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RESEARCH ARTICLE

Management and Long-Term Follow-up Outcomes of Appendiceal Neuroendocrine Tumor Patients: Evaluation of Single-Center Data

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ABSTRACT

Aim: Appendiceal neuroendocrine tumors (NETs) are rare NET that are often incidentally discovered following appendectomy performed for acute appendicitis. Herein, we report our institution's experience regarding the management and long-term follow-up of appendiceal NETs.

Method: This study included patients who underwent appendectomy for acute appendicitis and were diagnosed with appendiceal NETs between 2011 and 2020. Patient data were retrospectively retrieved from the hospital computer system. Clinical information, demographic details, tumor size, localization within the appendix, histopathological findings, and surgical procedures were evaluated.

Results: The study included data from 44 patients, with 22 men and 22 women, and a mean age of 31.1±12.7 years. All patients presented with symptoms consistent with acute appendicitis upon admission to the hospital. Tumors were distally located in 33 patients, centrally located in seven patients, and proximally located in four patients. Among the 44 patients included in the study, 42 underwent appendectomy, whereas two underwent primary right hemicolectomy during the initial surgery. One patient who underwent appendectomy required subsequent right hemicolectomy 3 weeks later. The mean follow-up duration was 5.4±2.5 years. During the follow-up period, metastasis was detected in only one patient with a tumor size larger than 2 cm located proximally. No recurrence or evidence of metastasis was observed in the remaining patients during long-term follow-up.

Conclusion: According to the results of this study, appendectomy may be sufficient for appendiceal NETs measuring <1 cm, and routine follow-up may not be necessary. For appendiceal NETs measuring 1-2 cm in diameter, further studies are needed to establish treatment protocols.

Keywords: Appendiceal neuroendocrine tumors, appendectomy, surveillance

Introduction

Appendiceal tumors are rare occurrences, found in approximately 1% of appendectomy specimens.[1,2] Appendiceal neuroendocrine tumors (NETs) are relatively uncommon tumors. The reported incidence of appendiceal NETs is 3-9 per 1,000 appendectomies, equating to approximately one NET per 150-300 appendectomies.[3,4]

Most appendiceal NETs are incidentally found during appendectomy. They are mostly submucosal and located in the distal third of the appendix, where they do not typically cause obstruction.[1,5] Symptoms are more likely in larger tumors and in the presence of metastases beyond regional lymph nodes. Approximately 10% of appendiceal NETs are located at the base of the appendix, where they may cause obstruction leading to appendicitis.[6]

When it comes to treatment, simple appendectomy is generally considered sufficient and curative for appendiceal NETs smaller than 1 cm, whereas tumors larger than 2 cm may require right hemicolectomy if relevant criteria are met.[7] The debate continues regarding the optimal treatment for tumors measuring 1-2 cm.

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Neuroendocrine neoplasms have the highest survival rates (>95%) compared with other tumor types found in the appendix.[8,9] The excellent prognosis may be attributed to factors such as localization, prompt identification, diagnosis, and excision, as well as the biopathology of the tumor itself or the size of the appendiceal NETs at the time of appendectomy.[9-12] Distant metastases primarily affect the liver, and extrahepatic metastases are extremely rare.[13-15]

In this paper, we report the management and long-term follow-up of patients diagnosed with appendiceal NETs at our center.

Materials and Methods

The study commenced following approval from the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (approval number: 170, date: 07.07.2023). Data of 6,823 patients who underwent appendectomy at our institution between January 1, 2011, and January 1, 2020, were retrospectively reviewed. Among them, 56 patients diagnosed with appendiceal NETs were included as the main study group. Patients with a history of additional malignancies, lack of follow-up continuity, death due to reasons unrelated to the study, or incomplete data were excluded, resulting in a total of 44 included patients. Pathologically measured tumor sizes, tumor locations, tumor differentiation, types of operations performed, tumor stages, metastatic status, Ki-67 indices, and mitotic rates were examined. A standard method to classify the location of appendiceal tumors is to measure their distance from the base of the appendix (where it joins the cecum). A tumor located within the first third from the base is considered proximal, whereas one in the middle third is considered middle and one in the last third distal. Additionally, imaging methods applied during patient follow-ups and assessments of recurrence and mortality were also investigated.

