literature that indicated that after a wide local excision, local recurrences developed in a high proportion of patients with malignant (35%) and borderline malignant (29%) phyllodes tumors.⁶

Our aim was to evaluate in a prospective study whether the addition of adjuvant radiation after breast-conserving resection of malignant and borderline malignant phyllodes tumors would decrease the rate of local recurrence.

PATIENTS AND METHODS

Women 18 years of age were eligible for enrollment if they met the following criteria.

First, histologic proof of phyllodes tumor of borderline or malignant grade was assessed according to World Health Organization criteria.⁷ This assessment was as follows: borderline malignant, 5–9 mitoses/10 high-power fields, pushing or infiltrating margins, 2+ (moderate) stromal cellularity and atypia; and malignant, 10 or more mitoses/10 high-power fields, predominantly infiltrating margins, usually 3+ (severe) stromal cellularity and atypia but occasionally 2+.

Second, the tumor was excised with a breast-conserving resection; no tumor was present at the resection margins. Patients with a local recurrence of a previously excised phyllodes tumor were eligible if the recurrence was in the area of the previous excision.

Third, no prior or concurrent breast carcinoma or ductal carcinoma-in situ was present in the ipsilateral breast.

Finally, to be included in the study, the patient had to have no history of irradiation of the ipsilateral breast.

All patients had their slides reviewed by the study pathologist (W.W.), who determined the phyllodes tumor grade and margin status. Clinical factors were reviewed by the principal investigator (R.B.), who determined eligibility. All patients provided written informed consent.

Adjuvant radiation was started within 12 weeks of local excision or breast re-excision. Fields encompassed the whole breast using standard tangent technique for a total dose of 5040 cGy at 180 cGy per fraction over 28 treatments provided 5 days a week. This was immediately followed by a boost to the tumor bed area, including the resection site plus a 2-cm margin, for a further 1000 cGy in five fractions of 200 cGy each.

Patients were examined in follow-up at 6-month intervals. They underwent mammography at 6 and 12 months after resection, and then annually. The local recurrence rate was estimated by dividing the number of recurrences by the total sample size. An exact 95% confidence interval (95% CI) for this rate was determined by binomial distribution.

The initial statistical design was based on a local recurrence rate of 35%, as found in our 1999 literature review.⁶ We proposed a sample size of 20 patients. If a local recurrence occurred in three or fewer of these patients, it was to be concluded that the experimental therapy was associated with a local recurrence rate of <35%. The protocol was modified in 2003 to allow accrual of new patients until the initial cohort of 20 patients was followed for at least 3 years.

To determine the published rate of local recurrence after margin-negative breast-conserving resections, a medical librarian searched Medline (January 1966–October 2008) for relevant articles. The medical subject headings (MeSH) terms ‘‘phyllodes tumor’’ and ‘‘breast neoplasms’’ were used. The search results were limited to English-language studies.

This study was approved by the Committee for the Protection of Human Subjects at Dartmouth-Hitchcock Medical Center and was reviewed annually by the Data and Safety Monitoring Committee of the Norris Cotton Cancer Center. It was registered at ClinicalTrials.gov (NCT00003404).

RESULTS

Forty-six patients were enrolled onto this study from a total of 30 different institutions (see Appendix for a list of institutions). Half of the patients were treated at community-based treatment centers, and half were treated at academic medical centers. Forty-three patients were enrolled after resection of a primary phyllodes tumor. Three patients had previously undergone excision of a phyllodes tumor, experienced recurrence, and then were entered onto the study after the recurrence was excised. A total of 30 patients had malignant phyllodes tumors, and 16 had borderline malignant phyllodes tumors (Table 1). The mean patient age was 49 years (range, 18–76 years). Tumor diameters ranged from 1 to 11 cm, with a mean of 3.7 cm. Thirty-seven percent of the patients had tumors >4 cm in diameter.

Eighteen patients (nine with borderline tumors and nine with malignant phyllodes tumors) had a negative margin after their first resection and did not undergo any further surgery. The distances from the tumor to the closest margin in these patients ranged from <.1 to 2 cm (Fig. 1). The median size of the negative margin was .35 cm. Eight of these 18 patients (2 with malignant disease and 6 with borderline malignant disease) had margins of <.2 cm and 16 had a margin of <1 cm.

