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Incidentally discovered, intentionally managed: a narrative review of the last decade's updates on the management of neuroendocrine tumor of the appendix

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Abstract

Appendiceal neuroendocrine neoplasms (aNENs) represent an increasingly recognized and heterogeneous subset of gastroenteropancreatic neuroendocrine tumors (NETs), most often identified incidentally on appendectomy specimens. Postoperative management relies on accurate risk stratification grounded in histopathological assessment and aligned with major international guidelines (WHO, ENETS), which distinguish between well-differentiated NETs (NET grades 1 to 3) and poorly differentiated neuroendocrine carcinomas. Critical prognostic determinants shaping therapeutic decision-making include tumor size, proliferative index (Ki-67), depth of invasion—particularly mesoappendiceal involvement—and lymphovascular invasion (LVI). Consensus recommendations suggest simple appendectomy as definitive treatment for low-risk tumors (<1 cm) and right hemicolectomy for high-risk lesions (>2 cm) or those exhibiting LVI. However, the management of intermediate-sized aNENs (1.0-2.0 cm) remains the principal area of clinical uncertainty, with emerging data suggesting that appendectomy alone may be sufficient for carefully selected patients without adverse pathological factors. This review synthesizes and critically appraises the most recent evidence and international guidelines with the goal of refining current clinical practice. In particular, it provides an updated framework for individualized risk stratification, evaluates the balance between oncological benefit and procedural morbidity in determining the optimal surgical approach, and outlines evidence-based surveillance strategies to support a more consistent, risk-adapted multidisciplinary management of aNENs.

Keywords Appendiceal neuroendocrine tumor, neuroendocrine neoplasms, surgical management, right hemicolectomy, ENETS guidelines

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Introduction

Neuroendocrine neoplasms (NENs) represent a biologically and clinically heterogeneous group of tumors arising from the diffuse neuroendocrine cell system, with the gastroenteropancreatic (GEP) tract recognized as the principal site of origin, a point repeatedly underscored by leading international guidelines [1]. While general guidelines provide a comprehensive overview of diagnosis and treatment, the specific clinical approach often requires further refinement based on the primary site [2]. Within the GEP system, appendiceal NENs (aNENs) constitute a distinct and relatively rare entity, typically accounting for a small percentage of appendectomy specimens [3]. These tumors are frequently

discovered incidentally during surgery for suspected acute appendicitis, initiating a complex postoperative management pathway [4].

Accurate management hinges on precise histopathological characterization and risk assessment. Current protocols that guide diagnostic and therapeutic procedures emphasize the pathological staging and grading based on morphology and proliferative index (Ki-67), distinguishing between well-differentiated neuroendocrine tumors (NETs) and poorly differentiated carcinomas (NECs) [5]. The primary therapeutic challenge involves determining the optimal extent of surgical intervention, balancing the goal of complete tumor eradication with the morbidity associated with aggressive procedures such as right-sided hemicolectomy [6]. The decision-making process is highly refined, having been recently clarified by the latest guidance papers from leading NET societies [7].

Current clinical guidelines utilize a combination of key prognostic factors to determine the required surgical extent [7,8]. The main parameters used to stratify the risk of recurrence and nodal metastasis are tumor size, histological grade (G1-G3), depth of invasion (especially involvement of the mesoappendix), positive or uncertain resection margins, and the presence of lymphovascular invasion (LVI) [6,9]. A general consensus dictates simple appendectomy for low-risk tumors (<1 cm) and mandatory extended resection for high-risk tumors (>2 cm) [6,7].

Crucially, the management of intermediate-sized aNENs measuring 1.0-2.0 cm represents the most significant area of clinical controversy and therapeutic variability [10]. Recent data emphasize that, for selected patients in this size group, a conservative simple appendectomy may be considered definitive treatment if adverse pathological features are absent [10]. This necessitates a rigorous review of postoperative pathology to identify patients who truly benefit from the added morbidity and cost of reoperation [6]. Furthermore, the post-treatment phase presents unique challenges regarding the validation of standardized surveillance strategies. The cost-effectiveness and clinical utility of serum biomarkers, such as chromogranin A (CgA), and the role of routine cross-sectional imaging or somatostatin receptor imaging in the long-term follow-up of completely resected low-risk aNENs, remain an area of ongoing debate that lacks universally validated protocols [5].

