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Pediatric phyllodes tumors: A review of the National Cancer Data Base and adherence to NCCN guidelines for phyllodes tumor treatment

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ABSTRACT

Background: Phyllodes tumors are fibroepithelial breast lesions that are uncommon in women and rare among children. Due to scarcity, few large pediatric phyllodes tumor series exist. Current guidelines do not differentiate treatment recommendations between children and adults. We examined national guideline adherence for children and adults.
Methods: We queried the NCDB (2004–2014) for female patients with phyllodes tumor histology, excluding patients with missing age or survival data. Patients were stratified by age (pediatric <21, adult ≥21), and compared based on patient characteristics, treatment patterns, and survival.
Results: We identified 2787 cases of phyllodes tumor (2725 adult, 62 pediatric). Median age was 17 years in children and 52 years in adults. Margin positivity rates and median tumor size were similar between adults and children. Treatment was discordant with NCCN guidelines in 28.6% of adults and 14.5% of children through use of axillary staging, chemotherapy, adjuvant endocrine therapy, and radiotherapy. Five-year and ten-year survival were comparable between both groups.
Conclusion: Children and adults present with similarly sized phyllodes tumors. Trends reveal high margin positivity rates, and overtreatment with regional axillary staging and systemic adjuvant therapies. Particularly in children, treatment decisions must consider risks of adjuvant therapy including radiation-related second primary cancers, given uncertain benefit.
Type of Study: Retrospective Comparative Study.
Level of Evidence: Level III.

Phyllodes tumors are rare fibroepithelial breast neoplasms with an incidence of 0.3–1.0% of all primary breast tumors, and are exceptionally rare among children [1,2]. First described by Johannes Müller in 1838 as "cystosarcoma phyllodes", these fibroepithelial lesions are composed of stromal and epithelial components with diverse biological behavior [3,4]. Structurally similar to fibroadenomas, phyllodes tumors exhibit a leaf-like growth pattern, cleft-like spaces lined by epithelium, hypercellular stroma, and may not be definitively differentiated by core needle biopsy [5].

Classical presentation includes a rapidly enlarging, palpable breast mass and abnormal imaging. Most are commonly diagnosed between ages 35–55, with a mean age of 40 at diagnosis in most large series [6–11]. Phyllodes tumors present one to two decades later than women diagnosed with fibroadenoma, the classic benign fibroepithelial breast mass in adolescent girls and young women [12,13]. The youngest age in large published series include 9 [13,14], 11 [7,8,10], 12 [6], 14 [9], & 15 [11] years at diagnosis. Very few large series of phyllodes tumors specifically in children exist due to the scarcity of this diagnosis [12,15], with most of the literature on the subject including small reports of fewer than 10 patients [16–18] or within series of pediatric fibroepithelial lesions [19–21].

Phyllodes tumors are classified by the World Health Organization (WHO) as benign, borderline, and malignant based on histopathologic characteristics including; stromal cellularity and atypia, mitotic activity, stromal overgrowth, and tumor margins [4]. These histologic subtypes have variable rates of recurrence and metastatic potential and are subject to significant subjectivity in diagnosis. National Comprehensive Cancer Network (NCCN) treatment guidelines for all subtypes include wide local excision without axillary staging, cautious consideration of

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radiation therapy, and adjuvant therapy [22]. Current guidelines do not distinguish treatment recommendations between children and adults. We sought to review the national experience with treatment of phyllodes tumors in children and adults. We then attempted to determine adherence to national guidelines for phyllodes tumors in children, compared to adults. We hypothesized that due to the rarity of phyllodes tumors in the pediatric population, children would experience higher rates of deviation from national treatment guidelines.

1. Materials and methods

1.1. Data source

The National Cancer Database (NCDB) is a national cancer registry containing patient information from over 1500 Commission on Cancer (CoC)-accredited facilities throughout the United States accredited by the American College of Surgeons and the American Cancer Society [23]. This dataset contains information regarding patient demographics, tumor characteristics, treatment patterns, short-term outcomes, and survival.

1.2. Data analysis

We utilized the NCDB to identify patients with histologically diagnosed phyllodes tumor (International Classification of Diseases for Oncology, 3rd Edition code: 9020) [24] from 2004 to 2014. Patients were stratified by age, based on current literature, defining pediatric patients as younger than 21 years old, and adult patients as 21 years or older [21,25]. Male patients and those with missing survival data were excluded from this analysis.

