

Challenges and predictive radiological findings in the diagnosis of neuroendocrine tumors in patients with acute appendicitis

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ABSTRACT

BACKGROUND: Acute appendicitis is one of the most common surgical emergencies. With antibiotic-first treatment strategies gaining importance, the risk of an appendiceal tumor as an incidental finding or as the cause of appendicitis presents an obstacle to a conservative approach. Neuroendocrine tumors, the most frequent type of appendiceal tumors, are difficult to diagnose preoperatively due to their small size. This study aims to identify predictive factors for neuroendocrine tumors in patients undergoing surgery for acute appendicitis by analyzing imaging and clinical characteristics, thereby enhancing preoperative diagnostic accuracy and guiding surgical interventions.

METHODS: This retrospective observational study included 1,298 patients who underwent appendectomy from January 2014 to May 2024. After excluding 59 patients with normal pathology results, 40 with variable pathologies, and 49 with inaccessible computed tomography (CT) images, 1,150 patients remained (1,135 with acute appendicitis and 15 with neuroendocrine tumors). Abdominal CT scans were evaluated for appendiceal diameter, wall thickness, cecal wall thickness, periappendiceal fat stranding, fluid collection, lymphadenopathy, intraluminal and free periappendiceal air, mucosal hyperenhancement, the presence of appendicolith, mural calcification, and mural nodules.

RESULTS: The presence of a mural nodule protruding into the lumen was significantly higher in neuroendocrine tumor patients compared to those with acute appendicitis, with a sensitivity of 53.3%, specificity of 95.8%, positive predictive value (PPV) of 31.9%, negative predictive value (NPV) of 99.4%, and accuracy of 97.9%. Intraluminal air was also more frequent in neuroendocrine tumor patients, with a sensitivity of 53.3%, specificity of 76.7%, PPV of 2.9%, NPV of 99.2%, and accuracy of 76.4%. Other imaging parameters did not show significant differences between the two groups.

CONCLUSION: This study identifies mural nodules and intraluminal air as significant predictors of neuroendocrine tumors in patients with acute appendicitis, emphasizing the importance of meticulous preoperative imaging evaluations. Incorporating these predictors into diagnostic protocols could improve the preoperative identification of neuroendocrine tumors, enabling more appropriate surgical interventions. Future research should validate these findings through prospective studies and explore advanced imaging techniques to further enhance the detection of appendiceal neoplasms, ultimately improving patient outcomes and reducing overlooked malignancies.

Keywords: Acute appendicitis; computed tomography; neuroendocrine tumor.

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INTRODUCTION

Acute appendicitis is one of the most common surgical emergencies, observed predominantly in individuals aged 10 to 20 years, with a lifetime risk of 8.6% for males and 6.7% for females.^[1] Despite advancements in diagnostic techniques, the clinical diagnosis of acute appendicitis can be challenging, as its presenting symptoms may mimic other intra-abdominal conditions. Contrast-enhanced computed tomography (CT) has become the gold standard imaging modality for diagnosing acute appendicitis due to its high sensitivity and specificity.^[2]

While the traditional approach to treating acute appendicitis has been urgent appendectomy to avoid complications, recent systematic reviews have determined that an antibiotic-first strategy can be safely employed in most cases of uncomplicated appendicitis.^[3] However, the primary obstacle to the antibiotic-first strategy is the possibility of an appendiceal neoplasm. Such neoplasms can either cause appendicitis by obstructing the lumen or be incidental pathological findings that may be overlooked, leading to disease progression. The incidence of appendiceal neoplasms in the literature ranges from 0.5% to 2.5% (4-6), with neuroendocrine tumors comprising more than 60% of these cases.^[4]

Detection rates of appendiceal neoplasms in patients with acute appendicitis are currently quite low. The most easily detected pathologies are low-grade mucinous tumors, thanks to the characteristic cystic dilation of the appendix lumen.^[5] In contrast, neuroendocrine tumors are the least likely to be diagnosed as they are generally less than 1 cm in size. While CT is the primary imaging modality for evaluating suspected appendicitis, it may fail to detect small appendiceal tumors, often only revealing signs of appendicitis, such as diffuse thickening of the appendix or periappendiceal fat stranding.^[6] Larger tumors, however, may be identified as soft-tissue masses within the appendix with minimal surrounding inflammatory changes, which are homogeneously enhancing, well-defined, and sometimes with calcification.^[7]

Given these challenges, the objective of our study is to identify predictive factors for neuroendocrine tumors in patients who undergo surgery for acute appendicitis. We aim to improve preoperative diagnostic accuracy by analyzing imaging and clinical characteristics and guide appropriate surgical interventions. This study seeks to enhance the understanding of how to effectively differentiate between acute appendicitis and appendiceal neuroendocrine tumors, ultimately leading to better patient outcomes and more tailored treatment strategies. To the best of our knowledge, this is the first study comparing imaging findings of appendiceal neuroendocrine tumors with acute appendicitis cases.

