Analysis of Appendiceal Tumors Detected in Appendectomy Specimens: Single Center Experience

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INTRODUCTION

ABSTRACT

Objective: The aim of this study is to identify appendiceal tumors (AT) detected in appendectomy specimens in our center and to analyze the incidence and clinicopathological features of these tumors.

Methods: A total of 6110 appendectomies performed in our hospital between January 2015 and December 2021 were evaluated retrospectively. Demographic characteristics and histopathological examinations of these cases were analyzed. Demographic characteristics such as age, gender, surgical procedures and histopathological results of cases with AT were analyzed.

Results: A total of 44 (0.72%) AT were detected in the histopathological examination of 6110 appendectomy specimens. These are basically divided into two. The first is appendiceal neuroendocrine tumors (ANET) with 33(75%) cases and the second is appendiceal non-carcinoid tumors (ANCT), that is, epithelial tumors, with 11 (25%) cases. ANCTs, that is, epithelial tumors, were detected in the following four features: Low-grade appendiceal mucinous neoplasm in six cases (54.5%), adenocarcinoma with mucinous component in two cases (18.2%), adenocarcinoma with metastasis to the appendix (operated with acute appendicitis clinic) in two cases (18.2%), and adenocarcinoma with ANET component in one case (9.1%). Only appendectomy was performed in 26 (78.8%) cases in ANETs, while secondary right hemicolectomy (RH) was performed in 7 (21.2%) cases. In ANCTs, only appendectomy was performed in 6 (54.5%) cases, wide local excision with perioperative appendectomy in 2 (18.2%), and secondary RH in 3 (27.3%) cases. Secondary RH was performed in 10 (22.7%) cases out of 44 AT patients. Two patients who metastasized to the appendix and one patient with appendiceal carcinoma, that is, 3 (0.05%) patients in total, died.

Conclusion: The possibility of malignancy in appendectomy materials is rare and is usually detected incidentally in pathological examinations after appendectomy. Therefore, it is recommended that all appendectomy specimens be routinely sent for histopathological examination. Carcinomas have a worse prognosis than ANETs. Complementary RH is recommended for advanced ANET and appendiceal epithelioid tumors.

Appendiceal tumors (AT) are rare and are usually detected as a result of histopathological examination of appendectomy specimens taken for acute appendicitis.^[1] AT is very rarely diagnosed before or during surgery. Although appendectomy for acute appendicitis is usually adequate treatment for most of these neoplasms,^[2] surgeons do not have many options without definitive pathological results. Depending on the histopathology and size of the tumor, there are surgical treatment options such as appendectomy or right hemicolectomy (RH). Adenocarcinomas, mucinous neoplasms, goblet cell carcinoid, and neuroendocrine tumors are the types of primary appendiceal neoplasms histopathology.^[3] Neuroendocrine tumors are the most common type of these neoplasms.^[2,4] Surgical resections are the main treatment options due to limited systemic treatments and tumor size.^[5] For neuroendocrine tumors smaller than I cm, appendectomy alone is sufficient treatment. RH is recommended for tumors larger than 2 cm. The treatment of I–2 cm tumors is still controversial.^[6] Patients with positive resection margins whose tumor is I–2 cm in size or with deep mesoappendix invasion, higher proliferation rate (Ki-67 index >2%) and/or angioinvasion, and oncologic RH should be performed within 3 months after appendectomy in all patients with tumor diameter exceeding 2 cm.^[6]

Appendiceal mucinous neoplasm (AMN) is a biologically and histologically different condition from colorectal cancer and colonic-type adenocarcinoma of the appendix. Because of the relationship between these two conditions, a concomitant colorectal adenocarcinoma should be excluded. The mean age is 60 years and there is no clear gender tendency and no known risk factor for this disease. ^[7,8] AMNs are often localized in the appendix, but they can also spread to the peritoneal cavity. The condition of AMNs characterized by localized or generalized gelatinous material accumulation in the peritoneal area is called pseudomyxoma peritonei.^[9,10]

The prognosis and treatment of AMNs depend on the histological type and staging of the disease. For non-perforated patients, complete surgical resection with appendectomy without mucin shedding is recommended. If there is pathologically T2 or higher grade disease, RH is typically recommended because of the high risk of lymph node involvement.^[11] If AMN has peritoneal spread, it is treated with cytoreductive surgery (CRS) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC).^[12–14]

In this study, we aimed to determine the incidence of ATs in pathological materials after appendectomy. In addition, we retrospectively analyzed the demographic characteristics, histopathological distribution, and surgical procedures of ATs.