In light of the continuous evolution in pathological classification, refined surgical risk stratification, and the need for standardized surveillance, this narrative review aims to provide a comprehensive and concise synthesis of the latest literature and major international guidelines. We focus on clarifying the contemporary multidisciplinary approach, translating the current evidence into a practical framework for the risk assessment, optimal surgical strategy, and recommended long-term surveillance protocols for aNENs. A summary of the current state of the art is provided in Fig. 1.

Materials and methods

This narrative review was conducted to provide a comprehensive and up-to-date synthesis of the literature regarding aNENs, focusing specifically on pathological classification, optimal surgical strategies, and long-term surveillance protocols. A targeted, non-systematic search of relevant publications was performed across the electronic databases PubMed/MEDLINE, Scopus and Google Scholar. The search was restricted to articles published from January 2015 up to November 2025 to ensure contemporary relevance. Search terms and MeSH headings used in various combinations included: "Appendiceal Neuroendocrine Neoplasm", "aNEN", "Appendiceal Carcinoid", "Appendiceal NET", "Right Hemicolectomy", "Extended Resection", "Lymphovascular Invasion", "LVI", "Goblet Cell Carcinoma", "MANEC", "Surveillance", "Follow-up", and "Risk Stratification". This review is not a systematic review and did not follow PRISMA guidelines; instead, it was conducted as a narrative synthesis of the available literature, with studies selected based on clinical relevance, methodological quality, and contribution to current understanding of aNENs. No language-based exclusion criteria were applied during study selection. We prioritized the inclusion of major international clinical practice guidelines (e.g., ENETS, NANETS), systematic reviews and meta-analyses, and large-cohort original studies (including retrospective and registry-based analyses) that assessed epidemiology, prognostic factors, surgical outcomes and long-term survival. Publications such as single case reports, letters to the editor, and conference abstracts were generally excluded, unless they provided unique and critical information. Data from the included literature were critically reviewed and synthesized thematically into sections covering Epidemiology, Etiopathogenesis, Clinical Presentation, Histology/Diagnosis, and Outcome/Surveillance, to construct a practical and evidence-based clinical framework.

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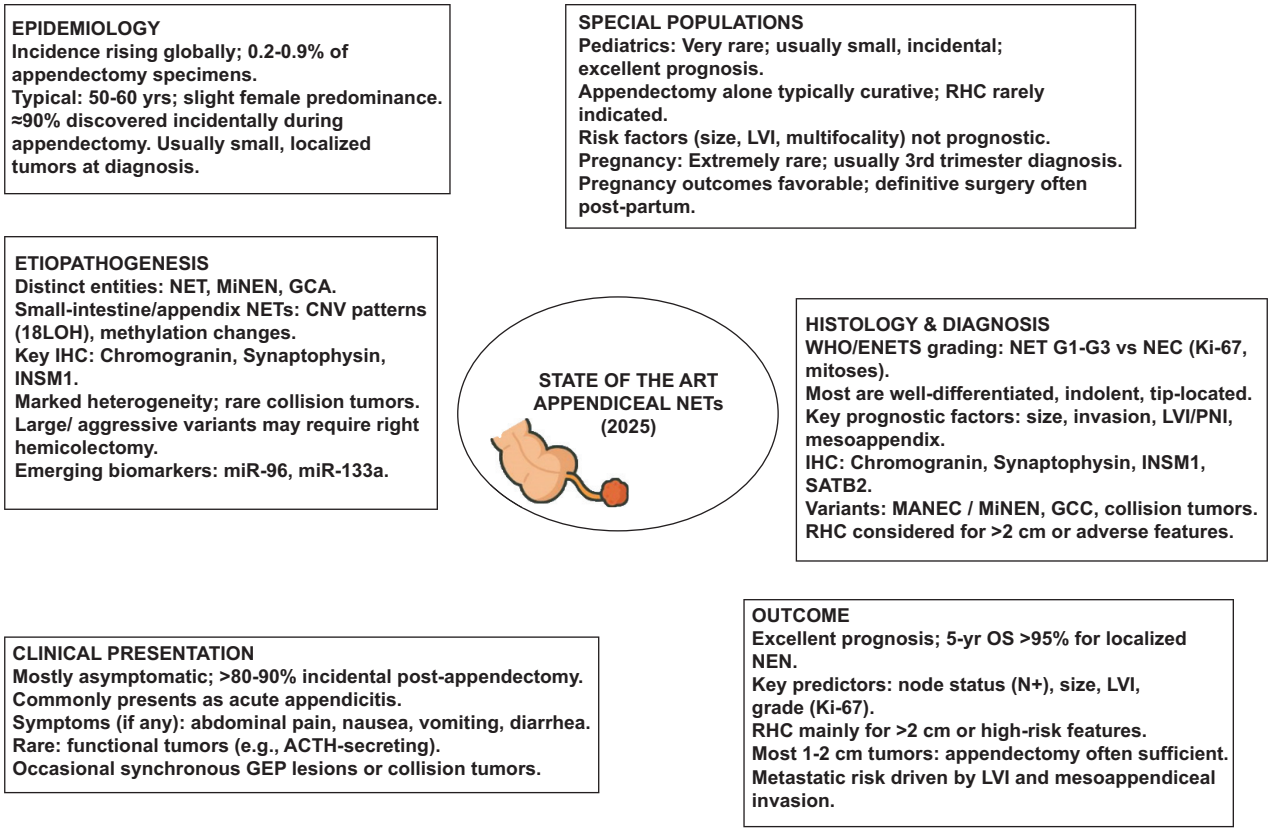