MATERIALS AND METHODS

Study Design

This retrospective observational study spanned from January

2014 to May 2024. Ethics committee approval was received on December 1, 2023 (Approval No. 831892).

Study Population

The study included 1,298 patients who had undergone appendectomy and had available pathology results. Out of these, 59 patients with normal pathology results and 40 patients with variable pathology results (e.g., granulomatous appendicitis and adenocarcinoma of the appendix) were excluded. Moreover, 49 patients who were diagnosed only via ultrasound and lacked accessible CT images in the Picture Archiving and Communication System (PACS) were also excluded. Consequently, the final analysis comprised 1,150 patients, including 1,135 with acute appendicitis patients and 15 with neuroendocrine tumors.

Imaging Protocols

All abdominal images were acquired using one of two CT scanners with 128 detectors: SOMATOM Definition AS (Siemens Healthcare, Forchheim, Germany) and Revolution HD (General Electric Systems, Waukesha, WI, USA). The CT scan parameters for the abdominal imaging protocol included a tube voltage of 100 kV, a current of 200 mA, a matrix size of 512 x 512, and a slice thickness of 1.25 mm.

Classification and Image Evaluation

Computed tomography features of neuroendocrine tumors were compared with those of complicated and uncomplicated appendicitis. The radiological findings investigated on CT images included the greatest appendiceal diameter including walls, appendiceal wall thickness, cecal wall thickness, the presence of periappendiceal fat stranding, periappendiceal fluid collection, the presence of lymphadenopathy with a short axis greater than 5 mm, air in the appendix lumen, free periappendiceal air, mucosal hyperenhancement of the appendix in comparison to the bowel mucosa, the presence of appendicolith within the lumen, presence of mural calcification in the appendix, and the presence of a mural nodule protruding into the lumen.

All CT scans were retrospectively reviewed through the PACS system by two radiologists (R.H. and E.Y.Ö.) who were blinded to the patients' clinical information and reviewed the images in consensus. In cases of disagreement, a consultation was made with one of the board-certified radiologists (S.Ş. or O.T.), with 7 and 18 years of experience, respectively, in abdominal imaging.

Statistical Analysis

Descriptive statistics for the data included mean, standard deviation, median, minimum, maximum, frequency, and percentage values. The distribution of variables was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. The Kruskal-Wallis and Mann-Whitney U tests were utilized for analyzing quantitative independent variables that did not follow a normal distribution. The Chi-square test was used to analyze qualitative independent variables, and when the as-

Table 1. Diagnostic values of mural nodule protruding into the lumen and air in the appendix lumen as individual findings

	TN	FN	FP	TP	Sensitivity (%)	Specificity (%)	PPV	NPV	Accuracy
Mural Nodularity	1118	7	17	8	53.3	95.8	31.9	99.4	97.9
Luminal Air	870	7	265	8	53.3	76.7	2.9	99.2	76.4

TN: True Negative; FN: False Negative; FP: False Positive; TP: True Positive; PPV: Positive Predictive Value.

assumptions for the Chi-square test were not met, Fisher's exact test was employed.

Software: All analyses were conducted using SPSS Statistics for Windows, Version 28.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Descriptive Statistics

The age of the patients ranged from 1 to 96 years, with a median age of 27.2 years and a mean age of 30.1±16.8 years. Among the 1,150 patients enrolled in the study, 1,135 were diagnosed with acute appendicitis (complicated and uncomplicated) and 15 with neuroendocrine tumors.

CT Findings

The presence of a mural nodule protruding into the lumen (Fig. 1) was observed in a significantly higher proportion of patients with neuroendocrine tumors compared to those with acute appendicitis. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy for mural nodularity were 53.3%, 95.8%, 31.9%, 99.4%, and 97.9%, respectively (Table 1). This indicates that mural nodularity is a highly specific and accurate predictor of neuroendocrine tumors in the appendix (Fig. 2).

