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Limited Reporting of Histopathologic Details in a Multi-Institutional Academic Cohort of Phyllodes Tumors: Time for Standardization

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Abstract

BACKGROUND: Phyllodes tumors are rare fibroepithelial neoplasms, which are classified by tiered histopathologic features. While there are protocols for the reporting of cancer specimens, no standardized reporting protocol exists for phyllodes.

METHODS: We performed an 11-institution contemporary review of phyllodes tumors. Granular histopathologic details were recorded, including the features specifically considered for phyllodes grade classification.

RESULTS: Of 550 patients, median tumor size was 3.0cm, 68.9% (N=379) were benign, 19.6% (N=108) borderline, and 10.5% (N=58) malignant. All cases reported the final tumor size and grade classification. Complete pathologic reporting of *all* histopathologic features was present in 15.3% (N=84) of cases, while an additional 35.6% (N=196) were missing only one or two features in the report. Individual details regarding the degree of stromal cellularity was not reported in 53.5% (N=294), degree of stromal atypia in 58.0% (N=319), presence of stromal overgrowth in 56.2% (N=309), stromal cell mitoses in 37.5% (N=206), and tumor border in 54.2% (N=298). The final margin status (negative vs. positive) was omitted in only 0.9% of cases, and the final negative margin *width* was specifically reported in 73.8%. Reporting of details was similar across all sites.

CONCLUSION: In this academic cohort of phyllodes tumors, one or more histopathologic features were frequently omitted from the pathology report. While all features were considered by the pathologist for grading; this limited reporting reflects a lack of reporting consensus. We recommend that standardized reporting in the form of a synoptic-style cancer protocol be implemented for phyllodes tumors, similar to other rare tumors.

Keywords

Phyllodes Tumor; Breast Neoplasms; Synoptic Reporting; Pathology

INTRODUCTION

Phyllodes tumors are rare fibroepithelial breast neoplasms, representing fewer than 1.0% of all primary breast tumors.[1,2] These tumors are currently classified by the World Health Organization (WHO) as either benign, borderline, or malignant based on assessment of stromal cellularity, stromal cell atypia, stromal cell mitotic activity, stromal overgrowth, tumor border, and the presence of malignant heterologous elements.[3–5] Confounding diagnostic certainty is the considerable histologic overlap on both ends of the histologic spectrum. At the lower end it may be difficult to distinguish a benign phyllodes tumor from a fibroadenoma. At the higher end, malignant phyllodes tumors may be difficult to distinguish from primary breast sarcomas and spindle cell metaplastic carcinomas.[5] In addition, grading of phyllodes tumors is fraught with challenges in precision and reproducibility due to a lack of objective criteria for differentiating most of the tiered histopathologic parameters, intratumoral heterogeneity, the rarity with which these tumors are seen by most pathologists, and lack of standardized reporting recommendations.[3–5]

For decades, pathology societies including the College of American Pathologists (CAP) and the Association of Directors of Anatomic and Surgical Pathology (ADASP) have published

guidelines for standardized reporting of malignant tumors. The American College of Surgeons (ACS) Commission on Cancer (COC), the accreditation board for cancer centers in the United States, strongly encourages the use of CAP protocols for the reporting of cancer specimens.[6] These have been published since 1986, and currently over 70 published CAP protocols exist for reporting cancer, which are classified into 18 categories such as “breast”, “endocrine system”, and “hepatobiliary”.[7] These cancer protocols are composed of two parts: (1) core data elements (obligatory reported) and conditional data elements (reported elements when present in specimen), and (2) optional data elements (as determined by local standard), formatted in a synoptic report. While these cancer protocols exist for some rare tumors such as gastrointestinal stromal tumors (GIST), no such protocol exists for phyllodes tumors, resulting in widely variable reporting by pathologists.[7]

We recently completed a multi-institutional review of contemporary (2007–2017) phyllodes tumor management, which included the abstraction of extensive histopathologic details.[8, 9] One of the objectives of this study was to validate a well-known phyllodes tumor nomogram for recurrence,[10] utilizing this large collaborative contemporary dataset. Herein we present the previously unpublished pathologic data from this multi-center review.