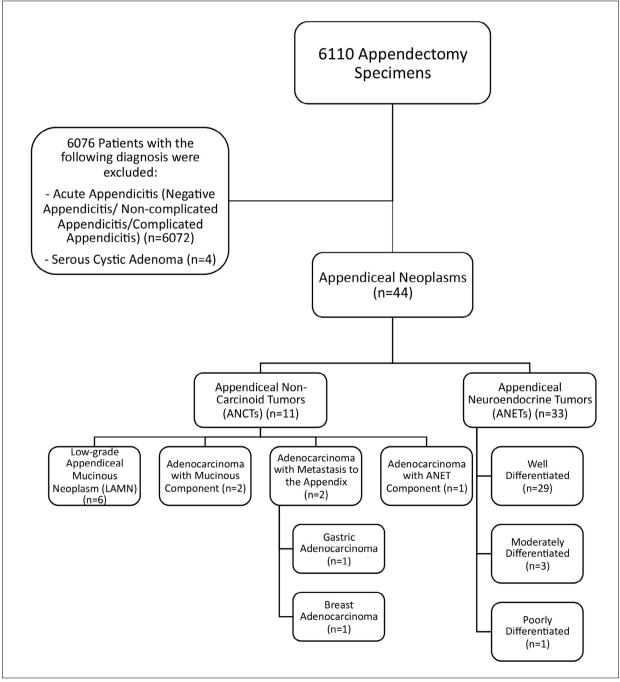


Figure 1. Flowchart of the study showing that exclusion and grouping of the patients.

MATERIALS AND METHODS

Our study was approved by the ethics committee of our hospital. A total of 6110 appendectomy materials performed between January 2015 and December 2021 in general surgery clinic of our hospital were evaluated retrospectively. Histopathological analysis of these appendectomy specimens was performed, and AT was detected in a total of 44 (0.72%) patients. These are basically divided into two. The first is appendiceal neuroendocrine tumors (ANET) with 33 (75%) cases and the second is appendiceal non-carcinoid tumors (ANCT), that is, epithelial tumors, with 11 (25%) cases. ANCTs, that is, epithelial tumors, were detected in the following four features: low-grade AMN (LAMN) in six cases (54.5%), adenocarcinoma with mucinous component in two cases (18.2%), adenocarcinoma with metastasis to the appendix (operated with acute appendicitis clinic) in two cases (18.2%), and adenocarcinoma with ANET component in one case (9.1%).

Benign pathologies of the appendix, acute phlegmonous appendicitis, complicated (perforated or gangrenous) appendicitis, and other malignancies that invaded the appendix were not included in our study. In addition, four mucinous adenoma cases detected in appendectomy specimens were not included in the study. ATs detected during gynecological, and colectomy was also not included in the study. In addition to, demographic characteristics of the patients such as gender and age, information including post-operative follow-up and survival time, tumor diameters, tumor grades, invasion, surgical margin, and TNM stage were obtained from a retrospective database. Among the patients who were found to have AT as a result of the pathological examinations, the patients who required further treatment according to the TNM staging were called for control. Patients who were planned for the RH underwent control imaging and colonoscopy was performed to

investigate synchronous colon tumors. The patients who underwent RH were followed up at 6-month and I-year intervals after the operation, with history, physical examination, colonoscopy, and radiological follow-up.

The flowchart of our study is presented in Figure I and the distribution of surgical treatment options is shown in Figure 2.

