



Optimizing Surgical Treatment for Phyllodes Tumor

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Abstract

Purpose This article aims to discuss the optimal surgical treatment for Phyllodes Tumor. A general overview of each grade will be presented along with relevant findings in recent literature. An argument for a modification to current practice standards and guidelines will be introduced as histological grading has become increasingly important.

Recent Findings Based on our literature review, benign phyllodes tumors have a mean local recurrence rate of 6.9% and a mean distant metastasis rate of 0.01%. Recent studies have revealed there is no statistical difference in local recurrence for patients with positive or negative margins following tumor resection of the benign grade.

Summary The National Comprehensive Cancer Network recommends wide local excisions with negative margins of 1 cm for all Phyllodes Tumors. However, we believe these guidelines are obsolete as the histological benign grade has extremely low rates of local recurrence and metastasis. In order to decrease patient morbidity, close surveillance and observation should be considered over standard practice following a positive margin in benign Phyllodes Tumors.

Keywords Phyllodes tumor · Surgical margin · Histology · Local recurrence · Radiation therapy

Introduction

Phyllodes tumors of the breast are rare fibroepithelial tumors accounting for 2–3% of fibroepithelial breast lesions [1]. Until the late 1970s, mastectomy was the standard surgical treatment for all patients with phyllodes tumors, irrespective of tumor size or histologic grade [2]. As evidence mounted, the total mastectomy became obsolete as breast-conserving surgery with wide local excision proved to be esthetically beneficial with no significant difference in disease recurrence. It is important to note that negative surgical margins have been thought to be crucial to the success of the procedure. Yet, there

is no consensus on the appropriate margin width required for a particular grade of phyllodes tumor [3]. Some investigators propose a surgical margin greater than or equal to 10 mm wide, whereas others do not believe the extent of resection margin affects survival [4–6]. In this review, we will provide a collective discussion on the current literature and treatment for each grade of phyllodes tumor.

Current Practice

It is widely accepted that the type of surgery performed (wide local excision vs. mastectomy) for phyllodes tumors has little to no prognostic value on local recurrence. Evidence identifies that the major risk factor for local recurrence is surgical margin status. A 2005 study by Chen et al. reported that a positive surgical margin was statistically correlated ($P < 0.001$) with local recurrence in a population of 172 patients with a mean follow-up of 71 months [7]. In 2012, Jang and colleagues further strengthened these results demonstrating that a positive resection margin was a strong prognostic factor for local recurrence ($P = 0.029$) among 164 patients. Therefore, the National Comprehensive Cancer Network (NCCN) guidelines recommend wide local excision with tumor-free margins of 1 cm or greater for all phyllodes tumors. These breast-conserving therapies, or lumpectomies, are the primary

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surgical choice. When negative margins are difficult to achieve, total mastectomy can be considered [8].

Risk Stratification by Histology and Its Impact on Surgical Treatment

Phyllodes tumors of the breast are classified into benign, borderline, and malignant grades based on the following histological characteristics: the degree of stromal hypercellularity, stromal atypia, mitoses, stromal overgrowth, and margin status [9]. Present NCCN guidelines suggest that these histological grades are less decisive in the prognosis of local recurrence than the surgical margin status. Thus, phyllodes tumor grades are often not discussed when differentiating treatment pathways in clinical practice. However, this modality is evolving and recent studies have begun to emphasize the gravity of histological subtyping. In 2013, Kim et al. [10] reported that patients with benign, borderline, and malignant phyllodes tumors had local recurrence rates of 5/145 (3.4%), 6/33 (18.2%), and 7/15 (46.7%), respectively. Moreover, the breast cancer study group of the Institut Curie [11•] noted that 7/114 (6.1%) of benign and 8/34 (23.5%) of borderline phyllodes tumors eventually developed local recurrence. In accordance with these results, we conducted an extensive literature review (Table 1) on phyllodes tumor to discuss and summarize the prevalence of isolated local recurrence and metastasis with or without local recurrence (Table 2). The results showed that isolated local recurrence occurred in 6.9, 14.7, and 8.9% for the benign, borderline, and malignant grades of phyllodes tumor, respectively. Alternatively, distant metastasis with or without local recurrence occurred in 0.01, 4.8, and 15% of the benign, borderline, and malignant grades of phyllodes tumor, respectively (Table 3). Survival outcomes were also investigated, but no pertinent conclusions were drawn due to a lack of standardization (Table 4). Additionally, we performed a comprehensive meta-analysis of 29 studies to examine the risk of local recurrence respective to grade. The results concluded that the overall local recurrence rates with a 95% confidence interval for benign, borderline, and malignant phyllodes tumor were 8, 19, and 24%, respectively. The manuscript describing these results is still under review for publication.

