Journal of SURGICAL ARTS
CERRAHİ SANATLAR DERGİSİ
"A word can save a life"
jsurgarts.com
1308-0709

**Original study**

# Appendix neuroendocrine tumors: A single center experience

# Appendiksin nöroendokrin tümörleri; Tek merkez deneyimi

**Haldun Kar[1], Erdinç Kamer[2], Halis Bağ[1], Cengiz Tavusbay[1], Özlem Sayın Gür[1], Betül Küçükzeybek[3], Mehmet Hacıyanlı[1]**

Department2 of General Surgery[1], and Pathology[3] Izmir Katip Celebi University Atatürk Training and Research Hospital, İzmir, Türkiye

Department of General Surgery[2], University of Health Sciences, İzmir Tepecik Training and Research Hospital, İzmir, Türkiye

**Corresponding address:** Dr. Haldun Kar, haldunkar@hotmail.com

**How to cite:** Kar H, Kamer E, Bağ H, Tavusbay C, Gür EÖ, Küçükzeybek B, Hacıyanlı M. Appendix neuroendocrine tumors: A single center experience. J Surg Arts: 2023;16(2):40-44.

Received: 14.07.2023 Accepted: 01.08.2023

**ABSTRACT**

Appendiceal neuroendocrine neoplasms (ANENs) comprise approximately 30-80% of appendicular tumors. ANENs are frequently encountered incidental and account for 0.1 percent to 3 percent of appendectomies. Well-differentiated ANENs have a favorable prognosis with a 5-year survival rate in almost all patients with local disease. In this study, we evaluated the clinical findings, risk factors, and clinical output data and revealed the most accurate approach in light of the literature.

In this retrospective single-center study, the files of patients who underwent an appendectomy either as appendicitis or as a part of another abdominal surgical procedure histopathological diagnosed with neuroendocrine tumors in the last 14 years were entered into the study.

Between January 2009 and January 2023, 5818 patients underwent appendectomy. The pathology of 36 patients (0.61%) was an appendiceal neuroendocrine tumor. Complementary right hemicolectomy was performed in 6 (20.6%) patients. Lymph node metastasis and/or residual tumor are not observed. In this group, three of the 4 patients in the gray zone had R1 resection and one had perforated appendicitis. Surgery was recommended for patients with a tumor diameter of 2 cm, mesoappendix invasion, and a tumor diameter of 2 cm located at the base, but the patients did not accept it. There is no recurrence or metastasis in the patients followed.

To reduce radical surgical procedures of appendiceal neuroendocrine tumors located in the gray zone, R1 resection, and perforation detected, the operation information and pathology reports of these cases should be evaluated in multidisciplinary tumor boards. High-volume studies with multicenter participation on this subject should be conducted.

**Keywords**: Appendix; neuroendocrine tumors; right hemicolectomy; overtreatment

**ÖZET**

Apendiks nöroendokrin neoplazmaları (ANEN'ler), apendiküler tümörlerin yaklaşık %30-80'ini oluşturur. ANEN'lere sıklıkla rastlantısal olarak rastlanır ve apendektomilerin yüzde 0,1 ila yüzde 3'ünü oluşturur. İyi diferansiye ANEN'ler, lokal hastalığı olan hemen hemen tüm hastalarda 5 yıllık sağkalım oranıyla olumlu bir prognoza sahiptir. Bu çalışmada klinik bulguları, risk faktörlerini ve klinik çıktı verilerini değerlendirdik ve literatür ışığında en doğru yaklaşımı ortaya koyduk.

Bu retrospektif tek merkezli çalışmada, son 14 yıl içinde apandisit veya başka bir abdominal cerrahi girişimin bir parçası olarak apandisit ameliyatı geçirmiş ve histopatolojik olarak nöroendokrin tümör tanısı almış hastaların dosyaları çalışmaya dahil edildi.

Ocak 2009 ile Ocak 2023 arasında 5818 hastaya apendektomi yapıldı. 36 hastanın (%0,61) patolojisi apendiks nöroendokrin tümörü idi. Altı (%20,6) hastaya tamamlayıcı sağ hemikolektomi uygulandı. Lenf nodu metastazı veya rezidüel tümör görülmez. Bu grupta gri bölgede bulunan 4 hastadan üçünde R1 rezeksiyonu, birinde perfore apandisit vardı. Tümör çapı 2 cm, mezoappendiks invazyonu, tümör çapı tabanda yerleşimli 2 cm olan hastalara cerrahi önerildi ancak hastalar bunu kabul etmedi. Takip edilen hastalarda nüks veya metastaz görülmedi.

