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SURGICAL MANAGEMENT OF APPENDIX TUMORS: A SINGLE-CENTER REVIEW OF 15 YEARS

APENDİKS TÜMÖRLERİNİN CERRAHİ TEDAVİSİ: 15 YILLIK TEK MERKEZLİ BİR İNCELEME

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ABSTRACT

Objective: Primary neoplasms of the appendix are rare and most clinicians are unfamiliar with them. The selected approach may differ, ranging from appendectomy to cytoreductive surgery. We aimed to present our clinical experience with the surgical management of appendix tumors.

Materials and Methods: 4,450 patients with a history of appendectomy from January 2006 to February 2021 were analyzed retrospectively. Patients diagnosed with "serrated lesion/polyp, low/high-grade appendiceal mucinous neoplasm (LAMN/HAMN), mucinous/non-mucinous/goblet cell adenocarcinoma, neuroendocrine tumor (NET)" were included in the study. Histological evaluations, surgical procedures, follow-up data, and survival outcomes were evaluated.

Results: Among 132 [F:87 (65.9%)] patients diagnosed with appendix tumors, 27 (20.5%) were in the benign group (Group A), 61 (46.2%) were in the borderline group (Group B), and 44 (33.3%) were in the malignant group (Group C). Appendectomy and right hemicolectomy were performed as the initial operations in 105 (79.5%) and 27 (20.5%) patients, respectively. Seventeen patients (12.9%) with a previous history of appendectomy received right hemicolectomy (n=9; due to surgical margin positivity) and Cytoreductive Surgery (CRS) with Hyperthermic Intraperitoneal Chemotherapy (HIPEC) (n=8; due to recurrence) as redo surgery during the follow-up period. Appendectomy was sufficient for 88 (66.6%) patients. Adenocarcinoma was revealed as a statistically significant factor for recurrence-free survival (RFS) (HR=7.28, p=0.049). Malignancy (HR=3.76, p=0.036) and age (≥60) (HR=3.86, p=0.006) were significant factors of overall survival (OS).

ÖZET

Amaç: Apendiksin primer neoplazmları, çoğu klinisyenin aşina olmadığı nadir bir durumdur. Seçilen yaklaşım apendektomiden sitoredüktif cerrahiye farklılık gösterebilir. Apendiks tümörlerinin cerrahi tedavisi ile ilgili klinik deneyimimizi sunmayı amaçladık.

Gereç ve Yöntem: Ocak 2006 ile Şubat 2021 arasında; apendektomi öyküsü olan 4450 hasta geriye dönük olarak incelendi. 'Tırtıklı lezyon/polip, düşük/yüksek dereceli apendiks müsinöz neoplazm (LAMN/HAMN), müsinöz/müsinöz olmayan/goblet hücreli adenokarsinom, nöroendokrin tümör (NET)' tanısı alan hastalar çalışmaya dahil edildi. Histolojik değerlendirmeler, cerrahi prosedürler, takip verileri ve sağkalım sonuçları değerlendirildi.

Bulgular: Apendiks tümörü tanısı konan 132 [K:87 (%65.9)] hastadan; 27'si (%20,5) benign (Grup A), 61'i (%46,2) borderline (Grup B) ve 44'ü (%33,3) malign (Grup C) grupta idi. Primer operasyon olarak sırasıyla 105 (%79,5) ve 27 (%20,5) hastaya apendektomi ve sağ hemikolektomi uygulandı. Daha önce apendektomi öyküsü olan 17 hastaya (%12.9) sağ hemikolektomi (n=9; cerrahi sınır pozitifliği nedeniyle) ve Hipertermik İntraperitoneal Kemoterapi (HIPEC) ile Sitoredüktif Cerrahi (CRS) (n=8; nüks nedeniyle) sekonder cerrahi olarak uygulandı. Takip süresi boyunca 88 (%66,6) hastaya sadece apendektomi uygulandı. Adenokarsinom, nüksüz sağkalım (RFS) için istatistiksel olarak anlamlı bir faktör olarak ortaya çıktı (HR=7.28, p=0.049). Malignite (HR=3.76, p=0.036) ve yaş (≥60) (HR=3.86, p=0.006) genel sağkalımın (OS) önemli faktörleriydi.

Sonuç: Apendektomi, işlemin düşük morbiditesi ve olumlu sağkalım sonuçları göz önüne alındığında, seçilmiş vakalarda apen-

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Conclusion: Appendectomy is efficient in the treatment of appendix tumors for selected cases considering low morbidity of the procedure and favorable survival outcomes. For advanced-stage tumors, extended resections combined with chemotherapy should be the preferred approach.