Figure 1 State-of-the-art summary of aNETs (2025)
Overview of key domains in the contemporary understanding of aNETs, including epidemiology, etiopathogenesis, clinical presentation, histopathology, special populations, and outcomes. Most aNETs are incidentally detected, well-differentiated, localized neoplasms with excellent prognosis. Prognostic stratification is driven by tumor size, grade, lymphovascular invasion, and mesoappendiceal invasion. Special considerations apply to pediatric and pregnant patients, in whom appendectomy is generally sufficient and outcomes are favorable
ACTH, adrenocorticotropic hormone; aNEN, appendiceal neuroendocrine neoplasm; cm, centimeters; CNV, copy number variation; e.g., for example; ENETS, European Neuroendocrine Tumor Society; G1–G3, grade 1–grade 3; GCA, goblet cell adenocarcinoma; GCC, goblet cell carcinoma; GEP, gastroenteropancreatic; IHC, immunohistochemistry; INSM1, insulinoma-associated protein 1; Ki-67, Ki-67 proliferation index; LOH, loss of heterozygosity; LVI, lymphovascular invasion; MANEC, mixed adenoneuroendocrine carcinoma; MiNEN, mixed neuroendocrine–non-neuroendocrine neoplasm; miR, microRNA; N+, positive lymph nodes/nodal involvement; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor; OS, overall survival; PNI, perineural invasion; RHC, right hemicolectomy; SATB2, special AT-rich sequence-binding protein 2; vs*, versus; WHO, World Health Organization; yr/yrs, year/years*

Epidemiology

The analysis of appendix tumor trends across population-based cohorts has demonstrated a conspicuous increase in incidence over time, consistent with the global epidemiological pattern for NENs [11]. As the most common primary site for NENs is the GEP tract [1], aNENs represent a different subset requiring site-specific clinical refinement [2]; therefore, the clinical management has to be defined according to the specific primary site of the tumor [3]. Early single-center series reported a prevalence of aNENs in approximately 0.2% of appendectomy specimens, occasionally noting a minor male predominance [4]. The majority of aNEN diagnoses typically occur in the 5th or 6th decade of life [5]. The increasing incidence of aNENs is a phenomenon attributed to diagnostic optimization [6]. The reported detection rate of aNENs in surgical specimens generally ranges from 0.2-0.9% [7], reinforcing the understanding that the appendix and small intestine collectively account for a high proportion of NENs arising from the GEP system [8]. ANENs are the most frequent primary tumor of the appendix [9], usually found incidentally and characterized by their small size [10]. This global increase in NEN incidence was confirmed by a large-scale cohort study in the USA (2000-2018), which reported a significant rise in age-adjusted incidence, with the most marked increases observed specifically in localized-stage and appendiceal tumors [12]. Enhanced precision was provided by the continuous monitoring of incidence and survival trends for gastrointestinal (GI) NENs through analyses of the SEER database [13]. A persistent rise in NEN incidence has also been confirmed by a retrospective, population-based study in England (1995-2018) [14], while sustained increments in incidence rates were similarly illustrated by epidemiological trends spanning 3 decades in Queensland, Australia [15].