METHODS

After institutional review board approval from each site, this study pooled data from 11 institutions to include all adult women with a phyllodes tumor from 2007–2017, who underwent surgical management for an initial, histologically proven phyllodes tumor. Patient demographics, obstetric/gynecologic factors, family history, genetic testing, surgical management, recurrence and outcome data from this multi-institutional cohort were previously published.[8, 9] This study retrospectively abstracted detailed surgical pathologic data including pathologic tumor size, final grade classification, stromal cellularity and stromal atypia (as mild, moderate, marked), presence (vs. absence) of stromal overgrowth, number of mitoses (per 10 high-power field, hpf), histologic tumor border (well defined/pushing vs. infiltrative/permeative), presence (vs. absence) of necrosis, final surgical margin status, and closest reported margin width. A “not reported” status was entered if the pathologic detail was omitted from the pathology report. These data were retrieved at each site from the electronic medical record, and de-identified data was aggregated by the coordinating site; pathology re-review was not performed by either a local or central pathologist. Pathologic characteristics were summarized by either number (%) or median (interquartile range, IQR), for all patients and by site. Differences between sites were tested using the Chi-square or Fisher exact test for categorical variables and analysis of variance or Kruskal-Wallis test for continuous variables. No adjustments were made for multiple comparisons. All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary NC).

RESULTS

We identified 550 women with phyllodes tumors from 11 institutions (N=91, 71, 62, 58, 55, 51, 47, 41, 34, 31, 9). Median age at diagnosis was 44 years (IQR 36–53), median tumor size was 3.0 cm (IQR 2.0–4.5) with an overall range of 0.3 – 29.0 cm. Phyllodes tumors

were classified as benign in 68.9% of cases (N=379), borderline in 19.6% (N=108), and malignant in 10.5% (N=58) (Table 1). Of note, details of the histologic parameters upon which phyllodes tumors are classified were frequently omitted in the pathology reports by all sites. Specifically, details regarding the degree of stromal cellularity was not reported in 53.5% (N=294), degree of stromal atypia in 58.0% (N=319), presence of stromal overgrowth in 56.2% (N=309), stromal cell mitoses in 37.5% (N=206), and tumor border in 54.2% (N=298). Four cases had no data abstracted or entered for any of these five histopathologic features. While not a feature used in WHO classification of phyllodes tumors, 77.6% did not report on the presence of necrosis. The final margin status (negative vs. positive) was omitted in only 0.9% of cases, and the final negative margin *width* was specifically reported in 73.8% (N=208/282), excluding cases in which a margin width would not be reported (e.g. positive margins and those with 'no residual phyllodes' after a margin re-excision). Complete pathologic reporting of *all* WHO classification features was present in 15.3% (N=84) of cases while an additional 21.4% (N=118) and 14.2% (N=78), were missing only one or two features in the report, respectively. In the remaining 48.4% (N=266) three or more features were omitted from the pathology report.

DISCUSSION

In this large, multi-institutional cohort study of 550 phyllodes tumors, one or more histopathological parameters used by the pathologist to assign the final phyllodes grade were omitted from pathology reports in 85% of the cases. Fewer than 50% of the reports included the specific categorization of the degree of stromal cellularity, stromal atypia, the presence of stromal overgrowth, or tumor border. The fifth parameter, the number of mitoses (per 10 hpf) was reported with a slightly higher frequency, and was included in 62% of reports, suggesting this factor may be weighted more heavily in the pathologist's decision-making for final phyllodes tumor classification. Alternatively, it may simply be that unlike the other features, this parameter has objective criteria (scaled numeric; <5, 5–9, or ≥10 per 10 hpf). Of note, none of the 11 institutions had a notably lower rate of omission of pathologic parameters from their reports than any other.