Gri zon yerleşimli, R1 rezeksiyon ve perforasyon saptanan apendiks nöroendokrin tümörlerinde radikal cerrahi girişimleri azaltmak için bu olguların operasyon bilgileri ve patoloji raporları multidisipliner tümör kurullarında değerlendirilmelidir. Bu konuda çok merkezli katılımlı yüksek hacimli çalışmalar yapılmalıdır.

**Anahtar kelimeler**: Apendiks; nöroendokrin tümör; sağ hemikolektomi; aşırı tedavi.

## INTRODUCTION

Neuroendocrine neoplasms (NEN) often originate from gastrointestinal and pancreatic tissues. Appendiceal NEN (ANEN) accounts for 38% of all gastrointestinal NEN. Annual incidence has been reported as 0.03 - 0.16 cases per 100,000, depending on geographical region and ethnicity (1).

Appendiceal neuroendocrine neoplasms (ANENs) comprise approximately 30-80% of appendicular tumors (2). ANENs are frequently encountered incidentally and account for 0.1 percent to 3 percent of appendectomies (3,4). Well-differentiated ANENs have a favorable prognosis with a 5-year survival rate in almost all patients with local disease (2).

According to the European Neuroendocrine Tumor Society (ENETS) guideline, in ANENs, size is important in determining the treatment protocol. Although the treatment protocol is clear in the treatment of tumors below 1 cm and above 2 cm, a consensus has not yet been reached on the approach to ANENs with a tumor diameter of 1-2 cm. This group called the gray zone, is influential in the decision of complementary right hemicolectomy in tumors with the Grade, invasion of mesoappendix, lymphovascular, perineural invasion, and positive or unclear margins information in the pathology report (2).

Due to the lack of a proven treatment protocol with prospective data, clinicians try to make the best decision in the treatment of gray zone cases by following current consensus-based guidelines in the multidisciplinary tumor boards.

However, since the majority of ANENs are more common at younger ages, progressing to an RHC is considered overtreatment by recent studies (5).

In this study, we evaluated the clinical findings, risk factors, and clinical output data and revealed the most accurate approach in light of the literature.

## MATERIAL and METHOD

In this retrospective single-center study, the files of patients who underwent an appendectomy either as appendicitis or as a part of another abdominal surgical procedure histopathological diagnosed with neuroendocrine tumors in the last 14 years were entered into the study.

Besides the clinical and demographic data of the patients, laboratory tests, operations performed, pathology of the appendix focused on location, size, immunohistochemical examinations, lymphovascular and perineural invasion, tumor grade and local extension of the tumor, additional work-up, additional treatment, thirty-day morbidity and mortality data, length of follow up, and our clinical results were evaluated.

All patients included in our study were discussed in our multidisciplinary tumor boards and ENETS criteria for surgical therapy of ANENs were used.

Other appendiceal benign, malignant tumors and cases under 16 years of age were excluded from the study.

The study was carried out in accordance with the principles of the Helsinki Declaration. As a routine procedure, written informed consent was obtained from each patient for all procedures and publications. Ethics committee approval was received for this study from the Clinical Trials Ethics Committee (22.12.2022/ 0563).

## RESULTS

Between January 2009 and January 2023, 5818 patients underwent appendectomy, 614 of which were laparoscopic. The pathology of 36 patients (0.61%) was an appendiceal neuroendocrine tumor. Twenty (55.6%) of 36 patients were female and 16 (44.4%) were male. The mean age of the patients is 35.7 (16-77). 27 (75%) patients with acute appendicitis, 3 (8.4%) patients with perforated appendicitis (two localized, one in generalized peritonitis), 2 (5.6%) patients with right colon tumor, 2 (5.6%) patients with gynecological malignancy, one (2.7%) patients were operated with the preliminary diagnosis of Spiegel hernia and one patient with interval appendectomy (2.7%). While 33 (91.7%) of the patients did not have mesoappendiceal invasion, surgical margins are positive in 3 patients. Mitosis was not detected in 25 cases. <2/10 BBA was observed in 10 cases, and 5-6/10 BBA mitosis was observed in 1 case. Ki-67 proliferation index ≤ 2% in 28 patients and 3% in 3 patients (Table 1).