As available data sets increase, we question whether the phyllodes tumor treatment guidelines should be reconsidered for individual histological grades. Currently, the recommendation is to excise 1 cm margin for all grades, but we argue that such a width is frequently unnecessary. This is markedly wider than the “no-ink” criteria utilized for breast conserving surgery in invasive or a 2-mm margin for in situ breast cancer [9, 12••]. Furthermore, Kim et al. reported that benign phyllodes tumors have a low rate of local recurrence (3.4%), regardless of surgical margin status or radiation therapy. Recent data even infers that surgical margin status is only associated

with the prognosis of malignant phyllodes tumors [10]. In 2011, a Danish retrospective study noted that only one (out of 354) benign and one (out of 89) borderline phyllodes tumors recurred after a mean follow-up of 98 months [11•]. Cowan and colleagues added that there was no statistically significant difference in the risk of local recurrence between patients with positive or negative margins in benign and low-grade fibroepithelial neoplasms [12••]. Shaaban et al. [15••] supported this notion reporting that 87% of patients with benign phyllodes tumors and focally positive margin involvement did not develop local recurrence. These authors advocate for a “wait-and-watch” policy and close surveillance.

This decision concerning further re-excision vs. surveillance for benign phyllodes tumors with positive margins is an ongoing debate. In 2016, Cowan and authors reported no statistical difference in local recurrence for patients with or without positive margins as well as no significant difference in local recurrence for patients with or without re-excision [15••]. Moo et al. [13••] substantiated these results with a 2017 study highlighting no difference in local recurrence among 246 patients with benign phyllodes tumors and positive margins who underwent re-excision as opposed to those that underwent observation.

We reported similar findings in a Chinese population at Sun Yat-sen Memorial Hospital of Sun Yat-sen University in 2015. We routinely utilized an ultrasound guided vacuum-assisted biopsy method to excise and analyze BI-RADs 3-4a lesions. Those patients diagnosed with benign phyllodes tumors after ultrasound guided vacuum-assisted biopsy did not receive additional surgical re-excision for positive margins. We compared the risk of local recurrence between those patients who had only ultrasound guided vacuum-assisted biopsy and those who completed surgical re-excision. In the end, there was no statistical difference in the 5-year relapse-free survival (RFS) (5 year RFS: 81.6 vs 88.7%, $P=0.11$) [16]. This study has been acknowledged and included as evidence in a recent international consensus conference on lesions of uncertain malignant potential in the breast (B3 lesions) [17]. The subsequent recommendations by the consensus state that benign phyllodes tumors on ultrasound guided vacuum-assisted biopsy require surveillance only. Re-excision is only justified in borderline and malignant phyllodes tumors as a means to obtain clear margins. As the benign grade comprises about 60 to 75% of all phyllodes tumors, these updated guidelines may prevent unwarranted surgeries and promote a better standard of care in clinical practice. Together, we believe these articles justify the need for continued histological analyses and a resolution of the 1 cm wide local excision recommendation for all phyllodes tumors.