Statistical Analysis

Statistical analysis was conducted using SPSS 26.0 for Windows. Descriptive statistics, including numbers and percentages for categorical variables, and mean, standard deviation (SD), median, minimum, and maximum for numerical variables, were provided. For comparisons of numerical variables between two independent groups, a Student's t-test was employed for variables meeting the normal distribution assumption, whereas the Mann-Whitney U test was used when the normal distribution assumption was not met. The chi-square test was utilized to analyze ratios between groups. A p-value of <0.05 was considered to indicate statistical significance.

Results

This study includes data from 44 patients. Of these patients, 22 were men and 22 were women, with a mean age (± SD) of 31.1±12.7. All patients were operated on due to acute appendicitis. The mean follow-up period was 5.4 years. Tumors were distally located in 33 patients, centrally located in seven patients, and proximally located in four patients. Among the patients, 37 had tumors measuring <1 cm, three had tumors measuring 1-2 cm in diameter, and four had tumors of >2 cm. Among the four patients with tumors >2 cm, only open appendectomy was performed in two patients with distally located tumors; right hemicolectomy was performed in two patients with proximally located tumors. Three of these four patients did not develop recurrence or metastasis during long-term follow-up, whereas one patient had a NET >2 cm with metastasis at the time of diagnosis. This patient received chemotherapy during the 3-year follow-up period without mortality. Among the patients with proximally located NETs, two had tumors measuring >2 cm and two had tumors of <1 cm. Three of these patients underwent right hemicolectomy, whereas one underwent laparoscopic appendectomy. Six patients (13.6%) had a Ki-67 index above 2, with two of these patients undergoing right hemicolectomy and four undergoing simple appendectomy. Patient and tumor characteristics are presented in Table 1.

Open appendectomy was performed in 29 patients, laparoscopic appendectomy in 12 patients, and right hemicolectomy in three patients. One of these three patients was proximal and metastatic at the time of diagnosis. One patient initially underwent a simple appendectomy, but since the tumor was proximally located and >2 cm, a right hemicolectomy was performed 1 month later. In the third patient, the tumor was located proximally and was <1 cm. Treatment strategies are presented in Table 2.

Patient follow-up was performed using computed tomography (CT) and clinical findings in the first 6 months, and the patients were subsequently followed up with annual tomography scans. The long-term follow-up involved symptoms and clinical follow-up. Aside from one patient who presented with the condition at admission, no patients in our series developed metastasis.

Discussion

Appendiceal NETs are rare neoplasms with a favorable prognosis. The preferred treatment options are either simple appendectomy or right hemicolectomy. Right hemicolectomy is considered the preferred treatment, especially for tumors measuring >2 cm or 1-2 cm with mesoappendiceal invasion. There is insufficient evidence to predict which patients require comprehensive surgical intervention for disease control.

Better patient selection for more extensive surgery may be achieved through multifactorial tumor assessment combining morphological and molecular analyses.

Appendiceal NETs are reported to have an incidence of 3-9 per 1,000 appendectomies, equating to approximately one NET per 150-300 appendectomies.[3,4] Our series showed a similar incidence rate of appendiceal NETs (7.9 per 1,000 cases), consistent with the literature. Histology is crucial in the diagnosis of appendiceal NETs, and most lesions are incidentally found following appendectomy. Endoscopy does not provide significant benefit in the diagnosis of appendiceal NETs since it only detects large tumors infiltrating the cecum.[7] Furthermore, colonoscopy is necessary for colorectal cancer screening in appendiceal NET patients, as up to 18% of cases may have concomitant neoplasms in the gastrointestinal system.[16]

Table 1. Patient and tumor characteristics

Age (mean ± SD) (years)		31.1±12.7
Gender (n, %)	Male (n, %)	22 (50%)
	Female (n, %)	22 (50%)
Tumor localization (n, %)	Distal (n, %)	33 (75%)
	Middle (n, %)	7 (15.9%)
	Proximal-root (n, %)	4 (9.1%)
Tumor size (n, %)	<1 cm	37 (84.1%)
	1-2 cm	3 (6.8%)
	>2 cm	4 (9.1%)
Tumor type (n, %)	Well-differentiated (n, %)	41 (93.2%)
	Middle-differentiated (n, %)	3 (6.8%)
Ki-67 status	<2%	38 (86.4%)
	2-20%	6 (13.6%)
Tumor grade	Grade 1	38 (86.4%)
	Grade 2	6 (13.6%)
Stage	Stage 1 (n, %)	31 (70.5%)
	Stage 2 (n, %)	11 (25.0%)
	Stage 3 (n, %)	1 (2.3%)
	Stage 4 (n, %)	1 (2.3%)
Follow-up time (mean ± SD) (years)	5.4±2.5	

