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Original Article

Clinicopathologic and prognostic features in appendiceal malignancies: Tumor invasiveness matters

Kazım Şenol[1], Murat Ferhat Ferhatoğlu[2], Deniz Tihan[3]

ABSTRACT

Objective: Appendiceal tumors are rare and mostly present as acute appendicitis. Its estimated lifetime prevalence has been reported as 8%, and the annual incidence is approximately 0.1% in Western countries. The only treatment approach is still surgery, but surgical management still remains unclear in appendiceal malignancy.

Material and Methods: Histopathological examination of 2840 specimens obtained from patients who underwent appendectomy between January 2012 and December 2015 was investigated. Data from 23 patients diagnosed with the malignancy had been analyzed in terms of age, gender, and preoperative and postoperative clinical parameters. The overall survival rates of the patients and prognostic parameters affecting survival were also evaluated. Statistical analyses were performed using the SPSS software. The study was performed according to the Declaration of Helsinki.

Results: The overall median age of the patients was 28 years with a male/female ratio of 1.55. Pediatric group between 1 and 6 years, late pediatric group between 7 and 11 years, and adolescent group between 12 and 17 years did not present appendix tumors. Carcinoid tumors were reported in 17 patients. Adenocarcinoma of the appendix was reported in 6 patients. Patients with carcinoid tumors were significantly younger than those with adenocancer (p=0.01). The mean tumor size of the carcinoid group was significantly smaller than that of the adenocancer group (p=0.02). Patients with adenocancer were significantly more likely to have tumor extension beyond the appendix (p=0.05). All patients in the adenocancer group and 4 patients in the carcinoid group with mesoappendix invasion underwent right hemicolectomy. Univariate analyses demonstrated that serosal invasion, advanced tumor stage, and tumor invasion depth were associated with poor survival rates.

Conclusion: Tumor subtype and tumor invasiveness are important risk factors for survival in appendiceal malignancies. Appendectomy alone presents satisfactory results, but complete staging of the tumor should always be considered. In addition, surgical choice is not presented as an effective factor for improved clinical outcomes and survival rates. Further prospective studies are needed to evaluate the proper staging of the tumors.

Keywords: Appendectomy, appendicitis, appendiceal malignancies, appendiceal tumors

ORCID IDs of the authors:
K.Ş. 0000-0001-6273-0664;
M.F.F. 0000-0002-8443-2630;
D.T. 0001-0002-4197-2709

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[1]Department of General Surgery, Koç University School of Medicine, İstanbul, Turkey
[2]Department of General Surgery, Okan University School of Medicine, İstanbul, Turkey
[3]Department of General Surgery, Bursa Yüksek İhtisas Training and Research Hospital, İstanbul, Turkey

Corresponding Author
Kazım Şenol
e-mail: kazimsenol@hotmail.com

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INTRODUCTION

Acute appendicitis is still the most frequent abdominal pathology requiring emergent surgery worldwide (1, 2). Its estimated lifetime prevalence has been reported as 8% (2). The annual incidence of this pathology is approximately 0.1% in Western countries (2-4). The most common pathogenesis of acute appendicitis is luminal obstruction of the appendix by a fecolith (2). However, all causes that may-directly or indirectly-obliterate the appendiceal cavity will lead the patient to an acute appendicitis. Appendiceal tumors are relatively rare, but, possible malignant appendiceal tumors may also obliterate the appendix lumen (5).

Despite the extensive use of antibiotics, appendectomy has been considered the standard treatment of appendiceal acute inflammation for decades (1, 2). Nowadays, the primary treatment approach is still surgery. Generally, open or laparoscopic removal of the appendix is the main aim of the surgical procedures. On the other hand, surgical management still remains unclear in appendiceal malignancy in the literature (6).

The aim of this study was to discuss the management of malignant disease of the appendix in light of our case series data in the present study.