The remaining 28 patients underwent re-excision because the initial margins were positive (26 patients) or very close (<.1 cm in 2 patients). Tumor was detected in the re-excision specimens of three of these patients, all of whom had malignant phyllodes tumors. The closest re-excision margin was 1 cm in these three patients.

All patients received adjuvant radiotherapy as specified in the protocol. No patients were lost to follow-up. Duration of follow-up ranged from 12 to 129 months, with a median follow-up of 56 months and a mean follow-up of 60 months. Ninety percent of the patients were followed for at least 2 years.

Two patients with malignant phyllodes tumors died of metastatic phyllodes tumor, at 9 and 14 months from diagnosis, respectively. The mortality of patients with malignant phyllodes tumors was 2 (7%) of 30. None of the 16 patients with borderline phyllodes tumors has died.

None of the 46 patients developed a local recurrence (local recurrence rate, 0%; 95% CI, 0–8).

We compared these results to similar patients in reported studies who were treated with a local excision that achieved a pathologically determined negative margin as the sole therapy. The results of our review of the literature are presented in Table 2. A total of 13 studies were identified.^{2,3,8–18} Local recurrences occurred in 37 (21%) of 174 patients. Twelve (24%) of 50 patients with borderline malignant tumors and 25 (20%) of 124 patients with malignant phyllodes tumors experienced a local recurrence. The median follow-up in these studies ranged from 3.1 to 10 years. It is notable that most recurrences occurred within 2 years of surgery: the median time to recurrence was 2 years in all but one of the studies.

DISCUSSION

The histologic criteria described by Pietruzka and Barnes in 1978 and adopted by the World Health Organization in 1982 allow pathologists to classify phyllodes tumors into benign, borderline, and malignant categories, which predict the likelihood of developing metastatic disease.^{7,19,20} Recently reported studies with 50 patients with malignant phyllodes tumors have found that 9% to 34% developed metastases and died.^{2–5} Borderline phyllodes tumors metastasize less commonly. In the review of Moffat et al., only 4% of patients developed metastases.²⁰ In the Rare Cancer Network study, metastases occurred in 2 of 80 patients with borderline phyllodes tumors.⁴ The mortality we observed in our patients with malignant and borderline malignant phyllodes tumors is consistent with these observations.

In 1998, at the initiation of this study, we reviewed the literature and concluded that these histologic criteria also predict the likelihood of local recurrence after breast-conserving surgery.⁶ After a wide local excision, where an attempt is made to remove 1 to 2 cm of normal tissue around the tumor, only 8% (17 of 212) of benign phyllodes tumors recurred in the breast, compared with 29% (20 of 68) of borderline and 36% (16 of 45) of malignant phyllodes tumors. Two recently reported large retrospective studies have also found that patients have a high local recurrence rate after wide local excision of malignant phyllodes tumors.^{4,21} The Rare Cancer Network study demonstrated that at 10 years of follow-up, 13% of 269 patients with benign phyllodes tumors developed a local recurrence after wide local excision, compared with 45% (44 of 98) of patients with borderline or malignant phyllodes tumors.⁴ In this study, at 5 years of follow-up, 35% (34 of 98) of borderline or malignant phyllodes tumor patients had developed a local recurrence. Pezner et al. extracted data from merged tumor registries from 130 hospitals and found that 21% of 169 patients with malignant phyllodes tumors undergoing wide local excision developed local a recurrence by 5 years.²¹

Each of these studies, however, is limited by a lack of knowledge regarding the microscopic histologic status of the surgical margin. Although the authors stated a wide local excision

was grossly obtained in the studies we reviewed in 1998, histologically negative margins were only documented in one of these.² In the Rare Cancer Network Study, the margins were described as negative in 43%, close or positive in 15%, and unknown in 42%.⁴ In the study of Pezner et al., the authors state that “many” cases lacked information concerning surgical margins.²¹ Because several studies have demonstrated a statistically significant association between a positive histologic margin and an increased local recurrence rate, the rates reported in these analyses may be higher than what one would expect after a margin-negative breast-conserving resection.^{3,4,8,16,22–24}