RESULTS

6110 appendectomy materials were evaluated retrospectively. Among these appendectomy specimens, AT was detected in a total of 44 (0.72%) patients. These are basically divided into two. The first is ANET with 33 (75%) cases and the second is ANCT, that is, epithelial tumors, with 11 (25%) cases. ANCTs, that is, epithelial tumors, were

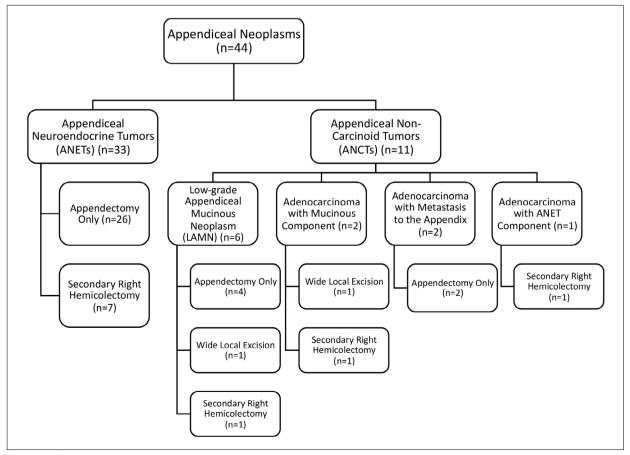


Figure 2. Surgical treatment options for appendiceal neoplasms.

| Table I. | Distribution of | the appendiceal | neoplasms |
|----------|-----------------|-----------------|-----------|
|----------|-----------------|-----------------|-----------|

| | n | % | Incidence |
|--------------------------------|----|------|-----------|
| Appendiceal Neuroendocrine | 33 | 75 | 0.54 |
| Tumors (ANET) | | | |
| Low-grade Appendiceal Mucinous | 6 | 13.7 | 0.1 |
| Neoplasms (LAMN) | | | |
| Adenocarcinoma with Mucinous | 2 | 4.5 | 0.032 |
| Component | | | |
| Adenocarcinoma with Metastasis | 2 | 4.5 | 0.032 |
| to the Appendix | | | |
| Adenocarcinoma with ANET | 1 | 2.3 | 0.016 |
| Component | | | |
| Total | 44 | 100 | 0.72 |

detected in the following four features: LAMN in six cases (54.5%), adenocarcinoma with mucinous component in two cases (18.2%), adenocarcinoma with metastasis to the appendix (operated with acute appendicitis clinic) in two cases (18.2%), and adenocarcinoma with ANET component in one case (9.1%).

Among ANETs, only appendectomy was performed in 26 cases (78.8%), while secondary RH was performed in seven cases (21.2%). Among the ANCTs, only appendectomy was performed in six cases (54.5%), wide local excision with perioperative appendectomy in two cases (18.2%), and secondary RH in three cases (27.3%). Thus, secondary RH was performed in 10 (22.7%) cases in AT. Residual tumor was detected in 2 (4.5%) patients who underwent secondary RH. One of the cases with residual tumor was ANET (Grade 3) and the other was adenocarcinoma with mucinous component, and surgical margins were reported as clean.

A total of three patients died, including two patients who metastasized to the appendix and one patient with appendiceal adenocarcinoma with a mucinous component. The mortality rate of the patients in our study was 0.05%. One of the cases that metastasized to the appendix had gastric adenocarcinoma (signet ring cell and total gastrectomy performed 2 years ago) and died 2 months after appendectomy. Our other patient was a patient with invasive ductal carcinoma of the breast (modified radical mastectomy was performed 9 years ago). The patient with invasive ductal carcinoma of the breast had perforated appendicitis and died due to COVID-19 infection in the early postoperative period. Our third patient who died was a patient with adenocarcinoma of the appendix with a mucinous component, and this patient had a RH after perforated appendicitis and died I year later.

The distribution of ATs is given in Table I, the demographic and histopathological features of ANETs are given in Table 2, and the demographic and histopathological features of ANCTs are given in Table 3.

