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Original article

Phyllodes tumors of the breast: Adjuvant radiation therapy revisited

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ABSTRACT

Background: Phyllodes tumors (PT) are rare entity and surgical resection is the cornerstone of treatment. No standard of care exists regarding adjuvant treatment especially radiation therapy (RT).
Patients and methods: We analyzed all patients with non-metastatic, resected phyllodes tumors who presented to our institution from January 2005 through December 2019. Primary study endpoints included local recurrence free survival (LRFS) and overall survival (OS).
Results: One hundred and eight patients were analyzed (patients with incomplete treatment and follow up data were excluded). Fifty patients had benign phyllodes, 26 patients had borderline and 32 patients had malignant phyllodes. In the benign group, no significant difference in LRFS was observed between patients who received adjuvant RT (n = 3) and those who did not (5-year LRFS 100% vs. 85% respectively, p = 0.49). The 5 year OS for patients who received RT was 60% vs. 89% for those who did not (p 0.40). In the borderline/malignant group, adjuvant RT significantly improved five year LRFS (90% in the RT group vs. 42% in the no RT group, p = 0.005). The 5 year LRFS in patients treated with margin negative breast conserving surgery and RT was 100% vs. 34.3% in patients who did not receive RT (p 0.022). Patients treated with mastectomy and RT had a 5 year LRFS of 100% vs. 83% for patients who did not receive RT (p 0.24). On multivariate analysis, radiation therapy was independently associated with decreased hazard of local failure (HR 0.21, CI 0.05–0.89, p = 0.03). No difference in OS was found between the RT and no RT groups (5-year OS was 52% vs. 45% respectively, p 0.54).
Conclusion: The results of the current study confirm the excellent prognosis of benign phyllodes tumors; warranting no further adjuvant treatment after margin-negative surgical resection. For patients with borderline/malignant phyllodes tumors, adjuvant radiation therapy significantly improved LRFS after margin negative wide local excision; however, patients treated with mastectomy did not attain the same benefit from adjuvant irradiation.

1. Introduction

Phyllodes tumors (PT) are rare pathologic entity comprising 1% of all breast neoplasms.[1, 2] In 1982 the WHO introduced a subclassification of these tumors into benign, borderline and malignant subtypes.[3,4] Surgical treatment remained the upfront standard of care for all patients[5-7]; however, further decision making regarding post-operative management is still unclear. Data regarding the role of adjuvant radiation therapy, in particular, were conflicting, partly due to the absence of prospective randomized evidence and also due to the small percentage of patients receiving radiation in the adjuvant setting in most of the published series.

The aim of the current study was to assess the impact of adjuvant radiation therapy on local recurrence free survival (LRFS) and overall survival (OS)in patients diagnosed with phyllodes tumors.

2. Materials and methods

After IRB approval with waived informed consent, the medical records of patients diagnosed with phyllodes tumors of the breast and treated at our institution from January 2005 to December 2019 were reviewed. Patients with metastatic disease at presentation, incomplete pathology information or incomplete treatment

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information were excluded. One hundred and eight patients with benign, borderline and malignant phyllodes tumors were included in the current analysis.

3. Treatment

3.1. Surgery

All patients underwent primary surgical resection, either wide local excision (n = 82) or mastectomy (n = 26). Surgical margins of less than 10 mm were considered close for the sake of the current analysis. Axillary nodal dissection was done in 6 patients.

3.2. Radiation therapy

Adjuvant radiation therapy was given to 32 patients; either to the whole breast or to the chest wall. All patients were treated using 3D conformal radiation therapy technique. In patients who were treated with breast conserving surgery, radiation fields encompassed the whole breast and chest wall, delivering a dose of 50Gy in 25 fractions over 5 weeks or 40.05 Gy in 15 fractions over three weeks. Tumor bed boost of 10 Gy in 5 fractions was given to all patients. The boost volume consisted of the tumor bed with a 2 cm expansion as clinical target volume (CTV) and planning target volume (PTV) was created as a 1 cm expansion from the CTV.

In patients who were treated with mastectomy, radiation fields encompassed the entire chest wall, delivering a dose of 50 Gy in 25 fractions over 5 weeks. Regional lymph nodes were not irradiated in any of the included patients.

Data regarding the dose volume constraints were available for 20 patients only. The median ipsilateral lung V20 Gy was 22% (range, 11–32) while the median heart mean dose was 345 cGy (range, 29–612).