Similarly, intraluminal air (Fig. 3) was detected more frequently in the neuroendocrine tumor group than in the acute appendicitis group. The sensitivity, specificity, PPV, NPV, and accuracy for intraluminal air were 53.3%, 76.7%, 2.9%, 99.2%, and 76.4%, respectively. While intraluminal air showed lower specificity and accuracy compared to mural nodularity, its high NPV suggests it is still a useful parameter in excluding neuroendocrine tumors when absent (Table 1).

Other imaging parameters, including appendiceal diameter, wall thickness, cecal wall thickness, periappendiceal fat



Figure 1. The presence of a soft tissue mass presenting as a noticeable nodular thickening on the wall of the appendix (arrow) is a warning sign for appendiceal neoplasm.

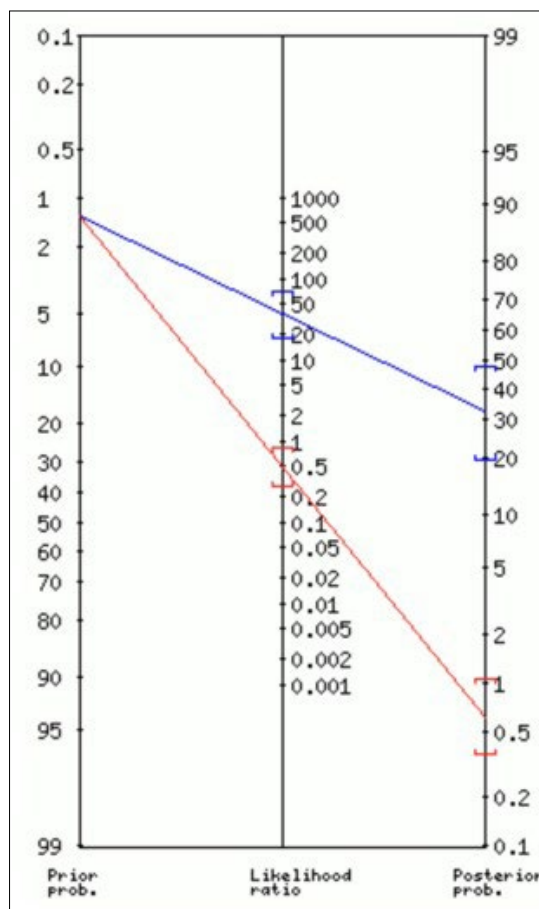


Figure 2. Likelihood ratio nomogram for predicting neuroendocrine tumors based on the presence of a mural nodule protruding into the lumen. The blue line represents the likelihood ratio if a mural nodule is detected, and the red line represents the likelihood ratio if a mural nodule is not detected.



Figure 3. Presence of intraluminal air (arrow) in the appendix. While typical of a healthy appendix, when combined with other findings, it serves as a specific marker of complicated appendicitis.

stranding, fluid collection, lymphadenopathy, free periappendiceal air, mucosal hyperenhancement, presence of appendicolith, and mural calcification, did not show significant differences between the two groups (Table 2).

DISCUSSION

In this retrospective study, we identified significant predictors for neuroendocrine tumors in patients undergoing surgery for acute appendicitis. Specifically, the presence of a mural

nodule protruding into the lumen and the presence of intraluminal air were found to be significant imaging features associated with neuroendocrine tumors.

Imaging findings of acute appendicitis and appendiceal neoplasms often overlap, making neuroendocrine tumors particularly challenging to diagnose due to their small size. In our study, mural nodularity protruding into the appendix lumen and the presence of intraluminal air emerged as the only significant predictors of neuroendocrine tumors in acute ap-

Table 2. Comparison of radiological and clinical characteristics between acute appendicitis and neuroendocrine tumors

