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Nationwide overview of survival and management of appendiceal tumors in children☆

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ABSTRACT

Introduction: There remains a paucity of literature on survival related to pediatric appendiceal tumors. The purpose of this study was to determine the incidence, surgical management, and survival outcomes of appendiceal tumors in pediatric patients.
Methods: The Surveillance, Epidemiology, and End Results (SEER) Registry was analyzed for pediatric appendiceal tumors from 1973 to 2011. Parameters analyzed were: tumor type, surgical management (appendectomy vs. extensive resection), tumor size, and lymph node sampling. Chi-square analysis for categorical and Student's t test for continuous data were used.
Results: Overall, 209 patients had an appendiceal tumor, including carcinoid (72%), appendiceal adenocarcinoma (16%), and lymphoma (12%). Patients undergoing appendectomy vs. extensive resection had similar 15-year survival rates (98% vs. 97%; $p = 0.875$). Appendectomy vs. extensive resection conferred no 15-year survival advantage when patients were stratified by tumor type, including adenocarcinoma (87% vs. 89%; $p = 0.791$), carcinoid (100% vs. 100%; $p = 0.863$), and lymphoma (94% vs. 100%; $p = 0.639$). There was no significant difference in 15-year survival between tumor size groups ≥ 2 and < 2 cm (both 100%) and presence or absence of lymph node sampling (96% and 97%; $p = 0.833$) for all patients with a carcinoid tumor.
Conclusion: Appendectomy may be adequate for pediatric appendiceal tumors. Extensive resection may be of limited utility for optimizing patient survival, placing patient at greater operative risk.
Type of Study: Retrospective Prognostic Study.
Level of Evidence: III

There remains a paucity of literature on pediatric survival outcomes related to appendiceal tumors with surgical management often extrapolated from the adult experience. This can be attributed to the rarity of appendiceal malignancies, found in approximately 1% of appendectomy specimens [1]. Even though primary appendiceal cancers are rare, there is a diverse histology. Neuroendocrine tumor of the appendix, previously termed carcinoid, is the most common gastrointestinal epithelial tumor in children and adolescents. While the majority of carcinoid tumors in children are <1 cm in size and uniformly managed with simple appendectomy, approximately 6% are >2 cm in size where traditionally, right hemicolectomy has been recommended given concerns for metastasis [2,3]. Findings concerning for local metastasis including mesoappendiceal, periappendiceal fat and lymphovascular invasion have also prompted clinicians to consider extensive resection over simple appendectomy [4]. Nonetheless, the malignant potential and operative schema of carcinoid tumors oftentimes remains unclear with lymph node involvement associated with larger tumor size [5]

Conversely, appendiceal adenocarcinoma is known for its highly malignant potential and early disease advancement. Based on adult experience, right hemicolectomy appears to be a reasonable management option for non-metastatic appendiceal adenocarcinoma, although its superiority to appendectomy alone has not been definitively proven in adults or children [6]. Likewise, the surgical management for other more rare but plausible appendiceal tumors such as non-Hodgkin's lymphoma (NHL) remains controversial with multimodality approach including surgery, radiation therapy and chemotherapy frequently implemented.

Overall, the survival benefit of extensive resection over appendectomy in pediatric patients with an appendiceal tumor including carcinoid, appendiceal adenocarcinoma and lymphoma remains unclear. Given the rarity of these tumors, previous reports have been limited by small case size. As such, there is no consensus on the role of appendectomy vs. extensive resection of appendiceal tumors in children. The purpose of this study is to determine the incidence, surgical management (appendectomy vs. extensive resection including partial

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colectomy) and survival outcomes of appendiceal tumors in pediatric patients.

1. Methods

The National Cancer Institute Surveillance, Epidemiology, and End results (SEER) database April 2013 release was used to identify and analyze all cases of appendiceal tumors in pediatric patients undergoing resection in the United States between 1973 and 2011. Cases were limited to children <20 years of age where based on current literature, a malignant lesion is most commonly discovered incidentally during routine appendectomy for acute appendicitis [7].

Tumor histology in the SEER database was identified using the International Classification of Diseases for Oncology, 3rd revision (ICD-O-3). All major types of appendiceal tumors were included in this study where histologic ICD-O-3 diagnoses and codes were carcinoid tumor not otherwise specified (NOS 8240/3), enterochromaffin cell carcinoid (8241/3), goblet cell carcinoid (8243/3), mixed adenoneuroendocrine carcinoid (8244/3), adenocarcinoid tumor (8245/3), neuroendocrine carcinoma (8246/3), atypical carcinoid tumor (8249/3), adenocarcinoma in villous adenoma (8261/3), mucinous cystadenocarcinoma (8470/3), appendiceal adenocarcinoma (8140/3), mucinous adenocarcinoma (8480/3), mucin-producing adenocarcinoma (8481/3), NHL NOS (9591/3), diffuse large B cell lymphoma NOS (9680/3), Burkitt's lymphoma (9687/3), peripheral T cell lymphoma NOS (9702/3). Only carcinoid tumors that were considered malignant were included. The data were retrospectively reviewed and parameters analyzed included demographics, clinicopathological characteristics, appendiceal tumor type, tumor size, surgical management consisting of appendectomy vs. extensive resection involving partial colectomy, lymph node sampling and survival outcomes using standard statistical methods. Patients with a primary malignancy other than appendiceal were excluded.