Keywords: Appendix tumors, Hyperthermic intraperitoneal chemotherapy (HIPEC), neuroendocrine tumor, low-grade appendicular mucinous neoplasia, serrated lesion, appendectomy

diks tümörlerinin tedavisinde etkilidir. İleri evre tümörler için kemoterapi ile birlikte genişletilmiş rezeksiyonlar tercih edilen yaklaşım olmalıdır.

Anahtar Kelimeler: Apendiks tümörleri, Hipertermik intraperitoneal kemoterapi (HIPEC), nöroendokrin tümör, düşük dereceli apendiküler müsinöz neoplazi, tırtıklı lezyon, apendektomi

INTRODUCTION

Unlike many other gastrointestinal (GI) tract tumors, less frequently-encountered appendix tumors have an incidence of approximately 0.001% in the US population (1). These infrequent tumors of the GI tract are mostly diagnosed during the postoperative period, at histopathological evaluations of the resected specimen, since they mostly present with clinical features of acute appendicitis at preoperative stage. Diversity in histological features has an influential role in their clinical course, thus acting as a determinant factor in their treatment as well.

Epithelial tumors are the most common tumors of the appendix. The histological classification of epithelial appendix tumors has been revised recently in the updated 5th edition of the WHO's "Classification of Digestive System Tumours" (2). In this last edition, they are classified as serrated lesions/polyps, mucinous neoplasms, adenocarcinomas (mucinous, non-mucinous, or goblet cell), and neuroendocrine neoplasms (NENs).

Appendix tumors were presented with colorectal tumors for the first time in the 6th edition of the American Joint Commission on Cancer (AJCC) Staging Manual (3). The tumor classification is guided by the absence/presence of mucinous components, low/high-grade histopathological features, and involvement of intra/extraperitoneal space (4).

In the presence of poor prognostic factors, such as lymphovascular invasion, deep tumor penetration, large tumor size (>1.5 cm), poor differentiation, and a high histologic grade, the preferred approach is to perform extended resections such as right hemicolectomy or Cytoreductive Surgery (CRS)+Hyperthermic Intraperitoneal Chemotherapy (HIPEC), depending on peritoneal involvement combined with neo/adjuvant oncological treatment in selected cases (5-7).

Although there are numerous published articles about the management of appendix tumors since the last revision of the AJCC staging manual in 2017, none have compared the clinical outcomes of those with different histopathological features in particular. We aimed to share our clinical experience about the management of these rare tumors of the GI tract and to make suggestions for treatment strategies according to results obtained from our patients.

MATERIAL AND METHOD

Patient selection and data collection

Patients older than 18 years of age and diagnosed with appendix tumors were included in the present study, following a retrospective analysis of medical records of the institute from January 2006 to February 2021. Those with appendicular tumors as a metastasis from distant site organs or a presenting lesion as an extension of other neighboring tumors were excluded from the study.

Patients with appendix tumors were classified into 3 groups: benign (Group A), borderline (Group B), and malignant (Group C). Histological grade (I-II-III), gender distribution, age, length of hospital stay, types of procedures (laparoscopic or open appendectomy, right hemicolectomy, CRS+HIPEC), postoperative complications, and follow-up data were evaluated.

The present study was conducted in compliance with the declaration of Helsinki, and all subjects gave their written informed consent according to new GDPR (General Data Protection Regulation) guidelines before their participation in the study. This study was approved by the Institutional Review Board (IRB) of the Istanbul Medical Faculty (IRB no: 2019/392).

Postoperative period

Treatment decisions were made based on current recommendations of the AJCC staging manual and WHO classification. Postoperative evaluations were done by different general surgeons in the outpatient clinics. Routine physical examinations, assessment of serum tumor markers (CEA, CA19-9, CA125, CgA, 5-HIAA), and control CT scans were performed at the postoperative first month as a base-line evaluation, every 3 months for the first year, and every 6 months within the second year. Patient follow-up was performed annually thereafter unless a problem occurred.

Statistical analysis

We used SPSS (Statistical Package for the Social Sciences) version 25.0 (IBM Corp., Armonk, NY, USA) for statistical analysis when evaluating the findings of the study.