Complementary right hemicolectomy (2 laparoscopic) was performed in 6 (20.6%) patients. Surgical margin positivity (R1) was performed in

three patients whose complementary surgery indications were operated on in the early period (within the first 4 months), perforated appendicitis generalized peritonitis in one patient, and right hemicolectomy to obtain a high-risk factor in one patient. A right hemicolectomy was performed on a patient who was found to have a recurrent mass 3 years later. Lymph node metastasis and/or residual tumor are not observed after the right hemicolectomy (Table 2). 11 patients have 59 months (5-156) long-term follow-up.

Postoperative follow-ups of the patients were performed with control abdominal tomography and tumor markers. Right hemicolectomy was performed in 3 of 4 patients with risk factors out of 7 patients in the gray zone. Surgery was recommended for patients with a tumor diameter of 2 cm, mesoappendix invasion, and a tumor diameter of 2 cm located at the base, but the patients did not accept it. There is no recurrence or metastasis in the patients followed.

**Tablo 1:** Clinicopathological characteristics of patients

| **Tumor localization in appendix** | **n (%)** |
|---|---|
| Body and tip | 34 (94.4) |
| Base | 2 (5.6) |
| **pT according to the ENETS* classification** | |
| pT1 | 26 (72.2) |
| pT2 | 9 (25.0) |
| pT3 | 1 (2.8) |
| **Tumor Grade** | |
| Grade 1 | 33 (91.6) |
| Grade 2 | 3 (8.4) |
| **Lymphovascular invasion** | |
| Yes | 2 (5.6) |
| No | 34 (94.4) |
| **Perineural invasion** | |
| Yes | 0 |
| No | 36 (100) |
| **Resection margin** | |
| R1 | 3 (8.4) |
| R0 | 33 (91.6) |

## DISCUSSION

Appendix Neuroendocrine tumors are rare, incidental, well-differentiated tumors with a slow course and good prognosis. (2, 5). The incidence of ANET is about (0.61%), frequently localized in the tip (80.6%), usually tumors < 1 cm (72.3%), and it is more common in female patients (55.6%) and the 2nd and 3rd decades of life (mean age 35.7 years) (6). Our study's incidence and epidemiological data are also compatible with the literature. ENETS, the American Neuroendocrine Tumors Society, and the National Comprehensive Cancer Network publish current guidelines on the disease's staging, treatment, and follow-up (2,7). According to these guidelines, appendectomy will be sufficient in differentiated ANETs with a common denominator less than 2 cm, and no specific follow-up is required. For tumors larger than 2 cm, a right hemicolectomy is recommended (6). It is recommended to discuss the right hemicolectomy option with the patient if there are risk factors such as Grade 2, vascular or lymphatic invasion, > 3 mm mesoappendix invasion, and positive or unclear margin in ANETs between 1-2 cm (2,6).

**Tablo 2:** Indications for right hemicolectomy

| **Patient no** | **Surgical indication** |
|---|---|
| 1 | Metachronous colonic mass (benign pathology) |
| 2 | pT3 and Grade 2 tumor, 6 mm mezoappendiceal invasion |
| 3 | Positive resection margin |
| 4 | Positive resection margin |
| 5 | Perforated appendicitis and generalized peritonitis |
| 6 | Positive resection margin, Grade 2 tumor |

Right hemicolectomy was recommended against the possibility of residual tumor and distant metastasis. However, with the multicentric Seer database studies conducted in recent years, these risk factors are seen with a low percentage in differentiated appendiceal ANETs.

In addition, recent studies show that positive lymph nodes do not adversely affect the prognosis (1,6,8,9). Although international guidelines recommend right hemicolectomy, recent retrospective, high-volume single-center studies have shown that lymph node metastasis and/or residual tumor are not observed after right hemicolectomy as in our study (10 -13). In addition, there are also studies in which no recurrent tumor and/or lymph node involvement was found in the follow-up of cases who were in the gray zone and had risk factors but did not accept right hemicolectomy (1,14,15). In our study, no pathology was found in the follow-ups of two patients who did not accept the right hemicolectomy.