Borderline phyllodes tumors are characterized by moderate stromal cellularity, stromal atypia, and number of mitoses of five to nine mitoses per ten high-power field (HPF). When

Table 1 Selected investigations on phyllodes tumors

Authors	Country	Sample size (<i>n</i>)	Follow-up (months)	Tumor grade		
				Benign	Borderline	Malignant
Kim et al. [10]	South Korea	193	65	145	33	15
Lin et al. [5]	Taiwan	33	33.6	8	13	12
Onkendi et al. [6]	USA	67	120	0	15	52
Chen et al. [7]	Taiwan	172	71	131	12	29
Chaney et al. [8]	USA	101	47	59	12	30
Jang et al. [4]	South Korea	164	33	82	42	40
Guillot et al. [11•]	France	165	12.65	114	37	14
Borhani-Khomani et al. [18]	Denmark	479	45.6	390*	89	0
Cowan et al. [12••]	USA	90	57.7	52	19	19
Moo et al. [13••]	USA	216	35.5	216	0	0
Ouyang et al. [16]	China	225	35.5	225	0	0
Kapiris et al. [20]	United Kingdom	48	108	0	0	48
Asoglu et al. [21]	USA	50	91	0	3	47
Spitaleri et al. [28]	Italy	172	85	68	42	62
Pandey et al. [29]	India	37	43	0	0	37
Barth et al. [30]	USA	46	56	0	16	30
Tan et al. [14]	Singapore	552	56.9	399	103	50

*Benign includes six uncertain and 30 possible phyllodes tumors

considering treatment, there is no standard approach with regard to the wide local excision procedure. A precise surgical margin width for the borderline grade has not been defined and, like the benign grade, is highly contested. Borhani-Khomani et al. [18] reported no correlation between the resection margin width and the risk of local recurrence. In this study, only 11% of patients with borderline phyllodes tumors received wide local excisions (negative margin of at least 1 cm), yet the overall local recurrence rate (9.0%) remained remarkably low. In parallel, Cowan et al. [12••] stated that recurrence rates in borderline tumors have no association with the original margin status. These authors argue that the decision to excise to negative margins is unproven and advocate for a more conservative management in borderline phyllodes tumor cases. In contrast to these reports, Kim and authors [10] asserted that the extent and type of surgery have significant correlation with local recurrence rates. This article revealed that 67% of women treated with a simple local excision had local recurrence, whereas 16.7% treated with wide local excision and 16.7% of mastectomies developed recurrence. Due to the varying evidence in the treatment of borderline phyllodes tumors, we believe in the more conservative approach and use of wide local excision until evidence-based data proves otherwise.

Malignant phyllodes tumors are characterized by marked nuclear pleomorphism, stromal cellularity, stromal overgrowth, and more than ten mitoses per ten HPF. These tumors are much more likely to have distant metastasis than benign

and borderline phyllodes tumors. The lungs, pleura, and bone are the most common sites of metastases [19, 20]. The presence of tumor cells in the resected margin is regarded as a strong prognostic factor for local recurrence in malignant phyllodes tumors. In 2013, Kim et al. [10] showed that positive surgical margins were significantly associated with a shorter disease free survival. A study by Asoglu and colleagues [21] suggested that a margin width less than 1 cm increased the risk for local recurrence fivefold in the malignant grade. Of note, a 2006 report of 821 cases between 1983 and 2002 by Macdonald et al. showed that mastectomy did not provide any survival benefit to breast-conserving surgery when considering treatment for malignant phyllodes tumors [22].

Biology Underlying Histologic Grades of Phyllodes Tumors

The exact biology that underlies the qualitative differences among each histological grade of phyllodes tumors is still imprecise. But, it is thought that genetic discrepancies may help account for the varying rates of local recurrence risk. Piscuoglio et al. [23] conducted an analysis of phyllodes tumors using massively parallel sequencing and showed that mutations affecting cancer genes (e.g., TP53, RB1, SETD2, and EGFR) were exclusively detected in borderline and malignant phyllodes tumors. This report proposed that there are, in fact, genetic differences between the three grades of