Descriptive statistical methods (number, percentage, median, etc.) were used when evaluating the study data. Whether the data showed normal distribution or not was evaluated with the Kolmogorov Smirnov test. Comparisons of more than two groups were made using the One-Way Analysis of Variance (One-way ANOVA) or the non-parametric Kruskal-Wallis test. The Tukey test was used to determine from which group the difference originated. The Pearson Chi-square test was used for qualitative comparisons between groups. Survival calculations were made using the Kaplan-Meier analysis method. The effects of various prognostic factors related to tumor and patient characteristics on recurrence-free (RFS) and overall survival (OS) were investigated through a Log-rank test. In addition, the effects of multiple prognostic factors on RFS and OS were investigated using the multivariate Cox regression test. The results were evaluated at the 95% confidence interval and the significance level of $p<0.05$.

This study was approved by the Istanbul Faculty of Medicine Ethics Committee. (Date: 15.03.2019, No: 05).

RESULTS

Patient characteristics

A total of 132 [M/F: 45(34.1%)/87(65.9%)] patients with the diagnosis of appendix tumors were included in the present study after a retrospective analysis. 27 (20.5%) patients were in the benign group (Group A), 61 (46.2%) were in the borderline group (Group B), and 44 (33.3%) were in the malignant group (Group C).

In Group A, all patients were diagnosed with serrated lesion/polyp. Patients with LAMN were evaluated in Group B. One patient (2.3%) with HAMN, 19 (43.2%) patients with adenocarcinoma (mucinous/non-mucinous/goblet cell), and 24 (54.5%) patients with NET were in Group C.

The calculated mean age of the whole cohort was 55.7±16.4, and the majority [56.1% (n=74)] were less than 60 years of age. The malignant group (Group C) was the youngest among other groups [47.5(±17.4)], which was statistically significant according to the Tukey test ($F=9779$, $p\leq0.001$). The median hospital stay of the whole study cohort was 5 (1-58) days which was the shortest for those with benign tumors. ($p=0.087$). The median follow-up period was 25 (0-172) months. Detailed information is given in Table 1.

Histopathological evaluation

The majority of the study population (79% (n=83)) was constituted by patients with low-grade (grade I) tumors ($\chi^2=38.584$, $p\leq0.001$). According to the AJCC staging, there were 48 patients (45.7%) in "stage 0," 13 patients (12.4%) in "stage 1," 22 patients (21.0%) in "stage 2," 4 patients (3.8%) in "stage 3," and 18 patients(17.1%) in "stage 4." As expected, most of the patients at advanced stages were present in the malignant group ($\chi^2=69,504$, $p\leq0.001$) (Table 1).

Surgical procedures

Appendectomy was performed for 105 (79.5%) patients and right hemicolectomy in 27 (20.5%) patients overall. Fifty-two patients in the appendectomy group and 11 in the right hemicolectomy group were resected laparoscopically. Appendectomy was the dominant procedure performed initially in all groups: the benign group [n=22 (81.5%)], the borderline group [n=47 (77%)], and the malignant groups [n=36 (81.8%)]. Of note, 14 (10.6%) patients with adenocarcinoma were treated by appendectomy.

In particular, right hemicolectomy was performed for 5 (18.5%) patients in the benign group. For 2 patients this was due to a non-removable polyp in the right colon, for 2 it was due to intramucosal adenocarcinoma as a result of endoscopic polypectomy, and for the last patient with acute abdomen it was due to ischemia in the ascending colon. Other than that, 14 (23%) patients in the borderline group, and 8 (18.2%) patients in the malignant group were also treated by right hemicolectomy.

Nine patients with a previous history of appendectomy had right hemicolectomy due to surgical margin positivity confirmed by histopathological evaluations of the resected specimens in the initial operation.

Cytoreductive Surgery (CRS) with Hyperthermic Intraperitoneal Chemotherapy (HIPEC) was conducted in 8 patients who had recurrence during the follow-up.

Follow-up data

The complication rates differed among the patient groups, as the benign group [n=2 (7.4%)] had markedly the least percentage of complications compared to the other groups. The borderline and the malignant groups had similar complication rates [(borderline group n=17 (27.9%)) vs (malignant group n=12 (27.3%))] ($p=0.087$).