MATERIAL AND METHODS

This was a retrospective clinical study. The study was conducted in the Department of General Surgery, Bursa Yüksek İhtisas Training and Research Hospital and Bursa State Hospital. Histopathological examination of 2840 specimens obtained from patients who underwent appendectomy between January 2012 and December 2015 was investigated retrospectively. Twenty-three of these 2840 specimens were diagnosed as appendiceal malignancies. In total, data from 23 patients had been analyzed in terms of age, gender, and preoperative and postoperative clinical parameters. The overall survival rates of the patients and prognostic parameters affecting survival were also evaluated. The study was performed

Table 1. Patient demographic data and tumor characteristics with primary appendiceal malignancies

Case	Gender	Age	Operation	Tumor size (mm)	Localization	Pathology	TNM	Follow-up (months)	Recurrence
1	Female	28	CA	5	Apex	Carcinoid tumors	Muscularis	59	None
2	Male	23	CA	10	Distal	Carcinoid tumors	Subserosa	58	None
3	Female	71	CA	11	Apex	Carcinoid tumors	Mucosa	53	None
4	Female	44	CA	7	Apex	Carcinoid tumors	Subserosa	52	None
5	Male	40	CA	2	Apex	Carcinoid tumors	Muscularis	47	None
6	Female	37	RHC	17	Distal	Carcinoid tumors	Subserosa	47	None
7	Female	34	CA	6	Apex	Carcinoid tumors	Subserosa	46	None
8	Male	23	CA	3	Distal	Carcinoid tumors	Submucosa	44	None
9	Male	19	CA	6	Apex	Carcinoid tumors	Submucosa	43	None
10	Female	24	CA	8	Apex	Carcinoid tumors	Muscularis	38	None
11	Male	36	CA	22	Body	Carcinoid tumors	Muscularis	35	None
12	Male	40	CA	4	Apex	Carcinoid tumors	Muscularis	31	None
13	Female	24	CA	3	Apex	Carcinoid tumors	Mucosa	26	None
14	Female	28	CA	12	Body	Carcinoid tumors	Serosa	59	None
15	Male	41	RHC	13	Distal	Carcinoid tumor	Serosa	57	None
16	Male	55	RHC	15	Distal	Carcinoid tumor	Serosa	42	None
17	Female	55	RHC	17	Body	Carcinoid tumor	Serosa	39	None
18	Male	68	RHC	21	Distal	Non-mucinous AC	Serosa	55	None
19	Male	54	RHC	17	Distal	Non-mucinous AC	Serosa	53	None
20	Female	48	RHC	13	Distal	Non-mucinous AC	Serosa	45	None
21	Female	41	RHC	12	Body	Mucinous	Submucosa	30	None
22	Female	60	RHC	20	Apex	Mucinous AC	Surrounding tissue	55	None
23	Male	49	RHC	13	Apex	Mucinous AC	Serosa	40	None

TNM: tumor node metastasis; CA: complete appendectomy; RHC: right hemicolectomy; AC: adenocarcinoma

in accordance to the Declaration of Helsinki and approved as a retrospective study by Institutional Review Board of Yüksek İhtisas Training and Research Hospital. A waiver of informed consent was requested, and approval was obtained.

Statistical Analysis

In descriptive analyses, mean ± standard deviation was used for data following normal distribution and median and minimum-maximum values for non-parametric data. Non-parametric values were compared using Mann-Whitney U test. Comparison of categorical variables, such as gender and histopathology, was conducted using Fisher's exact and chi-square tests. Factors identified as significant in univariate analyses were included in the multivariate logistic regression analysis.