While nearly half of the cases did not have three or more of the specific features required for grading within the pathology report, it does not, of course, mean that all features were not taken into consideration by the pathologist for grading; this may simply reflect institutional or individual reporting style. By analogy, many pathology reports of invasive carcinoma of the breast provide a combined histologic grade but do not report the categorization of the three features used for that grade determination (i.e. tubule formation, nuclear pleomorphism, mitotic rate). The importance of providing the granular histopathologic features in pathology reports, particularly for rare neoplasms like phyllodes tumors, is to permit cooperative data collection for large studies to better understand what drives the variable biological behavior and outcomes in this diverse group of tumors.

As historic rates of recurrence vary significantly by grade, a nomogram was created by the Phyllodes Tumour Network Singapore to predict clinical behavior of these tumors based on histopathologic factors and surgical margins.[10] This nomogram was created utilizing 605 cases of phyllodes tumors, evaluating multiple factors to determine those associated with

recurrence based on multivariate analysis. The nomogram includes cellular atypia (mild, moderate, marked), mitoses per 10 hpf (0–80), stromal overgrowth (absent vs. present), and surgical margin status (negative vs. positive) to predict recurrence-free survival at 1, 3, 5, and 10 years. This nomogram was superior to a total histological score derived from adding values assigned to each of the five histological parameters.[10] Since its publication in 2012 it has not been validated due to both the need for a very large cohort of this rare breast tumor, and associated granular histopathologic data. Due to the omission of the individual histologic parameters in so many of our cases, validation of the internationally recognized phyllodes recurrence nomogram was not possible in our large multi-center cohort. [10] Inability to validate this nomogram is a lost opportunity and highlights the importance of standardized reporting in order to advance this field and direct clinical care.

Accurate and reproducible grading of phyllodes tumors is important to predict clinical outcomes and guide treatment decisions. The histologic grades of phyllodes have variable biological behavior and metastatic potential. Therefore, surgical decision-making such as breast-conservation vs. mastectomy and margin management, as well as adjuvant treatment decisions are frequently influenced by grade. In large series, local recurrence rates are 8.0–10.9% for benign, 13–14.4% for borderline, and 18–29.6% for malignant phyllodes tumors.[10, 11] Distant metastases rarely occur in benign or borderline tumors (0.1% and 1.6%, respectively), however, they have been reported in 16.7% of malignant phyllodes.[5] Adjuvant radiation or systemic therapy is rarely recommended for women with phyllodes classified as benign or borderline, nor is there any standardized recommendation for oncologic follow-up.[12] Once metastatic, minimal treatment options exist for phyllodes tumors, and prognosis is dismal. Misclassification of the tumor grade therefore has implications for adjuvant therapy, surveillance, and the early detection of recurrences.

National Comprehensive Cancer Network (NCCN) guidelines were very recently updated to reflect a growing body of literature supporting observation alone following excisional biopsy for benign phyllodes tumors. [12] Some studies even suggest that an ultrasound-guided vacuum-assisted biopsy and observation alone may be adequate for small, benign phyllodes tumors.[13] NCCN guidelines now advise a wide local excision, with the intention of obtaining ≥1cm surgical margin, only for malignant and borderline phyllodes. [12] This major amendment in the guidelines, along with no specific oncologic follow-up recommended, highlights the critical need for accurate, precise and reliable grading.

While accurate grade classification was not a concern in this academic cohort, a standardized reporting template may aide in the accuracy and precision in phyllodes classification, particularly in settings of low volume prevalence. Mandating a standardized reporting template, including delineation of each of the tiered histopathologic features, may improve accuracy of grading, and warrants further study. This concept is similar to learners taking practice exam questions, during which the act of concretely selecting the answer improves learning. If the pathologists are required to classify each scaled histopathologic feature, they may be more likely to correctly assign the final grade classification, with each feature delineated. In addition, as most pathologists only review a few cases of these rare tumors per year, a reporting template would be an immediate review of the classification system.