SD: Standard deviation

Table 2. Treatment strategies

Treatment (n, %)	Open appendectomy (n, %)	29 (65.9%)
	Lap appendectomy (n, %)	12 (27.3%)
	Right hemicolectomy (n, %)	2 (4.5%)
	Open appendectomy + right hemicolectomy (n, %)	1 (2.3%)

The European Neuroendocrine Tumor Society guidelines do not recommend follow-up for patients with small tumors (<1 cm) that have been treated with appendectomy and excised with clear margins.[7,17] Additionally, follow-up is not mandatory for appendiceal NETs >1 cm that have undergone right hemicolectomy, provided there are no additional risk factors and histological examination reveals no lymphovascular invasion or residual disease.[17] Conversely, according to recent guidelines, long-term follow-up is required in cases of lymph node involvement, detection of locoregional disease post-surgery, and when the tumor is of high grade.[7,17] Regular follow-up is necessary for patients with tumors measuring 1-2 cm that exhibit features indicating a higher risk of lymph node spread, such as mesoappendiceal invasion of >3 mm, localization at the base of the appendix, vascular infiltration, or intermediate differentiation.[17] In the present study, the majority of patients had tumors smaller than 1 cm, and apart from one patient who was metastatic at the time of surgery, no metastasis or recurrence was observed during long-term follow-up in any patient.

Although appendiceal NETs appear to have a slight female predominance, small intestine NETs are more common in men. Unlike other appendiceal tumors and NETs, which tend to occur in older patients, appendiceal NETs exhibit the highest incidence rates in women aged 15-19 years and in men aged 20-29 years.[18] In the recent study by Pawa et al.[19], the average age of the patients was 33.2 years, with the majority being women (60.5%). In the present study, the average age was 31.1 years, and the incidence was equal in the men and the women.

Appendiceal NETs are typically located at the tip of the appendix, and only in some cases do those located in other parts cause appendiceal symptoms. Carcinoid syndrome is a rare condition and is usually associated with advanced forms of the disease.[20] In our series, only four patients (9.1%) had proximally located appendiceal NETs, and metastasis was detected in one of these cases; however, none of our patients developed carcinoid syndrome.

At presentation, the likelihood of regional and distant metastasis is related to tumor size. In a series of 902 well-differentiated NETs derived from the National Cancer Data Base, which examined the relationship between tumor size and metastasis risk, 12% of patients with tumors <2 cm had nodal metastases at diagnosis, and 43% of those with larger tumors had distant metastases.[21] Higher rates of nodal involvement have been reported in various studies for patients with tumors measuring 1-2 cm.[22,23] In a series from the Mayo clinic consisting of 150 patients with appendiceal NETs, none of the