3.3. Statistical analysis

Results were stratified according to the histologic subtype. Data management and analysis were performed using Statistical Package for Social Sciences (SPSS) V. 25. Numerical data were checked for normality and were statistically described as medians and interquartile range. Categorical data were described as numbers and percentages. Comparison between numerical variables was done using Student t-test if normally distributed and Mann Whitney *U* test if non- normally distributed. Chi square test or Fisher's exact test were performed for comparing categorical data as appropriate. Survival analysis was done using Kaplan-Meier method with comparison between two or more survival curves using log rank test. All statistically significant factors on Kaplan-Meier analysis entered the multivariate Cox regression analysis using forward likelihood-ratio method of variable selection. Overall survival (OS) was calculated from the date of diagnosis to the date of death or last follow-up. Local recurrence free survival (LRFS) rate was calculated from the date of surgery to the date of local recurrence, excluding patients with missing local recurrence data (2 in the benign group and 3 in the borderline/malignant group). Distant metastasis free survival (DMFS) was calculated from the date of surgery to the date of metastasis. Hazard ratios (HR) were computed for significant factors in the last step of cox-regression with 95% confidence interval (CI) estimates. All tests were 2 tailed and P-value < 0.05 was considered statistically significant.

4. Results

Median follow-up was 33 months (range, 9–180). Median age at diagnosis was 44 years (range, 15–81) for the entire cohort. Sixty eight patients (63%) were premenopausal while 40 patients (37%) were postmenopausal at the time of diagnosis. Eighty two patients (76%) were treated with breast conserving surgery while 26 patients (24%) were treated with mastectomy.

According to the WHO phyllodes tumor sub-classification, 50 patients (46%) had benign, 26 patients (24%) had borderline and 32 patients (30%) had malignant phyllodes.

Thirty two patients (30%) received adjuvant radiation therapy (3 in the benign and 29 in the borderline/malignant group).

Patient, tumor and treatment characteristics stratified according to the pathological subtype are detailed in Table 1.

4.1. Benign phyllodes

The 5 year Kaplan Meier estimated LRFS for this group was 87%. On univariate analysis of the factors affecting LRFS, patients of age <45 years had 5 year LRFS of 80% compared with 100% in patients ≥45 years, this difference had a trend towards significance (p 0.06). Three patients received adjuvant radiation therapy (one due to close margin and another one due to tumor size of 22 cm). Patients who received adjuvant radiation therapy had 5 year LRFS of 100% compared to 85% in patients who did not receive radiation; however, this difference was not statistically significant (p 0.49). Other factors included in the univariate analysis are presented in Table 2.

None of the patients in this group experienced distant metastases with a 5 year DMFS rate of 100%.

The 5 year OS was 86%. Patients with tumor size <5 cm had better 5 year OS when compared to patients with tumors ≥5 cm (92% vs. 79%, p 0.03). Radiation therapy administration was not found to affect the overall survival in this patient group. The 5 year OS for patients who received radiation therapy was 60% vs. 89% for those who did not (p 0.40).

4.2. Borderline/malignant phyllodes

The 5 year Kaplan Meier estimated LRFS for this group was 69%. On univariate analysis, patients with tumor size ≥8 cm had 5 year LRFS of 47% vs. 90% in patients with tumors <8 cm (p 0.032). Other factors examined in the univariate analysis are included in Table 3.

Twenty six patients received adjuvant radiation therapy. No

Table 1
Patient, tumor and treatment characteristics stratified according to the pathologic subtype.

	Benign	Borderline/Malignant	P value
	n (%)	*n* (%)	
Age(years) Median (range)	41(15–81)	44 (18–77)	0.29
Menopausal status			
Premenopausal	35 (70)	33 (57)	0.16
Postmenopausal	15 (30)	25 (43)	
Type of surgery			
BCS	45 (90)	34 (59)	0.001
Mastectomy	5 [10]	24 (41)	
Tumor Size (cm)			
Median (range)	5 (1–22)	8 (2.5–30)	0.001
Surgical Margin			
Negative	40 (80)	41 (71)	NA
Close	1 [2]	5 [8]	
Positive	0	8 [14]	
Unknown	9 [18]	4 [7]	
Radiation Therapy			
No	46 (92)	29 (50)	0.001
Yes	3 [6]	29 (50)	
Unknown	1 [2]	0 (0)	

Abbreviations: BCS = breast conserving surgery.

Table 2
Univariate analysis of factors affecting 5 y LRFS in benign phyllodes tumors.