Patients were followed up for 5 years after surgery. Death records were completed until January 2016. Overall survival (OS) was measured until the date of death from any cause. The relationship between clinicopathologic characteristics and OS was examined by Kaplan-Meier log-rank survival analyses and univariate Cox proportional hazards regression to calculate hazard ratios (HRs) and 95% confidence intervals (95% CIs). Statistically significant variables ($p<0.20$) were entered into a multivariate model using an entered method. The relationship between survival and prognostic parameters was examined using the X2 method for linear trend. In all statistical tests conducted as part of the study, α value was accepted as 0.05. A p-value <0.05 was considered as statistically significant. Statistical analyses were performed using the SPSS software (Statistical Package for the Social Sciences version 21.0; SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 2840 patient demographic data, clinical data, and pathology reports were analyzed retrospectively. The overall median age of the patients was 28 years (range: 1-89 years) with a male (n=1730, 60.9%)/female (n=1110, 39.1%) ratio of 1.55. Pediatric group between 1 and 6 years (n=73, 2.6%), late pediatric group between 7 and 11 years (n=146, 5.1%), and adolescent group between 12 and 17 years (n=228, 8%) did not present appendix tumors. Carcinoid tumors were reported in 17 (0.59%) patients. Adenocarcinoma of the appendix was reported in 6 (0.20%) patients in which 3 (0.1%) of the tumors were with mucinous histology. The median ages of the patients were 36 years (range: 19-71 years) in the carcinoid group and 51 years (range: 41-68 years) in the adenocancer group. Patients with carcinoid tumors were significantly younger than those with adenocancer (p=0.01). Carcinoid tumors were mostly located on the apex of the appendix in 9 (52.9%) patients, located at the base of the appendix in 5 (29.4%) patients, and located at the body of the appendix in 3 (17.6%) patients. The mean tumor size of the car-

Table 2. The relationship between clinical parameters and subtypes of appendiceal malignancies

	Carcinoid tumors (n=17)	Mucinous/non-mucinous adenocancer (n=6)	p (univariate analyses)	p (multivariate analyses)
Age* (years)	36.59±13.94	53.33±9.58	0.01	-
Gender#				
Male	8 (34)	3 (13)	0.63	-
Female	9 (39)	3 (13)		
Tumor size* (mm)	9.47 (5.83)	16 (3.90)	0.02	-
Tumor location#				
Distal	5 (21)	3 (13)	0.35	-
Body	3 (13)	1 (4)		
Apex	9 (39)	2 (8)		
Type of surgery#				
Appendectomy	13 (76)	-	0.002	-
Right hemicolectomy	4 (23)	6 (100)		
Tumor extension# (no/yes)				
Limited to the appendix	13/4	1/5	0.05	-
Serosa invasion	12/4 (23)	1/5 (83)	0.05	0.029
Mesoappendix invasion	11/4 (23)	1/5 (83)	0.02	-
Vascular invasion	11/6 (35)	2/4 (66)	0.19	-
Perineural invasion	9/6 (35)	2/4 (66)	0.26	-

Datas are presented as *: mean±standard deviation, #: n (%)

Table 3. The relationship between prognostic factors and survival of patients with appendiceal malignancies following surgery

Variables	Univariate analyses, HR (95% CI)	p	Multivariate analyses, HR (95% CI)	p
Age (15–40 years/40–65 years/>65 years)	0.54 (0.36-8.05)	0.489	-	-
Gender (male/female)	0.21 (0.52-2.92)	0.626	-	-
Tumor type (carcinoid/adenocancer)	0.12 (0.42-2.98)	0.805	-	-
Tumor site (base/body/apex)	0.27 (0.30-1.91)	0.560	-	-
Tumor stage (TNM)	1.96 (0.64-7.86)	0.108	0.23 (0.76-2.11)	0.361
Tumor invasion depth	1.63 (0.47-5.07)	0.179	1.31 (1.01-13.5)	0.047
Mesoappendix invasion (no/yes)	0.26 (0.54-3.10)	0,558	-	-
Vascular invasion (no/yes)	0.33 (0.60-3.21)	0.430	-	-
Perineural invasion (no/yes)	0.33 (0.58-3.31)	0.453	-	-
Serosal invasion (no/yes)	0.70 (0.81-5.04)	0.129	0.45 (0.33-7.36)	0.561
Tumor perforation (no/yes)	0.10 (0.13-9.44)	0.920	-	-