127 patients with tumors <2 cm developed metastasis, while 3 out of 14 patients with tumors measuring 2-3 cm and four out of nine patients with tumors >4 cm developed metastasis.[24] In a multicenter study, the survival rate for appendiceal NETs was reported as 99.05% at 5 and 10 years of follow-up, with no reported recurrences.[19] Reports of recurrence of the disease have been found in patients with long-term follow-up. In a series of 64 patients diagnosed with appendiceal NETs under the age of 40 and followed up for 10-33 years after surgery, only one recurrence was recorded in a patient with a regional tumor >2 cm.[25] In a study reporting a patient treated with right hemicolectomy for a tumor >2 cm with mesoappendiceal invasion and lymph node metastasis, it was noted that liver metastasis developed 6 years after the surgery.[26] Another report from Duke Hospital showed that for appendiceal carcinoids measuring 1-2 cm, right colon partial resection did not improve survival rates, even in those with higher-grade tumors. Collectively, these findings suggest that resection of the primary tumor alone is likely sufficient for carcinoids <2 cm.[27] In the present study, none of the patients with tumors <2 cm had metastasis or recurrence detected during long-term follow-up, whereas one out of four patients with tumors >2 cm had metastasis. Based on these findings, we believe that simple appendectomy can be safely performed in appendiceal NETs of <2 cm. The metastatic potential of appendiceal NETs is associated with their proliferative rate. A high Ki-67 index is indicative of an aggressive tumor and is often accompanied by a worse prognosis.[28] Therefore, it is recommended that tumors with excessive mitotic counts or significantly elevated Ki-67 indices are treated with right hemicolectomy.[7,24] In a recent multicenter study on appendiceal NETs treated via right hemicolectomy, it was noted that 17% of the study population expressed Ki-67 at a rate of more than 2%, and 50% of these cases (2 out of 4) had metastatic lymph node disease.[29] Well-differentiated G1 or G2 NETs have an overall indolent clinical behavior. All poorly differentiated neuroendocrine neoplasms are G3 neuroendocrine carcinomas with an aggressive clinical course.[30] Poorly differentiated NETs are usually widely metastatic and rarely produce symptoms related to the secretion of bioactive substances. Some poorly differentiated NETs lack morphological features of neuroendocrine differentiation.[31] In the present study, there were only six patients with grade 2 pathology results, and none with grade 3. In addition, there were six patients with a Ki-67 index between 2% and 20%, and none with a Ki-67 index above 20%. The fact that we did not have a high-grade patient and the small number of patients with a high Ki-67 index limits our ability to comment on this issue.

Data supporting the use of imaging in detecting residual disease are inadequate. The most effective imaging method [CT, magnetic resonance imaging (MRI), or ultrasound] has not yet been determined, and there remain issues regarding the appropriate number of tests during the follow-up period and the duration of the follow-up. Concerns about radiation exposure arise with CT imaging in these patients. As noted, appendiceal NETs are generally in early stages and are small in size, making the likelihood of detection with ultrasound quite low. Positron emission tomography (PET) imaging could be considered as an option, but further studies are needed in this regard.[32] Additionally, the role of colonoscopy is unconfirmed. In this context, MRI emerges as the most effective imaging modality for patients requiring long-term follow-up. Although not yet proven, a reasonable strategy would involve follow-up at 6 and 12-months post-surgery, followed by annual follow-ups thereafter.[17] Despite their indolent course, appendiceal NETs can recur. Therefore, tumors >2 cm or >1 cm with additional risk factors should undergo lifelong surveillance.[7,33] In our practice, we utilized CT or PET imaging for long-term follow-up of our patients, and since we did not have any cases of recurrence or new metastasis development, the effectiveness of the imaging modalities could not be evaluated.

Study Limitations

One of the most significant limitations of this study is its retrospective nature. Another limitation is that all patients were not followed up at the same frequency and using the same imaging method. Additionally, the number of tumors with a diameter of 1-2 cm was limited to only three. This situation makes it difficult for us to make interpretations regarding this group. Due to these limitations, this study can be seen as a preliminary study for further research.

Conclusion

Despite being rare, the evaluation of pathology examinations of appendectomy materials should not be overlooked due to appendiceal NETs mimicking acute appendicitis. Based on this study, we believe that simple appendectomy would suffice in patients with distal and mid-settled appendiceal NETs measuring <1 cm, consistent with the literature data. However, for tumors >2 cm and particularly those measuring 1-2 cm, right hemicolectomy should be considered the preferred treatment. The follow-up strategy for these patients remains debatable; however, based on this study's findings of no recurrence or metastasis during long-term follow-up in patients who underwent appendectomy for tumors <1 cm, routine follow-up may not be necessary in such cases.

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Ethics

Ethics Committee Approval: The study commenced following approval from the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (approval number: 170, date: 07.07.2023).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: Ö.A., M.G., H.O.Ş., U.O.İ., Concept: Ö.A., U.O.İ., Design: Ö.A., U.O.İ., Data Collection or Processing: Ö.A., M.G., C.T., Analysis or Interpretation: Ö.A., M.G., H.O.Ş. C.T., Literature Search: Ö.A., H.O.Ş., Writing: Ö.A., C.T., Critical Review: C.T., U.O.İ.

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