There is a high risk of lymph node involvement and distant metastasis in ANETs located at the base, especially in ANETs larger than 2 cm (6). In most current studies, there is no clear information about the localization of the primary tumor in patients who underwent right hemicolectomy due to involved margin (R1 resection). The tumor location has an essential role in the decision of complementary surgery. Pawa et al. performed right hemicolectomy in all 9 (4.2%) patients with positive resection margin, and LN metastasis was positive in 4 patients located at the base (1). In a similar study, 23 of 32

(8%) patients who underwent R1 resection underwent right hemicolectomy. Of these patients, 5 have LN metastases and 6 have residual tumor focus but tumor localizations after appendectomy are not specified (16).In recent studies, there was no residual tumor or lymph node metastasis in right hemicolectomy patients due to positive margin, and primary tumor localization was not specified in this study (10,17). Holmeger et al. in the study, right hemicolectomy was performed on 18 (5.3%) patients with positive resection margins. Of this patient group, 80% were on a primary basis. In conclusion, a positive resection margin is an independent risk factor for lymph node metastasis (18). Contrary to these studies, some centers did not perform the right hemicolectomy in patients with R1 resection (10%) in the appendectomy group, but these patients do not have detailed pathological data (8). In our study, right hemicolectomy was performed in 3 (8%) patients due to positive margins, consistent with the literature. Tumor localization in the 3 cases was in the base, corpus, and tip. Skeletonized appendectomy performed on these patients. Unblock excision of the mesoappendix was not possible due to the difficulty of detecting the tumor intraoperatively. Davenport et al. emphasized that unnecessary right hemicolectomy can be prevented by giving more accurate results in the ANEN staging of the routine unblock excision of the mesoappendix in laparoscopic appendectomy (17). In the literature review, the R1 resection result is more likely in terms of residual tumor and lymph node metastasis, especially in tumors located at the base. Indication of tumor localizations in patients whose pathology result is R1 resection in studies may be a guide for future treatment guidelines.

There is no consensus in the current literature on whether there is an indication for right hemicolectomy in patients with this relatively rare clinical picture who have been operated on with the diagnosis of perforated appendicitis and whose pathology result is ANEN. McCann et al. advocate right hemicolectomy in this clinical setting because of its feasibility with minimal morbidity and the chance to evaluate residual disease and lymph node spread (19). In the study of Galanopoulos et al., right hemicolectomy was performed in all 6 cases of perforated appendicitis, and no residual tumor was detected. Similarly, in the study of Petit et al., lymph node involvement was not observed in patients who underwent right hemicolectomy with the diagnosis of perforated appendicitis (5, 16). Perforated appendicitis was present in three patients in our series, two of which were localized and one was generalized. Laparoscopic right hemicolectomy was performed by discussing the risks with a 25-year-old female patient who had no risk factors other than the perforated appendicitis clinic located in the gray zone, and no residual and/or lymph nodes were observed in the additional imaging studies (CT, Doda PET). As a result of the pathology, no metastatic lymph nodes and/or residual tumors were observed. In most of the studies conducted in recent years, it is thought that right hemicolectomies performed especially for cases located in the gray zone may cause overtreatment, in line with the guidelines used in the treatment of well-differentiated appendix neuroendocrine tumors. It is widely believed that further studies and revision of guidelines on the contribution to survival are needed (1,16, 18, 20).

## Conclusion

To reduce radical surgical procedures of appendiceal neuroendocrine tumors located in the gray zone, R1 resection, and perforation detected, the operation information and pathology reports of these cases should be evaluated in multidisciplinary tumor boards.

High-volume studies with multicenter participation on this subject should be conducted. At the planning stage of these studies, the histopathological data of patients with risk factors for right hemicolectomy should be presented in more detail.