	Acute Appendicitis		Neuroendocrine Tumor (+)		
	Mean±SD/n-%	Median	Mean±SD/n-%	Median	
Appendiceal WT	3.2±1.3	3.1	3.4±0.9	3.4	0.185 ^m
Cecal WT	2.0±0.6	1.8	2.4±1.3	2.0	0.341 ^m
Appendiceal Diameter	11.1±3.4	10.5	11.0±3.0	10.3	0.840 ^m
LN Short Axis					
<5 mm	455 40.1%		6 40.0%		0.994 ^{X²}
≥5 mm	680 59.9%		9 60.0%		
Periappendiceal Fat Stranding					
(-)	134 11.8%		3 20.0%		0.408 ^{X²}
(+)	1001 88.2%		12 80.0%		
Periappendiceal Effusion					
(-)	443 39.0%		5 33.3%		0.653 ^{X²}
(+)	692 61.0%		10 66.7%		
Air in the Appendix Lumen					
(-)	870 76.7%		7 46.7%		0.007 ^{X²}
(+)	265 23.3%		8 53.3%		
Free Periappendiceal Air					
(-)	1018 89.7%		12 80.0%		0.200 ^{X²}
(+)	117 10.3%		3 20.0%		
Mucosal Hyperenhancement					
(-)	886 78.1%		9 60.0%		0.094 ^{X²}
(+)	249 21.9%		6 40.0%		
Mural Nodule Protruding into Lumen					
(-)	1118 98.5%		7 46.7%		0.000 ^{X²}
(+)	17 1.5%		8 53.3%		
Appendicolith					
(-)	907 79.9%		14 93.3%		0.196 ^{X²}
(+)	228 20.1%		1 6.7%		
Appendiceal Mural Calcification					
(-)	1130 99.6%		15 100.0%		1.000 ^{X²}
(+)	5 0.4%		0 0.0%		

m: Mann-Whitney U test; X²: Chi-Squared Test (Fisher's Test); SD: Standard Deviation; n: Number; WT: Wall Thickness; LN: Lymph Node.

pendicitis cases. This aligns with an earlier study by Pickhardt et al., which found that the presence of a discernible soft tissue mass was a sensitive indicator of appendiceal neoplasm.^[7] Our finding of mural nodularity may correspond with this observation.

Intraluminal air is a unique finding. While it is typical in a healthy appendix,^[8] numerous studies have shown that, when combined with other findings, it serves as a specific predictor of complicated appendicitis.^[9] In our study, the presence of intraluminal air was significantly higher in neuroendocrine tumor patients compared to those with acute appendicitis. This might be due to air entrapment by the tumor in the appendix lumen or the rate of complications caused by the tumor itself when it leads to acute appendicitis.

The diameter of the appendix has been identified as a sensitive sign of appendiceal neoplasm, with Pickhardt et al. suggesting a cut-off value of 15 mm.^[7] Other studies have also indicated appendiceal diameter as a risk factor for malignancy, with different cut-offs ranging from 10 mm^[10] to 14-15 mm.^[11] However, these studies often include mucinous carcinoma of the appendix, which is known to cause prominent dilation of the appendiceal lumen. In our study, the diameter of the appendix was nearly the same in both acute appendicitis (mean 11.1 mm) and neuroendocrine tumor (mean 11.0 mm) cases.

In their pictorial review, Leonards et al. describe imaging findings of appendiceal neuroendocrine tumors as small masses usually located in the distal third of the appendix, which may enhance in post-contrast images and sometimes contain calcifications.^[12] In our study, mucosal hyperenhancement was observed more frequently in neuroendocrine tumor patients, but the correlation was not significant. Interestingly, we did not encounter any calcifications in neuroendocrine tumors.

The results highlight the need for heightened awareness and careful assessment of these specific imaging characteristics during the diagnosis of acute appendicitis. Incorporating these predictors into diagnostic protocols could improve preoperative identification of neuroendocrine tumors, enabling more appropriate and timely surgical interventions. This approach may ultimately lead to better patient outcomes and a reduction in the incidence of overlooked appendiceal malignancies.

Our study has several limitations that should be acknowledged. First, the retrospective design may introduce selection bias and limit the generalizability of our findings. The relatively small number of neuroendocrine tumor cases also restricts the robustness of our conclusions. Additionally, relying solely on CT imaging without incorporating intraoperative findings or using advanced imaging modalities such as magnetic resonance imaging (MRI) or positron emission tomography-computed tomography (PET-CT) might have limited the comprehensiveness of our results. Future research should focus on prospective studies with larger sample sizes to validate our findings and explore additional predictors of neuroendocrine tumors in appendicitis patients. Investigating the ef-

ficacy of advanced imaging techniques and exploring genetic and molecular markers could provide further insights into the early detection and targeted treatment of these tumors. By addressing these limitations and pursuing these research directions, we can improve diagnostic accuracy and patient outcomes in cases of appendiceal neuroendocrine tumors.