Therefore, in the current study, we reviewed the literature and found that the local recurrence rate after a margin-negative breast-conserving resection of borderline or malignant phyllodes tumors is 21%. This rate is unacceptably high because there are many adverse consequences of in-breast recurrences, including substantial psychological morbidity and cosmetic morbidity: patients with recurrent phyllodes tumors will require wide local re-excision or mastectomy. Furthermore, several studies have shown that local recurrence is a strong predictor of metastatic spread.^{4,12,21} A multivariate analysis in one of these studies indicated that local recurrence of phyllodes tumors was associated with a greatly increased risk of death.²¹ Concern remains for the potential for local recurrences to metastasize, as was demonstrated in a recent meta-analysis of randomized prospective studies of patients with invasive breast cancer.²⁵ In this study, it was determined that for every four local recurrences that were avoided, one breast cancer death was prevented.

Radiotherapy has been used with varying success to treat patients with bulky metastatic or locally recurrent phyllodes tumors.^{26–33} Several studies describe the successful use of adjuvant radiotherapy in small numbers of patients after margin-positive mastectomies.^{11,34–36}

At the time we initiated the current study, only two case reports described adjuvant radiotherapy after breast-conserving resection of malignant phyllodes tumors.^{37,38} In 1998, Chaney et al. reported two additional patients who received adjuvant radiotherapy after margin-negative excisions and remained free of recurrence.³⁹ The recent retrospective report from the Rare Cancer Network provides strong support for the use of adjuvant radiotherapy after resection of phyllodes tumors.⁴ Of 159 patients with borderline or malignant phyllodes tumors, 109 were treated with breast-conserving surgery and 50 underwent mastectomy. Thirty-six received adjuvant radiotherapy. When all 159 patients were considered, the percentage free of local recurrence at 10 years in the group that received radiotherapy was significantly better than the group that did not receive radiotherapy (86 vs. 59%, $P = .02$). Of the 109 patients treated with breast-conserving surgery, 11 underwent radiotherapy and 68% were free of local recurrence at 10 years compared with 54% of the 98 patients who underwent lumpectomy without radiotherapy. Of the 50 mastectomy patients, 25 underwent radiotherapy and 92% were free of local recurrence at 10 years, compared with 78% of the patients undergoing mastectomy without radiotherapy. Although the trends in each of these subgroups favor radiotherapy, the differences were not statistically significant. In multivariate analysis, the only favorable independent prognostic factor was the use of radiotherapy.

According to recent SEER data, approximately 50% of patients with malignant phyllodes tumors undergo breast-conserving resections, and adjuvant radiotherapy is currently administered to a very low proportion (<5%) of these patients.^{1,5} We have now clearly demonstrated that margin-negative resection plus adjuvant radiotherapy is very effective local treatment for malignant phyllodes tumors. Some of the strengths of our study are that it was prospective, required central pathologic review, and involved 30 academic and community institutions, so we expect that the results will be generally applicable.

We have identified a comparable group of patients with borderline and malignant phyllodes tumors in the literature who have undergone margin-negative resections. The local recurrence rate observed in these patients (21%) is significantly higher than we observed after margin-negative resection plus adjuvant radiotherapy (0%, 95% CI, 0–8). Our median follow-up (4.7 years) is slightly shorter than some of the control studies cited. However, because the median time to recurrence is <24 months in almost all of the studies (Table 2), we think that it is highly unlikely that our results will substantially change with longer follow-up. Therefore, we conclude that adjuvant radiotherapy after breast-conserving resections of borderline malignant and malignant phyllodes tumors decreases the rate of local recurrence.

It remains to be determined whether a subset of patients can be identified who have a very low risk of local recurrence with surgery alone and can therefore forego radiation. The relationship between the size of the phyllodes tumor and local recurrence is controversial. Several studies have evaluated the effect of tumor size on local recurrence and found no statistically significant association.^{2,16–18} In contrast, others found that larger tumors were more likely to develop a local recurrence.^{3,4,12} However, the differences in recurrence rates in these studies were small, and the patients with smaller tumors still had a relatively high rate of local recurrence.