Table 2 Comparing prevalence of local recurrence and distant metastasis

Author	Sample size (<i>n</i>)	Number of isolated LR (%) ¹			Number of metastasis with or without LR (%)			
		Benign ²	Borderline	Total	Benign ²	Borderline	Malignant ³	Total
Kim et al. [10]	193	5/145 (3.4)	6/33 (18.2)	7/15 (46.7)	0	1/33 (3)	7/15 (46.7)	8/193 (4.1)
Lin et al. [5]	33	0	2/13 (15.4)	4/12 (33.3)	0	1/8 (7.7)	2/13 (16.7)	3/12 (9.1)
Onkendi et al. [6]	67	n/r	8/67 (11.9)	8/67 (11.9)	15/67 (22.4)	15/67 (22.4)		
Chen et al. [7]	172	19/131 (14.5)	0	0	0	1/12 (8.3)	2/29 (6.9)	3/131 (1.7)
Chaney et al. [8]	101	3/59 (5.1)	0	1/30 (3.3)	1/59 (1.7)	0	7/30 (23.3)	8/101 (7.9)
Jang et al. [4]	164	12/82 (14.6)	9/42 (21.4)	10/40 (25.0)	0	0	4/40 (10.0)	4/164 (2.4)
Guillot et al. [11•]	165	7/114 (6.1)	8/37 (21.6)	0	0	0	2/14 (14.3)	2/165 (1.2)
Borhani-Khomani et al. [18]	479	22/390(5.6)	8/89 (9.0)	n/r	0	1/89 (1.1)	n/r	1/479 (.02)
Cowan et al. [12••]	90	2/52 (2.8)	0	n/r	0	1/19 (5.3)	n/r	1/90 (1.1)
Moo et al. [13••]	216	4/216 (1.9)	n/r	n/r	0	n/r	n/r	0
Ouyang et al. [16]	225	5/225 (2.2)	n/r	n/r	1(.04)	n/r	n/r	1/225 (.04)
Kapiris et al. [20]	48	n/r	n/r	10/48 (20.8)	n/r	n/r	13/48 (27.1)	13/48 (27.1)
Asoglu et al. [21]	50	n/r	1/3 (33.3)	7/47 (14.9)	n/r	1/3 (33.3)	12/47 (25.5)	13/50 (26%)
Spitaleri et al. [28]	172	4/85 (5.9)	6/68 (14.3)	9/62 (14.5)	0	0	4/62 (6.5)	4/172 (2.3)
Barth et al. [30]	46	n/r	0	0	n/r	0	2/30 (6.7)	2/46 (4.3)
Tan et al. [14]	552	48/399 (12.0)	16/103 (15.5)	4/103 (8.0)	0	0	12/103 (24.0)	12/552 (2.2)

¹ LR local recurrence; isolated local recurrence also includes locoregional recurrence

² Benign category also includes possible, uncertain, and fibroadenomas with phyllodol features

³ Malignant category includes both high- and low-grade malignant phyllodes tumors

Table 3 Cumulative patient recurrence outcomes

Total patients = 2810	
Benign	1889
Borderline	436
Malignant	485
Mean of isolated local recurrence	
Benign	131/1889 = 6.9%
Borderline	64/436 = 14.7%
Malignant	53/448* = 11.8%
Total	247/2773* = 8.9%
Mean of distant metastasis with or without local recurrence	
Benign	2/1889 = .01%
Borderline	21/436 = 4.8%
Malignant	67/448* = 15.0%
Total	90/2773* = 3.2%

*Patients from Pandey et al. removed

phyllodes tumors. Furthermore, a 2015 study by Tan [24] and authors exposed, via exome sequencing, that borderline and malignant phyllodes tumors harbored more mutations in cancer-associated genes. Based on these studies, we suggest that borderline and malignant phyllodes tumors have similar genetic makeups and resulting biologic behavior. Therefore, the same treatment algorithm should be employed, whereas more conservative treatment can be applied to the benign grade of phyllodes tumor.