## REFERENCES

1. Pawa N, Clift AK, Osmani H, Drymousis P, Cichocki A, Flora R, et al. Surgical Management of Patients with Neuroendocrine Neoplasms of the Appendix: Appendectomy or More. Neuroendocrinology 2018;106(3):242-251.
2. 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):144-152.
3. Moris D, Tsilimigras DI, Vagios S, Ntanasis-Stathopoulos I, Karachaliou GS, Papalampros A, et al. Neuroendocrine Neoplasms of the Appendix: A Review of the Literature. Anticancer Res 2018;38(2):601-611.
4. Brighi N, La Rosa S, Rossi G, Grillo F, Pusceddu S, Rinzivillo M, et al. Morphological Factors Related to Nodal Metastases in Neuroendocrine Tumors of the Appendix: A Multicentric Retrospective Study. Ann Surg 2020;271(3):527-533.
5. Galanopoulos M, McFadyen R, Drami I, Naik R, Evans N, Luong TV, et al. Challenging the Current Risk Factors of Appendiceal Neuroendocrine Neoplasms: Can They Accurately Predict Local Lymph Nodal Invasion? Results from a Large Case Series. Neuroendocrinology 2019; 109(2):179-186.
6. Mohamed A, Wu S, Hamid M, Mahipal A, Cjakrabarti S, Bajor D, et al. Management of Appendix Neuroendocrine Neoplasms: Insights on the Current Guidelines. Cancers (Basel) 2022;15(1): 295.
7. Kunz PL, Reidy-Lagunes D, Anthony LB, Bertino EM, Brendtro K, Chan JA, et al. Consensus

guidelines for the management and treatment of neuroendocrine tumors. Pancreas 2013;42(4): 557-577.
8. Crown A, Simianu VV, Kennecke H, Lopez-Aguiar AG, Dillhoff M, Beal EW, et al. Appendiceal Neuroendocrine Tumors: Does Colon Resection Improve Outcomes? J Gastrointest Surg 2020;24(9):2121-2126.
9. Mehrvarz Sarshekeh A, Advani S, Halperin DM, Conrad C, Shen C, Yao JC, et al. Regional lymphnode involvement and outcomes in appendiceal neuroendocrine tumors: a SEER database analysis. Oncotarget 2017;8(59):99541-99551.
10. Khan K, Patil S, Roomi S, Shiwani MH. Appendicular Neuroendocrine Neoplasm is Associated with Acute Appendicitis- Don't Miss the Boat. Chirurgia (Bucur) 2019;114(4):461-466.
11. Yavuz Y, Şentürk M. 25 Carcinoid Tumor Cases Incidentally Detected After 4642 Appendectomies.Turk J Colorectal Dis2020;30:21-26.
12. Zhang HW, Jiang Y, Huang ZY, Zhou XC. Analysis of surgical treatment of appendix neuroendocrine neoplasms - 17 years of single-center experience. World J Surg Oncol 2023; 21(1):150.
13. Gumuşoglu AY, Donmez T, Kabuli HA, Onur ND, Ferahman S, Sakiz D, et al. Management of appendiceal neuroendocrine tumors in the light of newguidelines. Ir J Med Sci 2022;191(3): 1133-1137.
14. Eğin S, Kamalı G, Kamalı S, Gökçek B, Yeşiltaş M, Hot S, et al. Neuroendocrine tumor of the appendix: Twelve years of results from a single institution. Ulus Travma Acil Cerrahi Derg 2019;25(2):118-122.
15. Kunduz E, Bektasoglu HK, Unver N, Aydogan C, Timocin G, Destek S. Analysis of Appendiceal Neoplasms on 3544 Appendectomy Specimens for AcuteAppendicitis: Retrospective Cohort Study of a Single Institution. Med Sci Monit 2018;24:4421-4426.
16. Walter T, Rault-Petit B, Scoazec JY. Response to Comment on "Current Management and Predictive Factors of LymphNode Metastasis of Appendix Neuroendocrine Tumors: A National Study From the French Group of Endocrine Tumors (GTE)". Ann Surg 2019;270(2):e44-e46.
17. Davenport E, Courtney ED, Benson-Cooper S, Bissett IP. Appendiceal neuroendocrine neoplasm in the era of laparoscopic appendicectomy. ANZ J Surg 2014;84:337-340.
18. Holmager P, Willemoe GL, Nielsen K, Grøndahl V, Klose M, Andreassen M, et al. Neuroendocrine neoplasms of the appendix: Characterization of 335 patients referred to the Copenhagen NET Center of Excellence. Eur J SurgOncol 2021; 47(6):1357-1363.
19. McCann C, Schwartz J, Perry L, Cheng E. Perforated Carcinoid Tumor of the Appendix: Need for Guidelines for Management With Respect to Prognostic Factors. Am Surg 2021;31: 34820960027.
20. Twito O, Paran H, Avital S, Kravtsov V, Rosenblum RC, Rotman-Pikielny P, et al. Temporal trends in incidence, evaluation and management of neuroendocrine neoplasms of the appendix: 14 years' experience. Am J Surg 2021;221(5):1000-1004.