Another variable that has been evaluated for an association with local recurrence is the size of the margin. Asoglu et al. demonstrated that resection margins of <1 cm were associated with an increased risk of recurrence compared with margins of >1 cm.³ However, the risk of local recurrence in the >1-cm group remained quite high (25%). Margin size was also evaluated by Lenhard et al., who found no significant difference in the margin size of those who developed a local recurrence compared with those who remained free of recurrence.¹⁸ Therefore, although it makes intuitive sense that larger margins will be associated with a lower rate of recurrence, the evidence in support of this concept is limited. Furthermore, given the large size of most phyllodes tumors (median diameter, 4–5 cm), attempts to resect 1.5–2 cm of normal tissue around the neoplasm to achieve a minimum margin of >1 cm will leave many women with a poor cosmetic result. It is precisely for this reason that we specified that the eligibility criteria for this study was solely to have a histologically negative margin, without any minimum margin size. As shown in Fig. 1, a total of 16 of the patients in our study had margins of <1 cm. The absence of local recurrence in these patients indicates that the addition of radiotherapy allows these patients to be managed without recommending a re-excision.

On the basis of the foregoing discussion, we recommend adjuvant radiotherapy for all patients with malignant phyllodes tumors who undergo breast-conserving resections. We believe that adjuvant radiotherapy is also indicated after breast-conserving resection of patients with borderline malignant phyllodes tumors. Although the concern for the metastatic potential of a locally recurrent borderline phyllodes tumor is less than that for a locally recurrent malignant phyllodes tumor, borderline phyllodes tumors do metastasize in 2 to 4% of cases.^{4,20} Furthermore, it is well documented that recurrent phyllodes tumors can progress to a more malignant phenotype than that seen in the initial tumor.^{17,20,22,35,40} Finally, because borderline malignant phyllodes tumors locally recur as frequently as malignant phyllodes tumors after margin-negative resection, adjuvant radiotherapy can prevent the morbidity associated with the need for additional surgery in 20–25% of these patients.

Evidence is accumulating that adjuvant partial breast irradiation after resection of invasive adenocarcinoma of the breast results in rates of local recurrence that are comparable to those seen after whole breast radiotherapy.⁴¹ Because invasive breast cancer occasionally will manifest as multicentric tumors in other quadrants of the breast, there is the theoretical concern that partial breast irradiation might miss these distant sites. In contrast, it is rare for patients to have multicentric phyllodes tumors. Because local recurrences after breast-conserving resection of malignant phyllodes tumors are nearly always at the site of the initial resection, adjuvant partial breast irradiation may be as effective as whole-breast radiotherapy after resection of malignant phyllodes tumors.

Occasionally patients will have very close margins after mastectomy for large phyllodes tumors. Given an approximately 10% incidence of chest wall recurrence after mastectomy, evidence that adjuvant radiation can prevent local recurrence after margin positive mastectomies, and the data we have now described regarding the effectiveness of adjuvant radiation after margin-negative breast-conserving resections, it seems reasonable to consider adjuvant postmastectomy radiation in these patients.^{6,11,34–36}

In conclusion, margin-negative breast-conserving resections of borderline or malignant phyllodes tumors are associated with a substantial risk of local recurrence. In what is to our knowledge the first prospective study ever reported on patients with phyllodes tumors, we have demonstrated that margin-negative resection combined with adjuvant radiotherapy is an effective therapy for local control of borderline and malignant phyllodes tumors.

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APPENDIX

Participating institutions (and number of patients treated): Dartmouth-Hitchcock Medical Center, Lebanon, NH (13); U. of Massachusetts Medical Center, Worcester MA (4); Elliot Hospital, Manchester, NH (3). The following institutions each treated one patient: Jordan Hospital, Plymouth, MA; St. Francis Hospital, Hartford, CT; Central Maine Medical Center, Lewiston, ME; Maine Medical Center, Scarborough, ME; Lahey Clinic, Burlington, MA; Attleboro Surgical Associates, Attleboro, MA; Nashua Regional Cancer Center, Nashua, NH; Moore Regional Hospital, Pinehurst, NC; Hartford Hospital, Hartford, CT; Finger Lakes Radiation Oncology, Clifton Springs, NY; Ohio State University, Columbus, OH; 21st Century Oncology, Fort Myers, FL; Redwood Regional Oncology Center, Santa Rosa, CA; Northeast Regional Radiation Oncology Network, Manchester, CT; Holy Name Hospital, Teaneck, NJ; Exeter Hospital, Exeter, NH; Greater Baltimore Medical Center, Baltimore, MD; Carson Tahoe Regional Healthcare, Carson City, NV; Baptist Hospital East, Louisville, KY; St. Agnes Medical Center, Fresno, CA; Cancer Care of Maine, Bangor, ME; Radiant

Care, Lacey, WA; Oncologics Inc., Lafayette, LA; Memorial Medical Center, Springfield, IL; McLeod Health, Florence, SC; Virginia Commonwealth University, Richmond, VA.