Factors	N	5 y LRFS (%)	P value
Age Group (years)			
<45	29	80	0.06
≥45	19	100	
Menopausal Status			
Premenopausal	34	83	0.13
postmenopausal	14	100	
Type of Surgery			
BCS	46	86	1.0
Mastectomy	2	100	
Tumor Size (cm)			
≤5	27	92	0.36
>5	21	61	
Least Margin (cm)			
<1	13	80	0.43
≥1	6	100	
Radiation Therapy			
No	45	85	0.49
Yes	3	100	

Abbreviations: LRFS = Local Recurrence Free Survival, BCS = breast conserving surgery.

statistically significant differences were found between patients who received and those who did not receive radiation therapy with regards to median age, tumor size, type of surgery or margin status (Table 4).

Patients who received adjuvant radiation therapy had better 5 year LRFS (Fig. 1) when compared to patients who did not (90% vs. 42%, p 0.005).

Patients who were treated with breast conserving surgery with negative margins had a significantly improved 5 year LRFS with the use of adjuvant radiation as compared to those who did not receive radiation (100% vs. 34.3%, p 0.022). However, in patients treated with mastectomy and negative margins (n = 18), the improvement in the 5 year LRFS observed with adjuvant radiation was not statistically significant (100% vs. 83%, p 0.24). Seven patients had positive margins after surgery (4 of them received adjuvant irradiation). All patients (n = 7) with positive margins developed local recurrences.

Cox multivariate regression analysis was done including the significant variables on univariate level for LRFS (surgical margin, tumor size and radiotherapy administration).

Radiation therapy was independently associated with decreased hazard of local failure (HR 0.21, CI 0.05–0.89 and p 0.03).

Distant metastases developed in 17 (31%) patients in this group. Distant metastases as an isolated first recurrence developed in 7 patients and in 10 patients following or synchronous with local recurrence. The Kaplan Meier estimated 5 year DMFS was 69%.

The 5 year OS for this group was 48%. The occurrence of any recurrence was associated with worse OS on univariate analysis with an estimated 5 year OS of 10% vs. 69% in those who did not experience any recurrence (p 0.001). Radiation therapy administration was not found to affect survival. The 5 year OS for patients who received radiation therapy was 52% vs. 45% for patients who were not irradiated (p 0.54).

Table 3
Univariate analysis of factors affecting 5 y LRFS in borderline/malignant phyllodes tumors.

Factors	n	5 y LRFS (%)	P value
Age Group (years)			
<45	30	66	0.62
≥45	25	75	
Menopausal Status			
Premenopausal	32	67	0.76
Postmenopausal	23	73	
Type of Surgery			
BCS	33	58	0.08
Mastectomy	22	88	
Surgical Margin			
Negative/Close	45	79	0.03
Positive	7	0.0	
Tumor Size (cm)			
≤8	28	90	0.03
>8	22	47	
Least Margin (cm)			
<1	13	63	0.22
≥1	32	88	
Radiation Therapy			
No	29	42	0.005
Yes	26	90	

Abbreviations: BCS = breast conserving surgery.

5. Discussion

This is a single institutional retrospective review of 108 patients diagnosed with phyllodes tumors of the breast. Since the histologic subtype has been shown to affect the overall survival and local control in previously reported large series[2,8,9], we decided to analyze the benign and the borderline/malignant groups separately in the current study.

In this analysis, we reported an 88% and 69% LRFS rates at 5 years in patients with benign and borderline/malignant PT, respectively. These results fell in the 58–100% range that was previously published by several investigators.[5,10–12]

Factors found to affect local control of phyllodes tumors in literature included pathologic subtype, age, tumor size, type of surgery and surgical margin.[12–15] Data regarding the effect of adjuvant radiation therapy on local control and survival, in particular, were conflicting. This could be attributed to the low percentage of patients receiving radiation therapy in the adjuvant setting in most of the reported studies.[9,12,16,17]

In our cohort 34% of the patients (10% in the benign and 50% in the borderline/malignant group) received adjuvant radiation therapy. We were able to demonstrate a clear benefit from adjuvant radiation therapy on local control, both on the univariate and the multivariate levels in the borderline/malignant group.

The only prospective study available to date by Barth et al. had demonstrated a 100% local control at 56 months median follow-up in patients with negative resection margins who received adjuvant radiation therapy.[18]

The 5 year overall survival in our study was 86% and 48% in the benign and borderline/malignant groups, respectively. In the current analysis, we were not able to demonstrate a statistically significant overall survival advantage by using adjuvant radiation therapy; neither in the benign nor in the borderline/malignant group.

Some published data suggested worse overall and cause specific survival in patients with phyllodes tumors receiving radiation therapy.[19] However, most of these results were derived from the SEER database which provided no information regarding local or distant recurrences that could have affected survival in such group of patients.