Data from Asia, specifically Japan, contribute to this global picture, documenting thousands of diagnoses of GEP-NENs in a single year [16]. Clinical and pathological data analysis from dedicated cancer registries, such as the Belgian Cancer Registry, provides valuable, localized insights into the variable biological behavior and outcomes of aNENs [17]. A large multi-institutional US study further elucidated the epidemiology of aNENs, concluding they are the third most common NEN location along the digestive tract, and that patients were more likely to be female [18]. Tertiary care studies [19,20] demonstrated that a high prevalence of NETs is found during appendectomy performed for acute appendicitis, emphasizing the frequent incidental nature of the diagnosis, which often lead to unexpected histopathological findings [21]. One retrospective study specifically reported a 2% incidence of NETs in macroscopically normal appendices removed during laparoscopy for acute abdominal pain [22], and the association between aNEN and acute appendicitis has been clearly established [23]. Despite the high frequency of aNENs, data from 1 tertiary center in the Middle East indicated that the pancreas and small intestine were more common sites for GEP-NENs in that specific patient population [24]. Overall, aNENs constitute approximately 31% of all appendiceal tumors identified in 1 national cancer database analysis [25]. The epidemiological risk extends beyond the primary tumor, as population studies in England have reported that patients with NENs have an increased risk of developing second primary malignancies [26]. Finally, the epidemiology of more aggressive variants, such as appendiceal mixed adeno-neuroendocrine carcinoma (MANEC), has been characterized using the SEER registry, emphasizing the need for differentiated pathological and clinical management [27]. A synthesis of the major epidemiological studies describing incidence trends, demographic distribution, and prevalence of incidental aNENs is reported in Table 1.

Etiopathogenesis

The complex pathogenesis of appendiceal neoplasms demands precise differentiation among various pathological entities, extending beyond classical NETs to include hybrid and epithelial malignancies. This distinction is important to identify aggressive variants, such as mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs), which frequently exhibit unfavorable outcomes and whose specific clinical profile and survival patterns have been established through large genomic analyses utilizing comprehensive registry data [28]. Goblet cell adenocarcinomas, another entity within the range of aggressive appendiceal pathology, demonstrate a specific clinicopathological, immunological and genomic landscape that distinguishes them from classical well-differentiated aNENs [29]. NETs of the small intestine and appendix are known to exhibit extensive chromosomal and methylation alterations [30]. Molecular research has categorized multiple genomic variants using chromosomal copy number variation, specifically the loss of chromosome 18 (18LOH), and have revealed differential methylation patterns in G-protein coupled receptor signaling genes, including the somatostatin gene, which is a crucial target for both clinical imaging and therapeutic intervention [30]. Diagnostic precision and further histological analysis hinge largely upon immunohistochemistry (IHC), which constitutes a system essential for defining the proper oncological architecture [31]. While conventional neuroendocrine antigens, such as chromogranin A and synaptophysin, are still commonly utilized, the nuclear transcription factor INSM1 (insulinoma-associated protein 1) demonstrates superior selectivity regarding neuroendocrine maturation within the digestive system, facilitating exact clinical assessment protocols [32]. Nevertheless, a systematic review comparing IHC biomarkers between appendiceal neuroendocrine and epithelial cell neoplasms has revealed the necessity for future trials to identify the optimal marker combination [31,32]. In addition to the standard neuroendocrine pathways, the molecular profiles of non-neuroendocrine appendiceal lesions, including serrated lesions, polyps and mucinous neoplasms, demonstrate genotypic heterogeneity, emphasizing the complex and divergent carcinogenic pathways active within the appendix [33]. This intricate pathological environment occasionally results in rare appendiceal collision tumors, defined by the coexistence of a neuroendocrine carcinoid and a concomitant mucinous neoplasm, demonstrating the requirement for clinical plans that follow the oncologic rules of each distinct component neoplastic category found therein [34,35]. Given such variety, thorough evaluation of therapeutic strategies is important; for instance, the management of aggressive MiNENs (such as MANEC) has been studied by comparing right hemicolectomy versus appendectomy to clarify the optimal surgical approach and evaluate any survival advantage [36]. Similarly, the appropriate surgical strategy for large appendiceal carcinoids (those exceeding 2 cm) has been assessed using matching score analysis to verify whether right hemicolectomy provides a better survival benefit than simple appendectomy alone [37]. Lastly, new investigations explore novel prognostic markers, including specific microRNAs (miRNAs), such as miR-96 and miR-133a, in GI NENs to possibly help in evaluating the biological behavior and metastatic potential of these complex neoplasms [38].