While these data are retrospective, and there was no pathology re-review either locally or by a central pathologist, this dataset represents the largest United States cohort of phyllodes tumors, compiled from major academic, comprehensive cancer centers, during a contemporary time period. Institutional pathology re-review would allow us to validate the nomogram in an independent data set and central review would allow an assessment of inter-observer variability; however, neither of those would address the current issue of underreporting of the histopathologic criteria used to classify phyllodes tumors. As such, we believe our findings represent current real-world practice, bringing to light a major deficit of the current state in phyllodes tumor reporting and offering insights for improvement.

CONCLUSION

In this large multi-center academic cohort of 550 phyllodes tumors, one or more of the histopathologic features that determine final phyllodes tumor classification was omitted from the pathology report in 85% of the cases. While reporting the final phyllodes classification is essential for patient management, we believe that reporting each of the pathologic features considered in determining the final phyllodes tumor classification also are important for ensuring accurate and reproducible classification of phyllodes, as well as facilitating research into this rare tumor. We strongly recommend that standardized reporting in the form of a synoptic-style College of American Pathologists Cancer Protocol be implemented for phyllodes tumors, ideally following a multi-disciplinary consensus development conference to address these issues.

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Synopsis:

This multi-center academic cohort of 550 phyllodes tumors reveals limited reporting of the histopathologic details that were considered by the pathologist for phyllodes grading. Standardized reporting in the form of a synoptic-style template may improve reproducibility and facilitate research.

Table 1.

Multi-Center Phyllodes Tumor Histopathologic Factors, 2007 – 2017.