In addition to the genetic background, the microenvironment may also be an important factor in determining the biologic behavior and risk for local recurrence. Kim et al. [25] noted that the expression of cancer-associated fibroblast (CAF)-related proteins was significantly associated with an

increasing histologic grade of phyllodes tumor. Specifically, PDGFR α and PDGFR β expression was increased in malignant grades of phyllodes tumor. In 2017, Nie and colleagues advanced this understanding by studying tumor-associated macrophages. The authors demonstrated that these cells promote the malignant progression of breast phyllodes tumors by inducing myofibroblast differentiation [26]. Taken together, these reports imply that both the microenvironment and genetics play a significant role in the progression of phyllodes tumors. Continued research is necessary for a further appreciation of specific biologic behavior between grades and additional prevention of poor outcomes.

Radiation Therapy for Local Control

The role of radiation therapy in the treatment of phyllodes tumor is still controversial [27, 28]. The NCCN guidelines state that local radiation therapy to the breast or chest wall is only recommended if local recurrence has occurred [29]. Interestingly, the use of adjuvant radiation therapy has been increasing in recent years according to the Surveillance, Epidemiology, and End Results (SEER) program database, but its efficacy is lacking conclusive data [22]. A 2009 prospective, multi-institutional study indicated that margin-negative resection with adjuvant radiotherapy is extremely effective for local control of borderline and malignant phyllodes tumors [30]. In 2014, a data analysis of 3120 patients with malignant phyllodes tumors from the National Cancer Data Base also showed that the utilization of adjuvant radiotherapy reduced local recurrence; however, it had no effect on both disease-free survival and overall survival [31]. Although the evidence is incomplete, we support the NCCN guidelines on the use of local radiation for local recurrence

Table 4 Survival outcomes among relevant investigations

Authors	Sample size (n)	5-year DFS or RFS (%) ¹			5-year overall survival rate (%)	10-year overall survival rate (%)	5-year cancer-specific survival (%)
		Benign	Borderline	Malignant			
Lin et al. [5]	33		59 ²		81	n/r	n/r
Onkendi et al. [6]	67	n/r		67.9 ³	n/r	n/r	80
Chaney et al. [8]	101	n/r	n/r	n/r	88	79	n/r
Jang et al. [4]	164	77	65	45	n/r	n/r	n/r
Ouyang et al. [16]	225	85 ¹	n/r	n/r	n/r	n/r	n/r
Kapiris et al. [20]	48	n/r	n/r	54	n/r	n/r	n/r
Asoglu et al. [21]*	50	n/r	n/r	n/r	75	57	n/r
Spitaleri et al. [28]	172	n/r	n/r	n/r	n/r	94.6	n/r
Pandey et al. [29]*	37	n/r	n/r	60	74	n/r	n/r

¹ DFS disease-free survival, RFS relapse-free survival

² The average of each cohort’s 5-year relapse-free survival of all three grades

³ The average 5-year disease-free survival of the borderline and malignant grades

*These studies deal with malignant phyllodes tumor only

and advocate that it may also be considered for malignant phyllodes tumors if the width of the surgical margins is less than 1 cm.

Conclusion

The histologic grades of phyllodes tumors are emerging as important prognostic factors and should not be overlooked during clinical decision-making. It is apparent now, more than ever, that benign phyllodes tumors have a significantly lower risk of local recurrence than the borderline and malignant grades. Consequently, re-excision of positive surgical margins in benign phyllodes tumors may not be justified. Recent studies suggest that a period of close surveillance may be most appropriate. For borderline phyllodes tumors, a standardized margin width remains unclear, although we recommend similar treatment to that of malignant phyllodes tumors due to genetic similarities and recent biological studies. The malignant grade requires a wide local excision with negative surgical margins as supported by evidence. Radiotherapy should be advised in the event of local recurrences and malignant cases where negative margins are difficult to achieve.

Due to the low incidence and metastatic rates of phyllodes tumors, it is not practical to conduct prospective randomized studies. A multicenter, collaborative study using retrospective data is an ideal way to continue to provide high-quality evidence in order to guide clinical practices.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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