Clinical presentation

The clinical presentation of aNENs is variable, ranging from specific endocrine syndromes to the frequent scenario of incidental detection [39,40]. Although the majority of aNENs are non-functional, the pathological ranges include rare, but clinically significant, functional syndromes. One such case involved a patient presenting with ectopic Cushing syndrome from an ACTH-secreting appendicular carcinoid, where precise tumor localization was achieved using advanced nuclear medicine techniques such as 68-Ga-DOTATATE PET/CT [41]. Furthermore, exhaustive diagnostic investigation is essential, given the known multifocal behavior

Table 1 Summary of key epidemiological evidence on aNENs. This table synthesizes major population-based studies, national cancer registries, and large appendectomy series describing incidence trends, prevalence in surgical specimens, demographic patterns, and the global rise in detection of appendiceal neuroendocrine neoplasms. Together, these data confirm aNENs as increasingly common, predominantly incidental findings with overall favorable prognosis and significant geographic variability in reported incidence

First author, year [ref.]	Country/data source	Study design/ population	Key epidemiologic findings relevant to aNENs
Halfter, 2023 [11]	Population-based cohort of appendix tumors (Europe)	Retrospective, population-based study of appendix tumour trends and prognosis	Demonstrated increasing incidence of appendix tumors over time, with neuroendocrine neoplasms representing a distinct subgroup with favorable prognosis compared with other appendiceal malignancies, supporting the need for site-specific risk stratification.
Wu, 2023 [12]	USA, SEER (2000-2018)	Nationwide cohort of patients with NENs	Confirmed a marked rise in age-adjusted incidence of NENs over 2 decades, with the most pronounced increases observed in localized-stage and appendiceal tumors, reinforcing the perception of aNENs as an increasingly detected entity.
Liu, 2023 [13]	USA, SEER (1977-2016)	Population-based analysis of gastrointestinal NENs	Documented long-term trends in incidence and survival for GI NENs, showing a persistent rise in incidence over 4 decades; appendiceal NENs contributed to the growing burden of lower GI NENs with generally favorable survival.
White, 2022 [14]	England, national registry (1995-2018)	Retrospective population-based cohort of NENs	Reported a sustained increase in NEN incidence and improved overall survival in England; appendiceal NENs were among the most frequent lower GI primary sites, highlighting their growing epidemiological relevance.
Wyld, 2019 [15]	Queensland, Australia	State-wide registry over 3 decades	Showed steadily rising incidence of NENs across 30 years, including small bowel and appendiceal primaries, mirroring global epidemiologic trends and improved recognition of these tumors.
Masui, 2020 [16]	Japan, nationwide GEP-NEN database	Population-based study of GEP-NENs	Reported thousands of GEP-NEN diagnoses in a single year; appendiceal NENs represented a distinct, though less frequent, primary site in the Asian population, contributing to the global picture of increasing GEP-NEN incidence.
Ribeiro, 2021 [17]	Belgium Cancer Registry (2010-2015)	National registry focusing on aNENs	Characterized clinical and pathological features of aNENs at a national level, showing variable biological behavior but overall excellent prognosis, and underscoring the importance of detailed registry data for rare tumors.
Alkhayyat, 2021 [18]	USA, national database (2014-2019)	Population-based study of appendiceal NENs	Established that appendiceal NENs represent the third most common NEN location along the digestive tract and are more frequently diagnosed in females; confirmed increasing detection rates and predominantly localized disease at presentation.
Gobishangar, 2023 [19]	Tertiary centre, Sri Lanka	Cohort of appendectomies for acute appendicitis	Evaluated the prevalence of NETs in appendectomy specimens for acute appendicitis, confirming that aNENs are not rare incidental findings and reinforcing the need for routine histopathological examination of all appendectomy specimens.
Kamalı, 2023 [20]	Tertiary centre, multi-year series	Retrospective analysis of 6785 appendectomy histologies	Investigated uncommon causes of acute appendicitis, including appendiceal NENs, confirming their association with the clinical picture of acute appendicitis and contributing to estimates of their prevalence in routine surgical practice.
Limaiem, 2015 [21]	Single-centre, Tunisia	Retrospective review of 1627 appendectomy specimens	Analyzed unexpected histopathological findings in appendectomy specimens and identified appendiceal NETs among the most frequent incidental lesions, supporting systematic microscopic evaluation even when macroscopic findings are unremarkable.
Tartaglia, 2016 [22]	Italy, surgical cohort	Retrospective study in patients with acute right lower quadrant pain and "incidental" appendectomy	Showed that approximately 2% of macroscopically normal appendices removed during laparoscopy for acute abdominal pain harbored a neuroendocrine tumour, emphasizing the risk of missing aNENs without systematic histology.