	All Patients (N=550)	Site 1 (N=31)	Site 2 (N=51)	Site 3 (N=91)	Site 4 (N=62)	Site 5 (N=58)	Site 6 (N=71)	Site 7 (N=41)	Site 8 (N=47)	Site 9 (N=9)	Site 10 (N=55)	Site 11 (N=34)	P
Size on Final Pathology (mm) – Median (IQR)	30 (20 – 45)	25 (17 – 42)	30 (25 – 68)	26 (17 – 37)	27 (19 – 42)	25 (20 – 48)	27 (17 – 45)	35 (25 – 53)	35 (24 – 58)	62 (34 – 85)	33 (20 – 40)	30 (20 – 45)	0.04
Range	3 – 290	7 – 125	8 – 290	5 – 145	3 – 240	8 – 220	6 – 176	13 – 145	15 – 97	18 – 110	7 – 290	8 – 124	
Classification/ Subtype/ Grade													0.001
Benign (Grade 1)	379 (68.9%)	21 (67.7%)	35 (68.6%)	73 (80.2%)	48 (77.4%)	32 (55.2%)	50 (70.4%)	24 (58.5%)	29 (61.7%)	4 (44.4%)	43 (78.2%)	20 (58.8%)	
Borderline (Grade 2)	108 (19.6%)	6 (19.4%)	9 (17.6%)	12 (13.2%)	11 (17.7%)	17 (29.3%)	12 (16.9%)	11 (26.8%)	12 (25.5%)	0 (0%)	7 (12.7%)	11 (32.4%)	
Malignant (Grade 3)	58 (10.5%)	4 (12.9%)	7 (13.7%)	6 (6.6%)	2 (3.2%)	9 (15.5%)	7 (9.9%)	6 (14.6%)	6 (12.8%)	5 (55.6%)	3 (5.5%)	3 (8.8%)	
Stromal Cellularity													<0.001
Mild	104 (18.9%)	6 (19.4%)	6 (11.8%)	13 (14.3%)	14 (22.6%)	19 (32.8%)	8 (11.3%)	13 (31.7%)	11 (23.4%)	1 (11.1%)	10 (18.2%)	3 (8.8%)	
Moderate	121 (22%)	8 (25.8%)	9 (17.6%)	34 (37.4%)	11 (17.7%)	3 (5.2%)	8 (11.3%)	13 (31.7%)	15 (31.9%)	0 (0%)	10 (18.2%)	10 (29.4%)	
Marked	27 (4.9%)	3 (9.7%)	2 (3.9%)	7 (7.7%)	1 (1.6%)	0 (0%)	1 (1.4%)	5 (12.2%)	1 (2.1%)	0 (0%)	4 (7.3%)	3 (8.8%)	
Not Reported	294 **(53.5%)**	14 (45.2%)	34 (66.7%)	37 (40.7%)	35 (56.5%)	36 (62.1%)	52 (73.2%)	10 (24.4%)	20 (42.6%)	8 (88.9%)	30 (54.5%)	18 (52.9%)	
Stromal Atypia													<0.001
Mild	157 (28.5%)	14 (45.2%)	13 (25.5%)	40 (44%)	21 (33.9%)	12 (20.7%)	7 (9.9%)	11 (26.8%)	13 (27.7%)	1 (11.1%)	20 (36.4%)	5 (14.7%)	
Moderate	47 (8.5%)	4 (12.9%)	1 (2%)	6 (6.6%)	3 (4.8%)	4 (6.9%)	3 (4.2%)	8 (19.5%)	4 (8.5%)	1 (11.1%)	5 (9.1%)	8 (23.5%)	
Marked	23 (4.2%)	3 (9.7%)	0 (0%)	3 (3.3%)	0 (0%)	4 (6.9%)	3 (4.2%)	4 (9.8%)	1 (2.1%)	2 (22.2%)	1 (1.8%)	2 (5.9%)	
Not Reported	319 **(58.0%)**	10 (32.3%)	37 (72.5%)	42 (46.2%)	37 (59.7%)	38 (65.5%)	56 (78.9%)	18 (43.9%)	29 (61.7%)	5 (55.6%)	28 (50.9%)	19 (55.9%)	
Stromal Overgrowth Presence													<0.001
Absent	129 (23.5%)	11 (35.5%)	8 (15.7%)	16 (17.6%)	10 (16.1%)	17 (29.3%)	15 (21.1%)	18 (43.9%)	9 (19.1%)	1 (11.1%)	17 (30.9%)	7 (20.6%)	
Present	108 (19.6%)	3 (9.7%)	8 (15.7%)	47 (51.6%)	5 (8.1%)	5 (8.6%)	9 (12.7%)	8 (19.5%)	8 (17%)	2 (22.2%)	8 (14.5%)	5 (14.7%)	
Not Reported	309 **(56.2%)**	17 (54.8%)	35 (68.6%)	28 (30.8%)	46 (74.2%)	36 (62.1%)	45 (63.4%)	15 (36.6%)	30 (63.8%)	6 (66.7%)	29 (52.7%)	22 (64.7%)	
Mitoses (per 10 hpf)													<0.001
<5	215 (39.1%)	16 (51.6%)	19 (37.3%)	55 (60.4%)	26 (41.9%)	13 (22.4%)	17 (23.9%)	16 (39%)	14 (29.8%)	2 (22.2%)	25 (45.5%)	12 (35.3%)	