Recurrence was observed in 8 patients: 4 patients in the borderline group and 4 patients in the malignant group. All were recorded within the first 3 years of follow-up. By Kaplan-Meier survival analysis, 1-year, 2-year, and 5-year RFS rates of the whole study cohort were 96%, 91%, and 86.8% respectively. In the comparison of RFS among the groups with the Log-rank test, no statistically significant difference was found between borderline and malignant tumors (89% vs 83.7%, $p=0.496$) (Figure 1a). In particular, the RFS rate was 100% in NET patients, 89% for LAMN/HAMN, and 59.5% in adenocarcinoma patients ($p=0.007$) (Figure 1b). The RFS rate of grade 1 tumors was notably higher than the other groups (90.6% vs. 65.5%, $p=0.054$).

Twenty-seven (25.7%) patients died during the follow-up period. By Kaplan-Meier survival analysis, 1-year, 2-year, and 5-year OS rates of patients were calculated as 84.9%,

Table 1: Patient characteristics for tumor groups

	All	Benign[(A)] (n=27; 20.5%)	Borderline[(B)] (n=61; 46.2%)	Malignant[(C)] (n=44; 33.3%)			
Variables	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**Test**	***p value***	***Diff.***
Age, mean(SD)	55.7 (16.4)	57.7 (14.1)	60.8 (14.4)	47.5 (17.4)	**9.779**[a]	**<0.001***	*C<A,B*
Age group					**6.259**[b]	**0.044***	
<60	74 (56.1)	15 (55.6)	28 (45.9)	31 (70.5)			
≥60	58 (43.9)	12 (44.4)	33 (54.1)	13 (29.5)			
Gender					1.079[b]	0.583	
Female	87 (65.9)	17 (63)	43 (70.5)	27 (61.4)			
Male	45 (34.1)	10 (37)	18 (29.5)	17 (38.6)			
Surgical procedures					0.436[b]	0.804	
Appendectomy	105 (79.5)	22 (81.5)	47 (77)	36 (81.8)			
Right hemicolectomy	27 (20.5)	5 (18.5)	14 (23)	8 (18.2)			
Histologic grade (n=105)					**38.584**[b]	**<0.001***	
I	83 (79)	-	61 (100)	22 (50)			
II	19 (18.1)	-	0 (0)	19 (43.2)			
III	3 (2.9)	-	0 (0)	3 (6.8)			
Tumor type							
Serrated lesion/polyp	27 (20.5)	27 (100)	0 (0)	0 (0)			
LAMN	61 (46.2)	0 (0)	61 (100)	0 (0)			
HAMN	1 (0.8)	0 (0)	0 (0)	1 (2.3)			
Adenocarcinoma	19 (14.4)	0 (0)	0 (0)	19 (43.2)			
Neuroendocrine tumor	24 (18.2)	0 (0)	0 (0)	24 (54.5)			
AJCC stage(n=105)					**69.504**[b]	**<0.001***	
0	48 (45.7)	-	48 (78.7)	0 (0)			
I	13 (12.4)	-	0 (0)	13 (29.5)			
II	22 (21)	-	6 (9.8)	16 (36.4)			
III	4 (3.8)	-	0 (0)	4 (9.1)			
IV	18 (17.1)	-	7 (11.5)	11 (25)			
Complication					4.888[b]	0.087	
Yes	31 (23.5)	2 (7.4)	17 (27.9)	12 (27.3)			
No	101 (76.5)	25 (92.6)	44 (72.1)	32 (72.7)			
Clavien-Dindo classification (n=31)					11.800[b]	0.067	
Grade I	14 (45.2)	0 (0)	9 (52.9)	5 (41.7)			
Grade II	7 (22.6)	1 (50)	6 (35.3)	0 (0)			
Grade III	4 (12.9)	0 (0)	1 (5.9)	3 (25)			
Grade IV	6 (19.4)	1 (50)	1 (5.9)	4 (33.3)			
Grade V	0 (0)	0 (0)	0 (0)	0 (0)			
Hospitalization period (day), median (range)	5 (1-58)	4 (1-30)	5 (1-58)	5 (1-41)	4.894[c]	0.087	

*: p<0.05, a: One-Way ANOVA test, b: Chi-Square test, c: Kruskal-Wallis H test, Diff: Difference

79.3%, and 63.1%, respectively. In the comparison of OS with the Log-rank test, malignant tumors had a worse outcome than the borderline group. (55.7% vs. 68.3%, p=0.032) (Figure 1c). Grade 1 tumors had a statistically significant higher rate of OS than the grade 2-3 tumors. (68% vs. 44.4%, p=0.002). The lowest OS rate was noted for adenocarcinoma patients (42.5%)(p=0.008) (Figure 1d). According to the AJCC staging, the OS rate was