(*Contd...*)

Table 1 (*Continued*)

First author, year [ref.]	Country/data source	Study design/ population	Key epidemiologic findings relevant to aNENs
Khan, 2019 [23]	Single-center series	Clinical and pathological study of appendicular NENs	Confirmed the strong association between appendiceal NEN and acute appendicitis and highlighted that the tumour may be easily overlooked without careful pathological assessment, supporting the concept of aNEN as a common incidental finding.
Bazarbashi, 2023 [24]	Middle Eastern tertiary centre	Cohort of patients with GEP-NENs	Described site distribution and outcomes for GEP-NENs, noting that in this population pancreas and small intestine were more common primary sites than the appendix, illustrating geographic variation in the relative frequency of aNENs.
Marks, 2023 [25]	USA, national cancer database	Retrospective cohort of appendiceal tumors	Reported that aNENs accounted for≈31% of all appendiceal tumors in a large national dataset, confirming that they are the most common malignant appendiceal histotype and a major contributor to appendiceal tumour burden.
Russell, 2023 [26]	England, national NEN cohort	Population-based study of second primary malignancies	Demonstrated that patients with NENs, including appendiceal primaries, have a higher risk of developing second primary malignancies, an important consideration in long-term survivorship and epidemiologic burden estimates.
Brathwaite, 2016 [27]	USA, SEER registry	Population-based study of appendiceal MANEC	Characterized the incidence, demographics, and outcomes of appendiceal MANEC, illustrating the epidemiology of more aggressive appendiceal variants that must be distinguished from classical well-differentiated aNENs.

aNENs, appendiceal neuroendocrine neoplasms; aNETs, appendiceal neuroendocrine tumors; NENs, neuroendocrine neoplasms; NETs, neuroendocrine tumors; GEP-NENs, gastroenteropancreatic neuroendocrine neoplasms; SEER, Surveillance, Epidemiology, and End Results database; NCDB, National Cancer Database; MANEC, mixed adeno-neuroendocrine carcinoma

of NENs across the GEP tract; aNENs may co-occur with synchronous primary tumors in other GI sites, such as the small intestine, necessitating a full workup to exclude disseminated neuroendocrine disease [42]. The absence of pathognomonic symptoms implies that a high proportion of aNEN cases are discovered during routine histopathological analysis following an appendectomy [39,40]. In fact, the most frequent preoperative clinical manifestation linked to a subsequent eventual aNEN diagnosis is acute appendicitis, which the neoplasm is known to simulate [43,44]. The generic symptoms reported by patients often include abdominal pain, nausea, vomiting and diarrhea [41,42]. This mimicry is occasionally complicated by the presence of a mucocele detectable on CT scan, making the differential diagnosis more difficult [43]. The risk of a missed diagnosis remains high. One report highlighted the diagnostic hazards of conservative management when a NET G1 remained undetected until an interval appendectomy followed non-surgical treatment for acute appendicitis [45]. This phenomenon stems from the tumor's infiltrative or non-mass-forming growth architecture, which restricts visibility during preoperative radiological imaging [45]. The prevalence of incidental detection, observed across various patients groups, including young patients [40], underscores the importance of mandatory pathological assessment of all appendectomy specimens. Finally, the vague and potentially misleading clinical characteristics of appendiceal NETs, being highly similar to those of acute appendicitis, pose a persistent challenge for diagnosis, particularly in settings where the neoplasm is considered an atypical trigger of appendicitis [46].