Results of the previously reported series that evaluated the outcomes of patients with ATs are shown in Table 4.

| | n | % |
|--------------------------------|--------------|-------|
| Gender | | |
| Female | 20 | 60.6 |
| Male | 13 | 39.4 |
| Age (year) (mean) | 13–69 (33.6) | |
| Follow-up time (months) (mean) | 9–71 (35) | |
| Right hemicolectomy | | |
| No | 27 | 81.8 |
| Yes | 6 | 18.2 |
| Survival | | |
| Yes | 33 | 100 |
| Tumor location (n), (%) | | |
| Distal | 27 | 81.8 |
| Middle | 5 | 15.1 |
| Radix | I. I. | 3.1 |
| Total | 33 | 100 |
| Differentiation | | |
| Well | 29 | 87.8 |
| Moderate | 3 | 9.1 |
| Poor | I. I. | 3.1 |
| Total | 31 | 100.0 |
| Ki.67 index | | |
| <2 | 29 | 87.8 |
| 2–20 | 3 | 9.1 |
| 21–30 | I. I. | 3.1 |
| Total | 31 | 100.0 |
| Staging (TNM) | | |
| Tla | 5 | 15.1 |
| ТІЬ | 23 | 67.8 |
| T2 | 5 | 15.1 |
| Total | 31 | 100.0 |
| Tumor size (mm) | | |
| 0—1 | 5 | 15.1 |
| 2–20 | 23 | 67.8 |
| 21–30 | 5 | 15.1 |
| Total | 31 | 100.0 |
| Mean tumor diameter (mm) | 5.06 (1-30) | |

Demographic characteristics of appendiceal

neuroendocrine tumors

Table 2.

DISCUSSION

In this study, 44 patients (incidence; 0.72%, Table 4) with primary AT were identified among 6110 appendiceal specimens. This rate is similar to those reported in other studies (Table 4)^[2,15-18] Collins et al.^[19] reported that ATs were seen in 0.9-1.4% of 280,000 appendectomies performed in the USA. Studies have shown that the mean age at diagnosis for ANET is in the 3rd and 4th decades,^[6] and the mean age of patients with appendiceal adenocarcinoma is between the fifth and sixth decades.^[20,21] The data in our study are also in line with the literature in terms of both incidence and mean age (Table 4).

It is often difficult to diagnose appendiceal malignancies

| Table 3. Demographic characteristics of appendiceal non-carcinoid (epitheloid) tumors | | | |
|---|--------------|------|--|
| | n | % | |
| Gender | | | |
| Female | 6 | 54.5 | |
| Male | 5 | 45.5 | |
| Age (year) (mean) | 28–74 (55.8) | | |
| Follow-up time (months) (mean) | 0-71 (35) | | |
| Surgical procedures | | | |
| Appendectomy only | 6 | 54.5 | |
| Wide local excision | 2 | 18.2 | |
| Secondary right hemicolectomy | 3 | 27.3 | |
| Survival | | | |
| Yes | 8 | 72.7 | |
| Νο | 3 | 27.3 | |
| Staging (TNM) | | | |
| рТΙ | 6 | 54.5 | |
| pT2 | 2 | 18.2 | |
| рТ3 | I. | 9.1 | |
| pT4 | 2 | 18.2 | |
| Total | 11 | 100 | |
| Tumor Size (mm) | | | |
| 0–1 | 6 | 54.5 | |
| 2–20 | 2 | 18.2 | |
| 21–30 | I. | 9.1 | |
| >30 | 2 | 18.2 | |
| Total | П | 100 | |
| Mean tumor diameter (mm) | 7.2 (1–45) | | |

preoperatively. There is limited evidence in the literature on whether computed tomography (CT) can diagnose ATs.^[22-24] The most common clinical presentation of ATs is usually acute appendicitis. In our study, pre-operative CT scans were for the diagnosis of acute appendicitis.