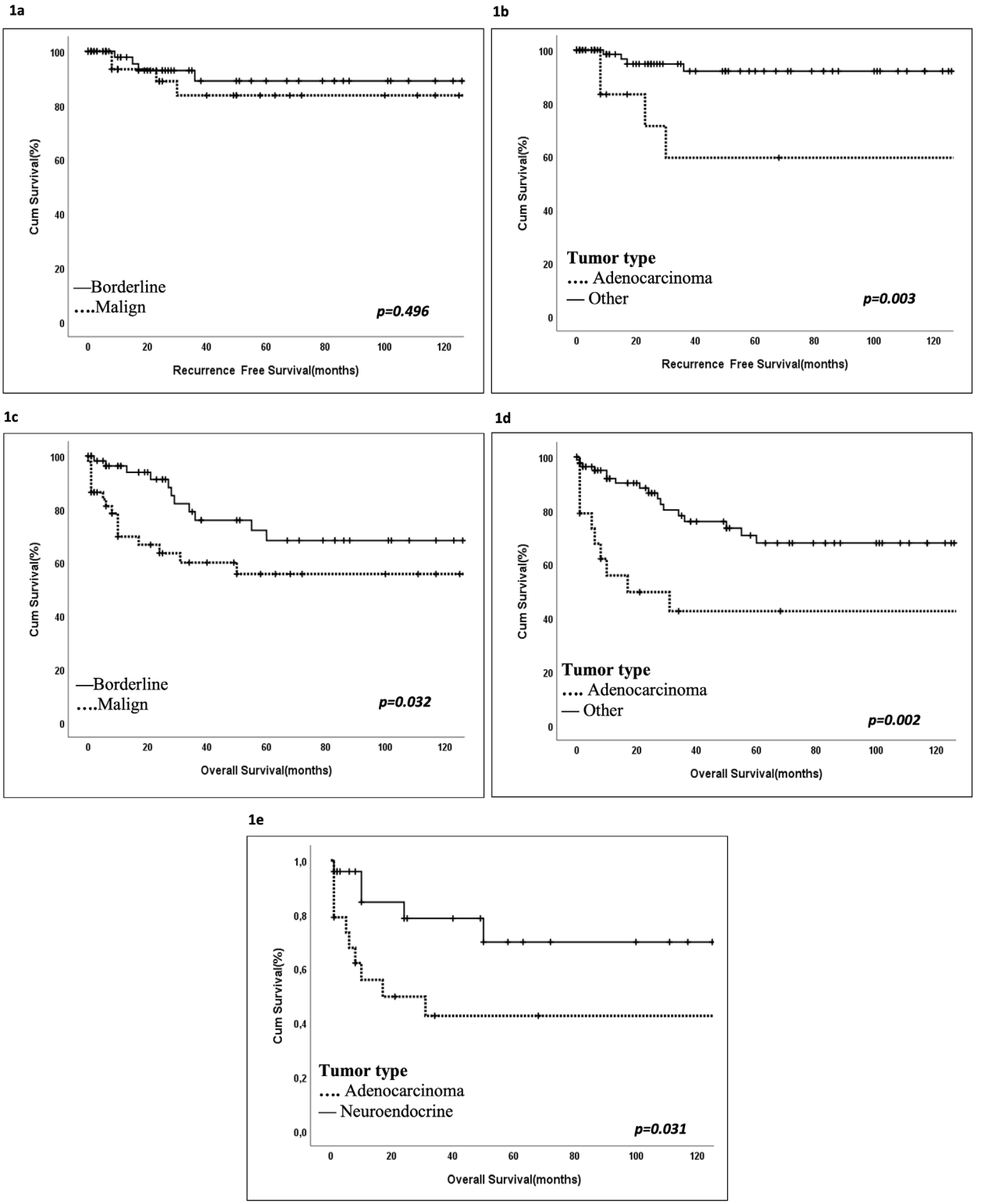


Figure 1: Recurrence-free and overall survival curves

Table 2: Five-year survival rates of patients

	All 5-year RFS		All 5-year OS		Borderline 5-year OS		Malignant 5-year OS	
Variables	**%**	***p-value***	**%**	***p-value***	**%**	***p-value***	**%**	***p-value***
Histopathological subtype		0.496		**0.032***		-		-
Borderline	89		68.3		-		-	
Malignant	83.7		55.7		-		-	
Age group		0.092		**0.011***		0.146		**<0.001***
<60	80.9		77.3		85		71	
≥60	95.8		48.4		59.5		33	
Gender		0.720		0.459		0.913		0.165
Female	88.3		61.8		70.9		47.2	
Male	83.7		65.8		75		70.2	
Surgical procedures		0.177		0.060		0.324		**0.046***
Appendectomy	84		67.4		73.2		59.2	
Right hemicolectomy	100		48.3		68.8		37.5	
Histologic grade		0.054		**0.002***		-		0.089
Grade I	90.6		68		-		66.7	
Grade II/III	65.5		44.4		-		44.4	
Tumor type		**0.007***		**0.008***		-		**0.031***
LAMN/ HAMN	89		67.2		-		-	
Adenocarcinoma	59.5		42.5		-		42.5	
Neuroendocrine tumor	100		69.8		-		69.8	
AJCC stage		0.239		**0.008***		0.212		**0.004***
0/I	91.4		68.8		74.2		63.5	
II/III	83.5		62.1		50		78	
IV	90.9		44.3		66.7		27.3	
Complication		0.905		0.226		0.841		0.160
Yes	88.5		60.6		74.7		55.6	
No	86.6		67.3		74.9		61	

*: p<0.05, Kaplan Meier Analysis (Log rank test), OS: Overall survival, RFS: Recurrence-free survival

68.8% in stage 0-1 tumors, 62.1% in stage 2-3 tumors, and 44.3% in stage 4 tumors. (p=0.008). In particular, NETs had better OS than adenocarcinomas (69.8% vs 42.5%, p=0.031) (Figure 1e) (Table 2).

According to the multivariate Cox Regression analysis, tumor type was defined as an independent predictive factor affecting RFS [HR: 7.28(1.002-52.91); p=0.049]. On the other hand, tumor type [HR: 3.76(1.09-12.98); p=0.036] and age [HR: 3.84(1.47-10.04); p=0.006] were revealed as independent predictive factors of OS. Detailed information is given in Table 3.

DISCUSSION

In the absence of poor prognostic factors, appendectomy provides satisfying outcomes for the surgical management of primary appendix tumors. Upgrade in histological grade and the AJCC tumor stage lead to worse survival rates. For the present analysis, malignancy and age status were revealed as independent parameters estimating OS. The tumor type was found as a predictive factor of RFS, but it had no significant impact on OS.