Expanding on these incidental observations, a single-center experience over a decade confirmed that NETs represented the most frequently observed incidental findings in appendectomy samples [47]. The clinical manifestation may also involve rare scenarios, such as the disease occurring within an incarcerated Amyand's hernia; here, an appendiceal carcinoid was identified inside the hernial sac, highlighting the necessity of high suspicion in atypical presentations [48]. Although clinical scores, such as the AIMS65 score (Albumin <3.0 g/dL, International normalized ratio >1.5, Mental status changes, Systolic blood pressure ≤90 mmHg, age ≥65 years) for upper GI bleeding [49], are often employed to evaluate patient prognosis in various conditions, the identification of aNENs depends primarily on pathological review. Nevertheless, the incidental finding of an aNEN, even with a complication such as a perforated appendix, emphasizes the unpredictable nature of its discovery, with 1 case describing a grade 1 appendiceal neuroendocrine tumor (aNET) found incidentally in a young female after emergency surgery for perforated appendicitis [50]. The complex management of these cases requires strict adherence to the oncological principles of the constituent malignancies [34,35]. The necessity for comprehensive workup is further evidenced by instances of synchronous quadruple primary neoplasms, including a collision neoplasm of a NET and a Schwann cell hamartoma in the appendix, along with a colon adenocarcinoma and a sessile serrated adenoma [51].

To underscore this diagnostic difficulty, recent research evidence has confirmed that neuroendocrine malignancies of the appendix often surface unexpectedly, intraoperatively or

following surgical resection for presumed inflammation, and represent significant clinical hurdles [52]. This histological range additionally encompasses goblet cell adenocarcinomas, primarily detected among individuals presenting with acute appendicitis symptoms, illustrating the neoplasm's inherent capacity to mimic benign inflammatory reactive conditions [53].

The likelihood of concurrent lesions remains high, as illustrated by a case involving the rare Leser-Trélat sign—an abrupt onset of multiple seborrheic keratosis—in a patient with synchronous well-differentiated NETs of both the ileum and the appendix [54]. Additionally, the unusual presentation of a NET within an Amyand's hernia has been confirmed, where the tumor with serosal involvement was found in the appendix during emergency surgery for acute appendicitis in an inguinal hernia [55]. Retrospective studies have highlighted the importance of universal histological examination, revealing that a significant percentage of macroscopically normal appendices removed during laparoscopy for acute right lower quadrant abdominal pain contained a NET [22]. The propensity for these tumors to present as an acute surgical emergency extends to the nearby cecum, where a carcinoid tumor of the cecum presented with the clinical picture of acute appendicitis [56]. Given the diversity in presentation and aggressiveness, comparative analyses are important, showing that the survival profile for typical carcinoids differs significantly from mixed adeno-neuroendocrine carcinomas and adenocarcinomas of the appendix [57]. Finally, the most complex presentations, such as perforated combined mucinous and NETs leading to *pseudomyxoma peritonei*, necessitate aggressive surgical approaches, including cytoreductive surgery and hyperthermic intraperitoneal chemotherapy [58].