ANET are the most common tumor type in ATs.^[2,4] If neuroendocrine tumors are smaller than I cm, only appendectomy is sufficient treatment. RH is recommended for tumors larger than 2 cm. However, optimal treatment of tumors between I and 2 cm is still controversial.^[6] In our case series, appendectomy was considered an adequate treatment for neuroendocrine tumors. In addition, RH was performed in seven cases out of 33 ANET cases. Of these seven cases, six were larger than 2 cm. (Grade 2, Grade 3

and Ki67 over 2%) Among these cases, one case was Grade I and the tumor size was between I and 2 cm and there was mesoappendix invasion. Residual tumor was seen in only one (Grade 3 and located at the root of the appendix) of ANETs who underwent RH. However, in the study of Egin et al.,^[16] 22 ANET cases were detected at TI and T2 stages, and RH was not performed on any of the patients. In the study of Egin et al.,^[16] no recurrence or residual tumor was detected, although the follow-up period was short.

Colorectal cancers may be associated with ANET. Bucher et al.^[15] reported that 14% of appendiceal neoplasms were synchronous colon cancers. In our current study, we could not find any association with colorectal cancers.

There is no doubt that appendiceal adenocarcinomas may require further surgical or oncological treatment. Whitfield et al.^[25] suggested that surgeons should be more careful when there is a periappendicular abscess and longer symptom duration, especially in elderly patients, and when a mass occurs. In our study, perioperative tumor was suspected in two cases (one with LAMN and the other with adenocarcinoma with mucinous component), wide local excision was performed, thus eliminating the need for RH in both patients. The patients are followed without tumor.

In our study, two patients with appendix metastases and one patient with adenocarcinoma with a mucinous component in the appendix died during follow-up. It was understood that a case that did not metastasize to the appendix (a case with adenocarcinoma with a mucinous component) died after 2 years of follow-up. RH was performed in this case, but in the first operation it was found that he had perforated appendicitis and formed a periappendicular abscess. As a matter of fact, the importance of "radical appendectomy" is emphasized in the study of Gonzales-Moreno and Sugerbaker on the approach to malignant tumors of the appendix. Radical appendectomy may be an alternative to right colon resection in patients with epithelial neoplasm of the appendix.^[26] In addition, radical appendectomy will provide the maximum amount of information required for optimal patient management decisions when malignancy is detected in appendectomy specimens.[26]

CONCLUSION

ATs are extremely rare and are usually detected incidentally. Because the preoperative diagnostic methods of ATs

Table 4. Results of the previously reported series that evaluated the outcomes of patients with appendiceal tumors

| Lead author | Number of patients enrolled | Number | Years | Incidence (%) |
|----------------|-----------------------------|--------|-----------|---------------|
| Connor | 7970 | 74 | 1979–1994 | 0.9 |
| Bucher | 2500 | 43 | 1991-2001 | 1.7 |
| Lee | 3744 | 28 | 2000–2005 | 0.7 |
| Egin | 3769 | 10 | 2006-2012 | 0.26 |
| Kunduz | 3554 | 28 | 2011-2017 | 0.78 |
| Current series | 6110 | 44 | 2015-2021 | 0.72 |
| | | | | |

are inadequate, neoplasms are often diagnosed by pathological examination. For this reason, routine appendectomy samples should be carefully examined for diagnosis. ANETs and LAMNs are diseases with a good long-term prognosis. However, the prognosis of other solid organ tumors that have metastasized to the appendix and locally advanced epithelial tumors of the appendix is poor. The treatment of ATs is directly related to the size and localization of the tumor, and the presence of lymphovascular and mesoappendix invasion. If the tumor size is smaller than 2 cm and there are no unfavorable prognostic factors, appendectomy is sufficient for treatment. RH should be performed if the tumor is larger than 2 cm in size and has tumor invasion below the appendix serosa, has unclear borders, or has deep mesoappendix invasion and angioinvasion. In cases where the appendix is not perforated, the prognosis for ANET and LAMN is very good. In case of perforation of the appendix in mucinous tumors, CRS and HIPEC should be considered. Patients should be monitored periodically for recurrence and development of synchronous and/or metachronous colorectal cancer.