SEER*Stat software, version 18.0 (National Cancer Institute; Bethesda, MD) was employed to obtain incidence and survival data. All data on incidence were age adjusted and normalized to the 2000 US standard population. Statistical analyses were conducted using SPSS, version 21.0 (IBM; Armonk, NY). Categorical variables were compared using χ^2 or Fisher's exact tests as appropriate. Normally distributed continuous data were compared using student's t tests, as appropriate. All tests were two-tailed, and statistical significance was considered at $p < 0.05$. Overall and disease specific survival curves were calculated using the Kaplan–Meier method. Survival curves were compared between groups using the log-rank test. Bonferroni method was used to adjust for multiple comparisons. All analyses were limited to available data.

The Institutional Review Board at the University of Miami Miller School of Medicine exempted this retrospective analysis from full review. The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

2. Results

Overall, 209 patients were identified as having an appendiceal tumor requiring operative resection with an overall age-adjusted incidence of 0.036 per 100,000 persons. Patients were most commonly female (60%), white (89%) and aged 15–19 years (62%) (Table 1). Most patients were diagnosed with carcinoid tumor (76%) followed by appendiceal adenocarcinoma (14%) and lymphoma (10%) (Table 1).

The overall mean survival was 98% for 474 months ± 6.7 where all 5 patient deaths were related to disease-specific mortality and occurred within the first 60 months post procedure. Among these 5 deaths, 1 patient had non-Hodgkin's lymphoma and the remaining 4 patients had appendiceal adenocarcinoma (n = 4). Based on final pathology, diagnosis included adenocarcinoma in villous adenoma (n = 1), appendiceal adenocarcinoma (n = 2), mucinous adenocarcinoma (n = 1) and Burkitt's lymphoma (n = 1). The patient with Burkitt's lymphoma was unstaged, whereas patients with appendiceal adenocarcinoma had either distant (n = 3) or regional (n = 1) disease. In terms of surgical resection, 3 patients underwent appendectomy, 1 underwent extensive resection and the final patient's operative procedure was unknown. Survival for females and males was statistically similar (98% vs. 96%, p = 0.325). When considering survival based on race, mean survival for blacks was lowest (90%) and highest for whites (98%), although this difference was not statistically significant (p = 0.26). Survival was lowest for patients in the oldest age group of 15–19 years (96%) as compared to younger age groups of 0–4 years, 5–9 year and 10–14 years (all 100%, p = 0.365).

Table 1
Survival rates of pediatric appendiceal tumors by demographics and clinical characteristics.

Characteristic	N (% of total)	Survival (%)	p-Value
Overall	209 (100%)		
Sex			0.325
Female	126 (60%)	98%	
Male	83 (40%)	96%	
Race			0.26
White	178 (89%)	98%	
Black	10 (5%)	90%	
Other	13 (6%%)	92%	
Age (y)			0.365
0–4	2 (1%)	100%	
5–9	5 (2%)	100%	
10–14	73 (35%)	100%	
15–19	129 (62%)	96%	
Disease staging			**0.0001**
Localized	133 (64%)	100%	
Regional	41 (20%)	98%	
Distant	4 (2%)	25%	
Unstaged	31 (15%)	97%	
Histologic subtype			**0.0001**
Carcinoid	109 (72%)	100%	
Appendiceal adenocarcinoma	24 (16%)	87%	
Lymphoma	18 (12%)	95%	
Procedure			0.875
Appendectomy	119 (79%)	98%	
Extensive resection	32 (21%)	97%	

Appendectomy was more commonly performed as compared to extensive resection in all racial groups including whites (78% vs. 22%), blacks (57% vs. 43%) and Asians/Pacific Islanders/Native Americans (90% vs. 10%). Among all patients undergoing appendectomy, 53% were female. Conversely, among all patients undergoing extensive resection, 69% were female, a more than two-fold increase as compared to males (p = 0.159). When stratified by age groups, appendectomy was more commonly performed in the oldest age group 15–19 years (66%) followed by 10–14 years (30%), 5–9 years (3%) and finally 0–4 years (1%). Similarly, extensive resection was more commonly performed in the oldest age group 15–19 years (59%) followed by 10–14 years (38%) and 0–4 years (3%).

Based on appendiceal tumor type, there was a significant difference in survival between patients with a carcinoid tumor (100%), appendiceal adenocarcinoma (87%) and lymphoma (95%, p < 0.0001) (Fig. 1). Similarly, when stratified by disease stage there was a significant difference in survival between children with localized (100%), regional (98%) and distant disease (25%, p < 0.0001) (Fig. 2). Interestingly, Kaplan–Meier curves demonstrated no significant difference in overall patient survival based on extent of surgical resection between appendectomy and extensive resection (98% vs. 97%, p = 0.875) (Fig. 3).

Appendectomy was performed in the majority of patients with carcinoid tumor, appendiceal adenocarcinoma and lymphoma (81%, 63% and 89%, respectively). Cross tabulation of survival based on cancer type and extent of surgery revealed that survival was highest in pediatric patients with a carcinoid tumor undergoing either appendectomy or extensive resection (both 100%) followed by lymphoma (94% vs. 100%, respectively) and appendiceal adenocarcinoma (87% vs. 89%, p =

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