Table 3: Results of Multivariate Cox Regression analysis

	Factors	Category	Recurrence Free Survival HR (95%CI)	*p-value*
	Tumor type	Other	1**	
		Adenocarcinoma	7.28 (1.002-52.91)	**0.049***
	Factors	**Category**	**Overall Survival HR (95%CI)**	***p-value***
ALL	**Histopathological subtype**	Borderline	1**	
		Malignant	3.76 (1.09-12.98)	**0.036***
	Age	<60	1**	
		≥60	3.84 (1.47-10.04)	**0.006***
	Histologic grade	Grade I	1**	
		Grade II/III	1.57 (0.38-6.52)	0.536
	Tumor type	Other	1**	
		Adenocarcinoma	1.32 (0.28-6.11)	0.725
	AJCC stage	0-III	1**	
		IV	2.02 (0.69-5.97)	0.202
MALIGNANT	**Age**	<60	1**	
		≥60	2.48 (1.06-5.80)	**0.037***
	Tumor type	Other	1**	
		Adenocarcinoma	2.82 (1.07-7.39)	**0.035***
	AJCC stage	0-III	1**	
		IV	1.94 (0.72-5.24)	0.188
	Surgical procedures	Appendectomy	1**	
		Right hemicolectomy	1.86 (0.79-4.34)	0.154

*: p≤0.05, Cox Regression Analysis, **: Reference value

Primary neoplasms of the appendix are mostly diagnosed during operations performed for acute appendicitis with an incidence of 1% (1-8). Tajima et al. put forward the incidence of appendix tumors in patients who received appendectomy as 2.3% (9). In the current analysis, it was found to be 2.9% of total appendectomies within 15 years period. Epithelial tumors were revealed as the most common primary tumors of the appendix tumors in the whole cohort.

In 2012, the Peritoneal Surface Oncology Group International (PSOGI) developed a classification that has helped to resolve much of the confusion surrounding diagnostic terminology of appendix tumors. According to this consensus, appendectomy was proposed as a safe and curative procedure for serrated lesions since they were not associated with postoperative recurrence (10). Serrated lesions have serrated features resembling those of sessile serrated adenoma in the colon (11). Serrated lesions are more likely to be located in the right colon and appendix, which may present with a more aggressive clinical course compared to adenomatous lesions of the colon and rectum (12). The majority of the patients [n=22 (81.5%)] diagnosed with serrated lesions were treated by appendectomy. Serrated lesions were detected incidentally in the patients with right hemicolectomy. No recurrence was recorded during postoperative follow-up.