Ethics Committee Approval

This study approved by the Kartal Dr. Lütfi Kırdar City Hospital Clinical Research Ethics Committee (Date: 26.08.2020, Decision No: 2020/514/184/10).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: A.B., M.A.; Design: A.B., M.F.B.; Supervision: A.B., M.A.; Fundings: A.B., M.A.; Materials: A.B., M.A.; Data: A.B., M.A., M.F.B.; Analysis: A.B., M.A., M.F.B.; Literature search: A.B., M.A.; Writing: A.B., M.A., M.F.B.; Critical revision: A.B., M.F.B.

Conflict of Interest

None declared.

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Apendektomi Spesimenlerinde Saptanan Apendiks Tümörlerinin Analizi: Tek Merkezli Deneyim

Amaç: Bu çalışmanın amacı, merkezimizde apendektomi spesimenlerinde saptanan apendiks tümörlerini belirlemek ve bu tümörlerin insidansı ile klinikopatolojik özelliklerini analiz etmektir.

Gereç ve Yöntem: Ocak 2015–Aralık 2021 tarihleri arasında hastanemizde yapılan toplam 6110 apendektomi olgusu geriye dönük olarak değerlendirildi. Bu olguların demografik özellikleri ile histopatolojik incelemeleri analiz edildi. Apendiks tümörü (AT) saptanan olguların yaşı, cinsiyeti gibi demografik özellikleri ile ameliyat prosedürleri ve histopatolojik sonuçları incelendi.

Bulgular: 6110 apendektomi örneğinin histopatolojik incelemesinde toplam 44 (%0.72) AT saptandı. Bunlar temel olarak ikiye ayrıldı. Birincisi apendiksin nöroendokrin tümörleri (ANET) 33 (%75) olgu ve ikincisi de 11 (%25) olgu ile apendiksin non-karsinoid tümörleri (ANCT) yani epiteliyal tümörleridir. ANCT yani epiteliyal tümörleri 6 (%54.5) olguda düşük dereceli müsinöz neoplazm (LAMN), 2 (%18.2) olguda müsinöz komponentli adenokarsinom, 2 (%18.2) olguda apendikse metastaz yapmış (akut apandisit kliniği ile opere edilen) adenokarsinom ve 1 (%9.1) olguda da ANET komponentli adenokarsinom saptandı. ANET'lerden 26 (%78.8) olguya sadece appendektomi yapılırken 7 (%21.2) olguya sekonder olarak SH yapıldı. ANCT'lerdeki 6 (%54.5) olguya sadece apendektomi, 2 (%18.2) olguya peroperatif apendektomi ile bir-likte geniş lokal eksizyon, 3 (%27.3) olguya da sekonder olarak sağ hemikolektomi (SH) yapıldı. 44 AT içinden toplamda 10 (%22.7) olguya sekonder sağ hemikolektomi yapılmış oldu. Sekonder SH yapılan 2 (%4.5) olguda rezidü tümör saptandı. Apendikse metastaz yapan iki hasta ile apendiks müsinöz komponentli adenokarsinom olup cerrahi sınırlar temiz olarak raporlandı. Apendikse metastaz yapan iki hasta ile apendiks müsinöz komponentli adenokarsinom ulan bir hasta, yani toplamda 3 (%6.8) hasta hayatını kaybetti. Çalışmamızda saptanan müsinöz adenomlu 4 olgu çalışmaya dahil edilmedi.

Sonuç: Apendektomi materyallerinde malignite olasılığı nadirdir ve genellikle apendektomi sonrası patolojik incelemelerde tesadüfen saptanır. Bu sebeple bütün apendektomi örneklerinin rutin olarak histopatolojik inceleme için gönderilmesini öneririz. Karsinomlar, ANET'lere göre daha kötü bir prognoza sahiptir. İleri evre ANET ve apendiks epiteloid tümörlerinde tamamlayıcı sağ hemikolektomi önerilmektedir.

Anahtar Sözcükler: Akut apandisit; apendiks karsinomları; apendiksin nöroendokrin tümörleri.