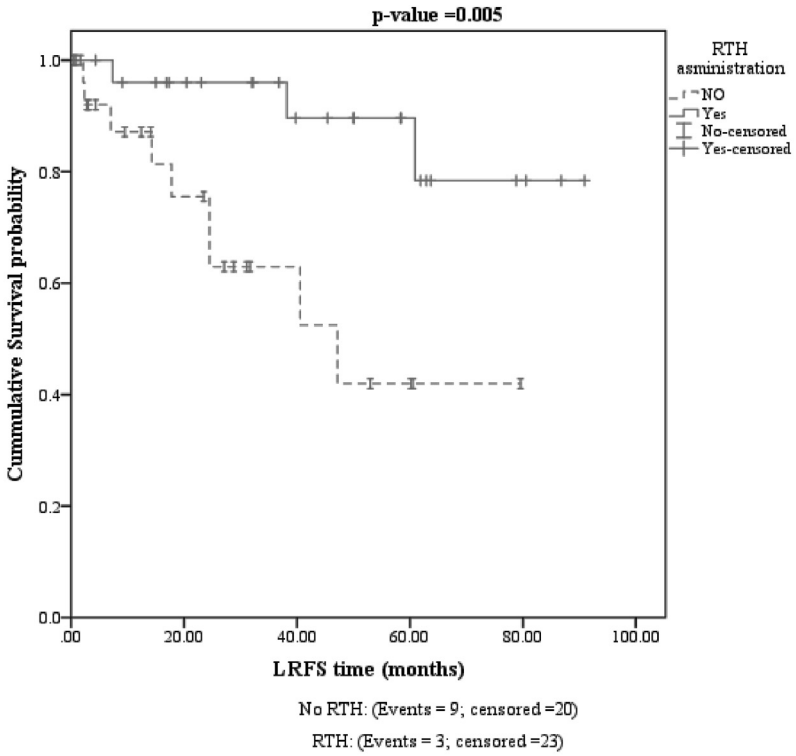
No distant recurrences were observed in the benign group and all local recurrences were salvageable which was reflected on the excellent overall survival in this group and consequently, the lack of benefit from adjuvant radiation therapy.

In the borderline/malignant group, seventeen patients (31%) developed distant recurrence allowing less time for the favorable effect of adjuvant radiation on the local control to be translated into an overall survival advantage.

One of the limitations of the current study is its retrospective

Table 4
Patient, treatment and tumor characteristics stratified according to radiation therapy administration in borderline/malignant phyllodes tumors.

	Radiation Therapy	No Radiation Therapy	P value
Age (years)			
Median (range)	43 (18–62)	40 (19–77)	0.82
Type of surgery			
Mastectomy	11 (38%)	12 (41%)	0.07
Breast conserving surgery	18 (62%)	17 (59%)	
Tumor Size (cm)			
Median (range)	6 (2.5–30)	5 (2.5–27)	0.42
Margin Status			
Close/positive	7 (24%)	6 (21%)	0.95
Negative	20 (69%)	21 (72%)	
Unknown	2 (7%)	2 (7%)	



Local Recurrence Free Survival (LRFS) in relation to radiotherapy administration in the borderline/malignant group

Fig. 1. Local Recurrence Free Survival (LRFS) in relation to radiotherapy administration in the borderline/malignant group

nature which makes it liable to selection bias. One other limitation was the inability to provide more specific recommendations regarding which groups would show more benefit from adjuvant irradiation. This is attributed to the small sample size and the small number of events; preventing further subgroup analyses.

6. Conclusion

The results of the current study confirm the excellent prognosis of benign phyllodes tumors; warranting no further adjuvant treatment after margin-negative surgical resection. For patients with borderline/malignant phyllodes tumors, adjuvant radiation therapy significantly improved LRFS after margin negative wide local excision; however, patients treated with mastectomy did not attain the same benefit from adjuvant irradiation.

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Availability of data and material

All data generated and analyzed during this study are included

in this manuscript.

Authors' contributions

All authors contributed to the study conception and design. Material preparation and data collection were performed by Sandy Khair, Yasser Abdelazim, Maher H. Ibraheem and Ahmed Farahat. Data analysis was performed by Sarah Nasr. The first draft of the manuscript was written by Rimoun Boutrus, Yasser Abdelazim and Medhat El Sebaie and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval

The Institutional Review Board of the National Cancer Institute, Cairo University approved this study.

Consent to participate

Informed consent was waived by the local Ethics Committee of the National Cancer Institute, Cairo University in view of the retrospective nature of the study and that all the procedures being performed were part of the routine medical care.

Declaration of competing interest

The authors declare they have no conflict of interest.

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