TNM: tumor node metastasis

cinoid group (9.47±5.83 mm) was significantly smaller than that of the adenocancer group (16±3.90 mm, p=0.02). Histopathology revealed that all of the adenocarcinomas originated from the adenoma. In the adenocarcinoma group, except 1 (16.6%) submucosal mucinous tumor (T1N0M0), 5 (83.3%) patients presented with serosal invasion (T4N0M0). In the carcinoid group, 2 (11.76%) patients presented with mucosal and submucosal invasion, 5 (29.41%) patients with lamina muscularis propria invasion, and 4 (23.52%) patients with subserosa and serosa invasion. Patients with adenocancer were significantly more likely to have tumor extension beyond the appendix, whereas patients with carcinoid tumors tended to be limited to the appendix (p=0.05). Mucinous/non-mucinous adenocarcinoma histology interpretation also showed significant serosal (p=0.05) and mesoappendix invasion (p=0.002). All patients in the adenocancer group and 4 (23.52%) patients in the carcinoid group with mesoappendix invasion underwent right hemicolectomy (p=0.002). Multivariate analyses of statistically significant factors in univariate analyses presented serosal invasion as a sole independent risk factor for the mucinous and non-mucinous adenocancer group (HR: −2.70, 95% CI: 0.006-0.755, p=0.029). Tables 1 and 2 show the tumor characteristics of patients.

The median follow-up time was 48 months (range: 28-61 months). All patients were alive and disease-free since the last follow-up. The estimated median survival rates of the carcinoid tumors, mucinous, and non-mucinous adenocarcinomas were 48 (95% CI: 44-52), 55 (95% CI: 42-68), and 42 (95% CI: 26-58) months, respectively. Additionally, disease-specific survival rates of carcinoid tumors, mucinous, and non-mucinous adenocancers were 36 (95% CI: 32-40), 30 (95% CI: 13-46), and 43 (95% CI: 30-55) months, respectively (p=0.748).

Univariate analyses demonstrated that serosal invasion (p=0.129), advanced tumor stage (p=0.108), and tumor invasion depth (p=0.179) were associated with poor survival rates. On multivariate analyses, tumor invasion depth was the only independent prognostic factor affecting survival (HR=1.31, 95% CI: 1.01–13.5, p=0.047). Table 3 shows the relationship between clinicopathologic characteristics and survival.

DISCUSSION

Appendiceal tumors are broadly classified as epithelial and non-epithelial tumors. Epithelial tumors include adenoma, mucinous tumors with uncertain malignant potential, and adenocarcinoma (7). Appendiceal adenocarcinomas represent 4%-6% of the overall appendiceal malignancies and are notably rare tumors (8). Primary appendiceal adenocancers are mostly observed in the sixth and seventh decades of life with an equal male/female ratio (9). The presentation of appendiceal adenocancers differs in the clinical setting. The tumor should be presented as an incidental finding following acute appendicitis, as a pelvic mass, or as peritoneal carcinomatosis with or without ascites (10). Acute appendicitis is the most common presentation (11). Therefore, there have been difficulties in determining the most appropriate classification system while defining appendiceal adenocarcinomas (12). There are no designated World Health Organization (WHO) and American Joint Committee on Cancer (AJCC) staging systems for all subtypes of primary appendiceal carcinomas regarding the rarity of the disease (5). Pai and Longacre classified appendiceal epithelial tumors into mucinous and non-mucinous (intestinal and signet ring cell) types (13). Mucinous adenocarcinoma represents 60% of the overall primary appendiceal adenocarcinomas, followed by intestinal-type adenocancers and signet ring cell carcinomas (14). Whether the differences in tumor characteristics, tumor progression, and overall disease-free survival rates suggest that all subtypes of appendiceal adenocancers are distinct pathologies, to achieve the exact removal of the tumor with clear margins is determined as curative therapy. While simple appendectomy is described as a therapeutic method in local disease, adjunctive right hemicolectomy presented better survival rates (6). In our study, all patients in the adenocancer group underwent right hemicolectomy, but there was no significant survival benefit between the groups even though the median survival rate of the mucinous group was higher than that of the non-mucinous group. Similar to our findings, McCuskey et al. mentioned in a review of 1061 cases that patients with mucinous and intestinal-type adenocancer histology did not show any significant difference in survival rates (9). In the literature, peritonitis on diagnosis, histological subtype, tumor grade, extent of surgery, and pre- or peroperative peritoneal dissemination and intraperitoneal chemotherapy are well-defined prognostic factors affecting survival and tumor recurrence (5, 15-17). In addition to these prognostic factors, including extended disease and age, aggressive tumor histology, such as poorly differentiated adenocarcinomas and signet ring cell-type carcinomas, is associated with a 5-year survival rate of only 7% and worst prognosis (14, 18).