Mucinous neoplasms of the appendix are classified according to their degree of grading, such as LAMN and HAMN. For patients diagnosed with LAMN or HAMN that is confined to the appendix, appendectomy is mostly sufficient unless it is perforated (13). If there is a positive surgical margin on the appendectomy specimen, some suggest additional cecectomy or ileocecal resection (14), whereas, Arnason et al. stated that involvement of appendectomy surgical margin by the tumor does not have an impact on RFS and OS, and so the patients can be managed safely by appendectomy only (15). There is no clearly defined algorithm for the management of stage

T4a tumors. CRS + HIPEC was performed in 4 patients at stage T4a to reduce the potential risk of pseudomyxoma peritonei (PMP) in the future. Future studies are needed to elucidate the clinical outcomes for these patients.

Intestinal-type (non-mucinous) tumors of the appendix usually present with worse clinical outcomes compared to the other primary tumors of the appendix (16). González-Moreno et al. reported higher frequency of nodal metastases for intestinal-type appendix adenocarcinomas (17). Right hemicolectomy is suggested for patients with intestinal-type appendix tumors according to The American Society of Colon and Rectal Surgeons guidelines (5). CRS + HIPEC may provide benefit in the presence of peritoneal invasion.

Landry et al. defined tumor size, lymph node status, and the presence of distant metastases as independent parameters of OS for NENs (18). Appendectomy is sufficient for NETs less than 1 cm. In the case of surgical margin positivity or located tumor at the base of the appendix, then right hemicolectomy is recommended (19). We performed appendectomy for 21 patients (87.5%) diagnosed with NET and right hemicolectomy for 3 (12.5%) patients because of the diagnosis of right colon tumor perforation (histopathological diagnosis: lymphoma). In addition, right hemicolectomy was performed in 5 of 21 patients who underwent an appendectomy in the first operation due to lymphovascular and mesoapendicular invasion in the final pathological evaluation. In the pathological examination after the secondary operation, lymph node metastasis was detected in 3 of 5 patients. No recurrence has occurred for these patients.

Another subject of discussion is when to perform cytoreductive surgery for appendix tumors. We know that cytoreductive surgery does not provide superiority in terms of OS when performed for adenocarcinomas constituting a high grade of peritoneal carcinomatosis index (PCI) score (20). Survival is best when surgery can be done with R0 resection.

The present study has some limitations. It is a study based on retrospective analysis of previously collected data over a long period during which the accuracy of imaging modalities, the perioperative management, etc. may have changed to some extent. The patients in the benign group were not considered in the survival analysis due to the expectant advantage of survival that would lead to a bias in the interpretation of the results when compared to the other groups. This has led to a considerably lower number of patients analyzed in the analysis. Insufficient histopathological data may have prevented certain factors from being relieved in the statistical analysis. The presented findings may be supported with a larger cohort of patients.

Another important drawback in the current analysis is the lack of data about neo/adjuvant therapy, which would certainly affect the survival outcomes and inherently the interpretation of the results. One last limitation that should be mentioned is that the treatment decisions of the patients were made by surgeons independently instead of being approved by a council. Treatment management of these patients should be agreed upon by the members of a multi-disciplinary team involving medical oncologists, radiologists, surgeons, and radiation oncologists.

CONCLUSION

The low morbidity of the procedure and favorable survival outcomes support the appendectomy procedure for the surgical management of primary appendix tumors when diagnosed at an early stage. The presence of malignancy and older age are poor prognostic factors for OS. Complete tumor removal is of the utmost importance for curative treatment. The management of these tumors must be handled in experienced centers within a multidisciplinary approach to achieve optimum results.