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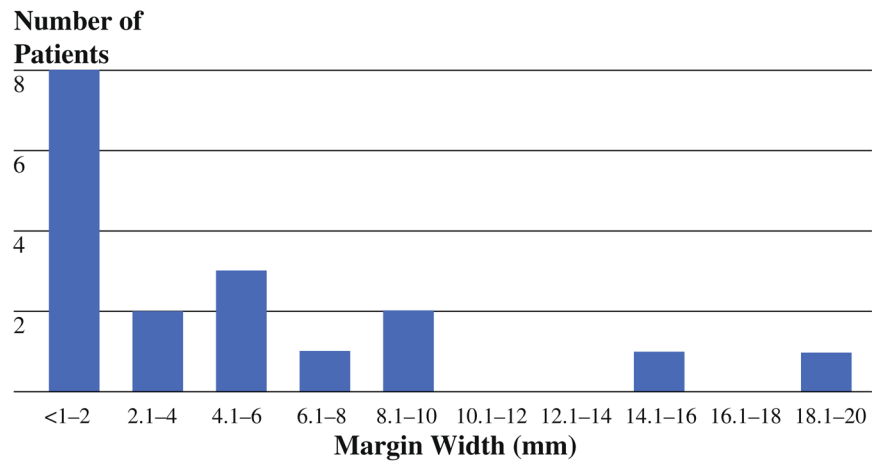


FIG. 1. Nearest margin width for phyllodes tumor patients who had 1 excision

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TABLE 1

Patient, tumor, and treatment characteristics

Characteristic	Borderline	Malignant	Total
Phyllodes tumor	16	30	46
Patient age (y)			
Mean	48	50	49
Range	23–65	18–76	18–76
Tumor diameter			
Mean (cm)	3.3	3.9	3.7
Range (<i>n</i>)			
1–1.9 cm	6	4	10
2–3.9 cm	5	14	19
4–5.9 cm	3	6	9
6–7.9 cm	1	4	5
> 8 cm	1	1	2
Surgery (<i>n</i>)			
One excision	9	9	18
Re-excision	7	21	28
Tumor in re-excision	0	3	3

Local recurrences after margin-negative breast-conserving resections of borderline malignant and malignant phyllodes tumors

TABLE 2

Study	Year	No. of local recurrences/total patients			Total	Median follow-up (y)		Median time to recurrence (mo)
		Borderline	Malignant	Total				
Reinfuss et al. ²	1996	3/15	0/4	3/19	8		< 20	
de Roos et al. ⁸	1998	0/1	0/1	0/2	ND		-	
Zissis et al. ⁹	1998	-	0/3	0/3	6.6		-	
Holthouse et al. ¹⁰	1999	0/2	0/2	0/4	10		-	
Chaney et al. ¹¹	2000	-	0/6	0/6	4		-	
Kapiris et al. ¹²	2001	-	4/14	4/14	9		10	
Kok et al. ¹³	2001	1/3	1/1	2/4	3.1		8	
Asoglu et al. ³	2004	2/3	6/19	8/22	7.5		17	
Fou et al. ¹⁴	2006	-	4/17	4/17	4.3		14	
Abdalla et al. ¹⁵	2006	4/11	2/5	6/16	5		ND	
Taira et al. ¹⁶	2007	0/5	1/6	1/11	8.2		18	
Barrio et al. ^{17a}	2007	-	5/40	5/40	8.3		24	
Lenhard et al. ¹⁸	2007	2/10	2/6	4/16	7.1		72	
Total		12/50 (24%)	25/124 (20%)	37/174 (21%)				

ND not described

^aNo distinction was made between borderline and malignant tumors in this study