	All Patients (N=550)	Site 1 (N=31)	Site 2 (N=51)	Site 3 (N=91)	Site 4 (N=62)	Site 5 (N=58)	Site 6 (N=71)	Site 7 (N=41)	Site 8 (N=47)	Site 9 (N=9)	Site 10 (N=55)	Site 11 (N=34)	P
5–9	71 (12.9%)	3 (9.7%)	7 (13.7%)	20 (22%)	6 (9.7%)	6 (10.3%)	5 (7%)	12 (29.3%)	5 (10.6%)	0 (0%)	2 (3.6%)	5 (14.7%)	
≥10	54 (9.8%)	4 (12.9%)	8 (15.7%)	10 (11%)	1 (1.6%)	5 (8.6%)	4 (5.6%)	8 (19.5%)	2 (4.3%)	2 (22.2%)	4 (7.3%)	6 (17.6%)	
Not Reported	206 **(37.5%)**	8 (25.8%)	17 (33.3%)	6 (6.6%)	28 (45.2%)	34 (58.6%)	43 (60.6%)	5 (12.2%)	26 (55.3%)	5 (55.6%)	23 (41.8%)	11 (32.4%)	
Number of Mitoses – Median (IQR)	4 (1.5 – 7)	2 (2 – 8)	5 (2 – 10)	3 (1 – 5)	2 (1 – 5)	5 (3 – 7.5)	3 (2 – 4)	5.5 (4 – 8)	3 (1 – 6)	8.5 (2 – 22)	2.5 (1 – 4.5)	6 (2 – 12)	0.34
Range	0–70	0–22	0–30	1–70	0–30	1–19	0–10	0–20	0–21	1–30	0–20	0–60	
Histologic Tumor Margin													<0.001
Well-defined	142 (25.8%)	17 (54.8%)	15 (29.4%)	25 (27.5%)	18 (29%)	2 (3.4%)	18 (25.4%)	7 (17.1%)	6 (12.8%)	2 (22.2%)	21 (38.2%)	11 (32.4%)	
Infiltrative	106 (19.3%)	3 (9.7%)	6 (11.8%)	33 (36.3%)	8 (12.9%)	14 (24.1%)	5 (7%)	8 (19.5%)	5 (10.6%)	3 (33.3%)	14 (25.5%)	7 (20.6%)	
Not Reported	298 **(54.2%)**	11 (35.5%)	30 (58.8%)	33 (36.3%)	35 (56.5%)	42 (72.4%)	46 (64.8%)	26 (63.4%)	36 (76.6%)	4 (44.4%)	19 (34.5%)	16 (47.1%)	
Presence of Necrosis													<0.001
No	90 (16.4%)	2 (6.5%)	4 (7.8%)	6 (6.6%)	19 (30.6%)	3 (5.2%)	17 (23.9%)	2 (4.9%)	7 (14.9%)	6 (66.7%)	17 (30.9%)	7 (20.6%)	
Yes	29 (5.3%)	1 (3.2%)	8 (15.7%)	2 (2.2%)	3 (4.8%)	2 (3.4%)	2 (2.8%)	2 (4.9%)	5 (10.6%)	0 (0%)	3 (5.5%)	1 (2.9%)	
Not Reported	427 **(77.6%)**	28 (90.3%)	39 (76.5%)	83 (91.2%)	39 (62.9%)	53 (91.4%)	50 (70.4%)	37 (90.2%)	35 (74.5%)	3 (33.3%)	34 (61.8%)	26 (76.5%)	
Final Surgical Margin Status													<0.001
Negative: NO tumor touching ink	310 (56.4%)	23 (74.2%)	24 (47.1%)	34 (37.4%)	39 (62.9%)	30 (51.7%)	62 (87.3%)	17 (41.5%)	28 (59.6%)	6 (66.7%)	28 (50.9%)	19 (55.9%)	
Positive: ANY tumor touching ink	231 (42%)	8 (25.8%)	25 (49%)	57 (62.6%)	22 (35.5%)	28 (48.3%)	7 (9.9%)	24 (58.5%)	19 (40.4%)	3 (33.3%)	23 (41.8%)	15 (44.1%)	
Not Reported	5 **(0.9%)**	0 (0%)	2 (3.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (5.5%)	0 (0%)	
Was Another Operation Performed?													<0.001
No	337 (61.3%)	20 (64.5%)	26 (51%)	39 (42.9%)	46 (74.2%)	44 (75.9%)	56 (78.9%)	17 (41.5%)	32 (68.1%)	4 (44.4%)	34 (61.8%)	19 (55.9%)	
Yes	209 (38%)	11 (35.5%)	25 (49%)	52 (57.1%)	15 (24.2%)	14 (24.1%)	13 (18.3%)	24 (58.5%)	15 (31.9%)	5 (55.6%)	20 (36.4%)	15 (44.1%)	

Percentages may not add up to 100 due to rounding or missing values.