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REFERENCES

1. Marmor S, Portschy PR, Tuttle TM, Virnig BA. The rise in appendiceal cancer incidence: 2000-2009. J Gastrointest Surg 2015;19(4):743-50. [CrossRef]
2. Nagtegaal ID, Odze RD, Klimstra D, Paradis V, Rugge M, Schirmacher P, et al. The 2019 WHO classification of tumours of the digestive system. Histopathology 2020;76(2):182-8. [CrossRef]
3. Greene FL, Page DL, Fleming ID, Fritz AG, Balch CM, Haller DG, et al. Colon, and Rectum. In: AJCC Cancer Staging Manual 6th ed. Chicago: Springer 2002:113-24. [CrossRef]
4. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. Appendix. In: AJCC Cancer Staging Manual 7th ed. Chicago: Springer 2010:133-42. [CrossRef]

5. Glasgow SC, Gaertner W, Stewart D, Davids J, Alavi K, Paquette IM, et al. The American Society of Colon and Rectal Surgeons, Clinical Practice Guidelines for the Management of Appendiceal Neoplasms. Dis Colon Rectum 2019;62(12):1425-38. [CrossRef]
6. Pape UF, Perren A, Niederle B, Gross D, Gress T, Costa F, et al. ENETS Consensus Guidelines for the management of patients with neuroendocrine neoplasms from the jejuno-ileum and the appendix including goblet cell carcinomas. Neuroendocrinology 2012;95(2):135-56. [CrossRef]
7. Turner KM, Hanna NN, Zhu Y, Jain A, Kesmodel SB, Switzer RA, et al. Assessment of neoadjuvant chemotherapy on operative parameters and outcome in patients with peritoneal dissemination from high-grade appendiceal cancer. Ann Surg Oncol 2013;20(4):1068-73. [CrossRef]
8. Turaga KK, Pappas SG, Gamblin T. Importance of histologic subtype in the staging of appendiceal tumors. Ann Surg Oncol 2012;19(5):1379-85. [CrossRef]
9. Tajima T, Tajiri T, Mukai M, Sugiyama T, Hasegawa S, Yamamoto S, et al. Single-center analysis of appendiceal neoplasms. Oncol Lett 2018;15(5):6393-9. [CrossRef]
10. Hatch QM. Appendiceal Neoplasms. Dis Colon Rectum 2017;60(12):1235-8. [CrossRef]
11. Carr NJ, Cecil TD, Mohamed F, Sobin LH, Sugarbaker PH, González-Moreno S, et al. A Consensus for Classification and Pathologic Reporting of Pseudomyxoma Peritonei and Associated Appendiceal Neoplasia: The Results of the Peritoneal Surface Oncology Group International (PSOGI) Modified Delphi Process. Am J Surg Pathol 2016;40(1):14-26. [CrossRef]
12. Bariol C, Hawkins NJ, Turner JJ, Meagher AP, Williams DB, Ward RL. Histopathological and clinical evaluation of serrated adenomas of the colon and rectum. Mod Pathol 2003;16(5):417-23. [CrossRef]
13. Misdraji J. Mucinous epithelial neoplasms of the appendix and pseudomyxoma peritonei. Mod Pathol 2015;28(Suppl 1):S67-79. [CrossRef]
14. Chicago Consensus Working Group. The Chicago Consensus on Peritoneal Surface Malignancies: Management of Appendiceal Neoplasms. Ann Surg Oncol 2020;27(6):1753-60. [CrossRef]
15. Arnason T, Kamionek M, Yang M, Yantiss RK, Misdraji J. Significance of proximal margin involvement in low-grade appendiceal mucinous neoplasms. Arch Pathol Lab Med 2015;139(4):518-21. [CrossRef]
16. Cortina R, McCormick J, Kolm P, Perry RR. Management and prognosis of adenocarcinoma of the appendix. Dis Colon Rectum 1995;38(8):848-52. [CrossRef]
17. González-Moreno S, Sugarbaker PH. Right hemicolectomy does not confer a survival advantage in patients with mucinous carcinoma of the appendix and peritoneal seeding. Br J Surg 2004;91(3):304-11. [CrossRef]
18. Landry CS, Woodall C, Scoggins CR, McMasters KM, Martin RC 2nd. Analysis of 900 appendiceal carcinoid tumors for a proposed predictive staging system. Arch Surg 2008;143(7):664-70. [CrossRef]
19. Pape UF, Niederle B, Costa F, Gross D, Kelestimur F, Kianmanesh R, et al. ENETS Consensus Guidelines for Neuroendocrine Neoplasms of the Appendix (Excluding Goblet Cell Carcinomas). Neuroendocrinology 2016;103(2):144-52. [CrossRef]
20. Dubé P, Sideris L, Law C, Mack L, Haase E, Giacomantonio C, et al. Guidelines on the use of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in patients with peritoneal surface malignancy arising from colorectal or appendiceal neoplasms. Curr Oncol 2015;22(2): e100-12. [CrossRef]