Patients were compared based on age classification to determine differences in disease presentation, patient management, and survival. Patient management was examined using NCCN guidelines to determine the relative adherence of providers to established treatment recommendations [22]. Current guidelines for phyllodes tumor recommend against axillary dissection and chemotherapy use. Additionally, they recommend cautious use of radiotherapy, particularly in young patients.

Patient characteristics were summarized with N (%) for categorical variables and median (range or interquartile range) for continuous variables for all patients and for pediatric vs. adult patients. Chi-square or Fisher's exact tests were used to compare categorical variables, and Wilcoxon rank sum tests or t-tests were used to compare continuous variables, as appropriate.

Overall survival was defined as the time from diagnosis to death or last follow-up. Kaplan–Meier curves were used to visualize unadjusted overall survival and the log-rank test was used to estimate the difference between pediatric and adult patients. The Kaplan–Meier method was used to estimate 5- and 10-year survival rates and 95% confidence intervals (CIs) for each group. A multivariate Cox Proportional Hazards model was used to identify factors associated with overall survival. A robust sandwich covariance estimator was used in this model to account for the correlation of patients treated at the same hospital. A two-tailed significance level of 0.05 was used for all statistical tests and no adjustments were made for multiple comparisons. Only patients with complete data for all covariates included in a given model were included in each analysis, and effective sample sizes are reported for each table/figure. All analyses were conducted with R version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria) or SAS version 9.4 (SAS Institute, Cary, NC).

2. Results

2.1. Patient characteristics

We identified 2787 cases of phyllodes tumors (62 pediatric, 2725 adult). We excluded 262 patients due to unknown or missing survival data (5 children, 257 adults) and two patients due to male gender. Patient characteristics demonstrated similarities between children and adults based on insurance status, Charlson-Deyo comorbidity score, and geographic location (Table 1). Treatment setting varied between the two populations. Children were more likely to be treated at an academic institution, while adults were more likely to be treated in a community setting, comprehensive center, or integrated network. Baseline differences between children and adults reflected a higher proportion of African American children and Caucasian adults developing phyllodes

Table 1
Baseline characteristics of patients with phyllodes tumor.

	All patients N = 2787	Pediatric N = 62	Adult N = 2725	p-Value
Age	52 (43–61)	17 (16–19)	52 (43–61)	<.001
Insurance Status				.28
Government	830 (29.8%)	17 (27.4%)	813 (29.8%)	
Private	1718 (61.6%)	41 (66.1%)	1677 (61.5%)	
Not Insured	184 (6.6%)	1 (1.6%)	183 (6.7%)	
Race				<.001
Asian	190 (6.8%)	4 (6.5%)	186 (6.8%)	
Black	378 (13.6%)	23 (37.1%)	355 (13%)	
White	2116 (75.9%)	31 (50%)	2085 (76.5%)	
Other	53 (1.9%)	1 (1.6%)	52 (1.9%)	
Charlson-Deyo Comorbidity Score				.10
0	2516 (90.3%)	61 (98.4%)	2455 (90.1%)	
1	229 (8.2%)	1 (1.6%)	228 (8.4%)	
≥ 2	42 (1.5%)	0 (0%)	42 (1.5%)	
Treatment Facility Type				.04
Academic	984 (35.3%)	30 (48.4%)	954 (35%)	
Community	273 (9.8%)	3 (4.8%)	270 (9.9%)	
Comprehensive	1124 (40.3%)	17 (27.4%)	1107 (40.6%)	
Integrated Network	336 (12.1%)	5 (8.1%)	331 (12.1%)	
Facility Location				.51
Midwest	633 (22.7%)	13 (21%)	620 (22.8%)	
Northeast	616 (22.1%)	11 (17.7%)	605 (22.2%)	
South	959 (34.4%)	14 (22.6%)	945 (34.7%)	
West	463 (16.6%)	12 (19.4%)	451 (16.6%)	

Categorical variables listed as N (%), Continuous variables listed as median (IQR).
Percentages may not add up to 100 due to rounding or missing values.