Non-epithelial tumors of the appendix are endocrine-carcinoid tumors, lymphomas, and sarcomas. In contrast to appendiceal adenocancers, carcinoid tumors of the appendix are diagnosed at a much younger age of 32–42 years with female predominance (14, 19). However, there have been reports regarding a decrease in the overall percentage of appendiceal endocrine neoplasm among all gastrointestinal neuroendocrine tumors, and the prevalence of carcinoid tumors among all primary tumors of the appendix ranges between 43% and 57% (20, 21). WHO classified endocrine tumors according to histological differentiation and graded the tumors as benign and malignant well differentiated tumors and mixed exocrine-endocrine malignant tumors (goblet cell carcinoid) (22). Goblet cell carcinoid (adenocarcinoma) is also a rare tumor containing both epithelial and neuroendocrine features with progressive clinical course in 20%–40% of the cases presented with early nodal involvement (23). Appendectomy with clear margins is defined as sufficient surgical option for early stage tumors of primary appendiceal malignancies except goblet cell adenocancer. Locally advanced adenocarcinoma or carcinoid tumors and goblet cell adenocarcinoma have a relative indication for right hemicolectomy with completion of tumor staging. Localization and size of the carcinoid tumors are prognostic factors in addition to tumor differentiation. The AJCC staging system for carcinoid tumors is based on the tumor size but does not consider tumor invasion depth and tumor grade. Mitotic activity, mesoappendix, and lymphovascular invasion are also independent prognostic factors for carcinoid tumors. Although serosal involvement is not interpreted as a risk factor for carcinoid tumors, mesoappendix invasion is presented with poor prognosis (24). The European Neuroendocrine Tumor Society defined staging system including these important histological features, tumor grade, and mesoappendix invasion (25).

The present study showed how the clinicopathologic characteristics of the tumor are affecting survival of the patients undergoing curative resection of appendiceal malignancies. These data support the routine histological sampling of the tumor and preoperative and postoperative clinical outcomes of the patients. In the present study, surgical choice between tumor subtypes was not associated with poor clinical outcomes. Statistical analyses between tumor subtypes revealed that patients with adenocarcinoma presented with an advanced age, larger tumor size, and more extended disease at diagnosis. Carcinoid tumors were mostly located at the apex of the appendix with local disease. As expected, the presence of serosal invasion was referred to as an independent high-risk factor for patients with adenocancer of the appendix. Although the estimated median survival rates between tumor subtypes were in close range, there was no disease related to death and recurrence during the follow-up in all subtypes of appendiceal malignancies. The survival rates of the patients between tumor subtypes were not statistically significant. Among all clinical and pathological parameters identified pre- and postoperatively, tumor invasion depth was found as a sole risk factor affecting survival. Increased tumor invasion was found to be associated with decreased disease-specific survival rates.

There are several limitations regarding the multicenter and retrospective nature of our study. Several surgeons and surgery departments participated and provided invaluable clinical and pathological data. Interpretation of the pathological specimens differed among centers and in between pathologists. Unfortunately, there were no reports of signet ring cell carcinoma and goblet cell carcinoid tumors. Therefore, the present study could not present the risk factors and survival rates of these groups of tumors. Our study also suggests that cooperation between referral clinics in defining the confirmed histological outputs and processing the data prospectively should be more effective to obtain better clinical outcomes with more reliable data.

CONCLUSION

Tumor subtype and tumor invasiveness are important risk factors for survival in appendiceal malignancies. In addition, surgical choice is not presented as an effective factor for improved clinical outcomes and survival rates. Appendectomy alone presents satisfactory results, but complete staging of the tumor should always be considered. Further prospective studies are needed to evaluate the proper staging of the tumors.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Yüksek İhtisas Training and Research Hospital.

Informed Consent: Written informed consent was obtained from patients who participated to the study.

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