CONCLUSION

In this study, we identified key imaging features that can help predict neuroendocrine tumors in patients undergoing surgery for acute appendicitis. Specifically, the presence of a mural nodule protruding into the lumen and intraluminal air were found to be significant predictors of neuroendocrine tumors. These findings underscore the importance of meticulous preoperative imaging evaluations, as traditional CT imaging alone may not be sufficient to detect small or incidental neoplasms. Future research should focus on validating these findings through prospective studies and exploring advanced imaging techniques to further enhance the detection of appendiceal neoplasms.

Ethics Committee Approval: This study was approved by the Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty Ethics Committee (Date: 01.12.2023, Decision No: 1094756).

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ORJİNAL ÇALIŞMA - ÖZ

Akut apandisit hastalarında nöroendokrin tümörlerin tanısında zorluklar ve prediktif radyolojik bulgular

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AMAÇ: Akut apandisit, en yaygın cerrahi acilerden biridir. Antibiyotiklerle tedavi stratejileri önem kazandıkça, apandisit nedeni olarak veya tesadüfi bir bulgu olarak apendiks tümörü olasılığı, konservatif yaklaşım için bir engel teşkil etmektedir. Apendiks tümörleri içinde en sık görülen ancak küçük boyutu nedeniyle preoperatif tanı en zor konan tip olan nöroendokrin tümörler bu konuda özellikle zorluk oluşturmaktadır. Bu çalışma, görüntüleme ve klinik özellikleri analiz ederek akut apandisit nedeniyle ameliyat edilen hastalarda nöroendokrin tümörler için öngörücü faktörleri belirlemeyi, böylece preoperatif tanı doğruluğunu artırmayı ve cerrahi müdahaleleri yönlendirmeyi amaçlamaktadır.

GEREÇ VE YÖNTEM: Bu retrospektif gözlemsel çalışma, Ocak 2014 ile Mayıs 2024 arasında apendektomi yapılan 1298 hastayı içermektedir. Normal patoloji sonuçları olan 59 hasta, değişken patolojilere sahip 40 hasta ve erişilemeyen BT görüntüleri olan 49 hasta dışlandıktan sonra, 1150 hasta kaldı (1135 akut apandisit ve 15 nöroendokrin tümör). Abdominal BT taramaları, apendiks çapı, duvar kalınlığı, çekum duvar kalınlığı, peria-pendiküler yoğunluk artışı ve effüzyon, lenfadenopati, lümen içi ve serbest peria-pendiküler hava, mukozal kontrastlanma artışı, apendikolit varlığı, mural kalsifikasyon ve mural nodüller açısından değerlendirildi.

BULGULAR: Lümene protrüde olan mural nodül varlığı, nöroendokrin tümörlü hastalarda akut apandisitli hastalara kıyasla anlamlı derecede daha yüksekti. Bu durum, %53.3 duyarlılık, %95.8 özgüllük, %31.9 pozitif öngörü değeri (PPV), %99.4 negatif öngörü değeri (NPV) ve %97.9 doğruluk ile ölçüldü. Lümen içi hava da nöroendokrin tümörlü hastalarda daha sık görüldü ve %53.3 duyarlılık, %76.7 özgüllük, %2.9 PPV, %99.2 NPV ve %76.4 doğruluk ile değerlendirildi. Diğer görüntüleme parametreleri iki grup arasında anlamlı fark göstermedi.

SONUÇ: Bu çalışma, akut apandisitli hastalarda nöroendokrin tümörlerin öngörücüleri olarak mural nodüller ve lümen içi havanın önemli belirteçler olduğunu belirlemektedir. Bu bulguların tanı protokollerine dahil edilmesi, nöroendokrin tümörlerin preoperatif tanısını destekleyebilir ve daha uygun cerrahi müdahalelere olanak tanıyabilir. Gelecek araştırmalar, bu bulguları prospektif çalışmalarla doğrulamalı ve apendiks tümörlerinin tespiti için ileri görüntüleme tekniklerini keşfetmelidir, bu da nihayetinde hasta sonuçlarını iyileştirecek ve gözden kaçan maligniteleri azaltacaktır.

Anahtar sözcükler: Akut apandisit; bilgisayarlı tomografi; nöroendokrin tümör.

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