Histology and diagnosis

Establishing a clinical diagnostic pathway for aNENs requires comprehensive histopathological classification and grading [59], employing globally accepted systems from the World Health Organization (WHO) and ENETS guidelines to distinguish between well-differentiated NETs (NET G1-G3) and poorly differentiated NECs, mainly through assessment of the Ki-67 proliferative index and mitotic count [59]. Most cases of aNENs are typically well-differentiated NETs, which usually follow an indolent course when the disease remains localized upon diagnosis [59]; microscopically, aNENs appear morphologically similar to midgut NETs, despite the broad pathological spectrum [9,60]. Well-differentiated NETs of the appendix (A-WDNETs) display diverse tumor growth patterns, including solid, nest, insular, trabecular and acinar formations [61]—a specific single-center study examining these A-WDNETs identified elevated expression levels of the innovative neuroendocrine marker INSM1 throughout those various growth morphologies [61]. Beyond the typical carcinoid form, the pathological spectrum is complicated by other primary appendiceal tumors, such as MANECs and goblet cell carcinomas, which represent highly aggressive, distinct entities requiring tailored classification and management strategies [9,59]. Apart from grading and basic phenotyping, the histopathological report should detail crucial prognostic variables that determine the requirement for extensive surgical resection (right hemicolectomy), including tumor size, depth of invasion (e.g., mesoappendiceal involvement), and the presence of angio- and neuro-invasion [59,61], with the importance of accurate tumor staging (TNM) widely recognized for predicting prognosis, as some studies suggest staging is more reliably associated with adverse clinical outcomes than is grading [59]. Additionally, the condition remains pathologically complex: investigations assessing tumor cellular subtyping imply that, whereas primary small intestinal NETs comprise serotonin-producing EC-cells, the appendiceal variants might contain different cell lineages (e.g., L-cells producing PYY) necessitating further study regarding clinical importance [62]. IHC extends beyond grading: IHC analysis of GEP-NETs has been used in large single-center experiences to investigate the expression of conventional markers, such as synaptophysin and chromogranin A, confirming that most aNENs are typically found incidentally at the tip and exhibit an indolent nature [63]. Research into targeted next-generation sequencing of well-differentiated appendiceal NETs is currently ongoing to discover particular molecular hallmarks, thereby enhancing the underlying genetic knowledge of these specific malignancies [64]. Monitoring the expression of individual transcription factors remains key for assigning the primary site of origin in NETs; strong expression of SATB2 (special AT-rich sequence-binding protein 2) occurs only in well-differentiated tumors arising from the lower GI tract (including the appendix and rectosigmoid), providing a diagnostic tool to distinguish them from tumors of foregut or midgut origin [65]. IHC challenges persist in mixed tumors, where INSM1 demonstrates positivity in a significant portion of the aggressive adenocarcinoma ex-goblet cell carcinoids, even though the majority of tumor cells lack staining for conventional neuroendocrine markers [66]. Chemokine receptor 4 (CXCR4) in GI NENs constitutes the focus of retrospective study, with IHC analysis aiming to characterize its prognostic presence in these tumors [67]. Finally, emerging research is focusing on molecular biomarkers such as miRNAs, with studies aiming to evaluate their use as adjunct tissue markers for classifying and grading well-differentiated GEP-NETs, potentially providing additional tools for assessing the biological behavior of aNENs [68].

Undoubtedly, the primary challenge in the diagnostic pathway of appendiceal neoplasms is achieving accurate preoperative localization and characterization, often within the context of acute abdominal pain, and the overall diagnostic process must recognize the pathological heterogeneity of appendiceal tumors, which constitute a wide spectrum of diseases encompassing typical NETs (TNETs), goblet cell carcinoids and signet-ring cell tumors, all exhibiting different patterns of presentation and, crucially, distinct outcomes [69]. Ultrasound (US) is a primary noninvasive imaging tool utilized for evaluating children presenting with acute right iliac fossa pain and suspected appendicitis; a specific study evaluated the diagnostic accuracy of US in this pediatric population, highlighting its role in the differential

diagnosis [70]. This precise histopathological differentiation is crucial, as the final diagnostic classification directly guides the major therapeutic decisions [71]. The diagnostic workup must account for rare functional syndromes, such as ectopic Cushing syndrome, where precise localization is crucial and can be achieved using advanced nuclear medicine techniques such as 68-Ga-DOTATATE PET/CT [39]. Given that aNENs are often incidentally discovered during appendectomy [6], postoperative management hinges on risk stratification, particularly regarding the need for complementary right hemicolectomy (RHC) [71]. For incidental tumors less than 20 mm in diameter located at the appendiceal base, the absence of poor prognostic factors at histopathological examination remains an important indication of whether a simple appendectomy is sufficient [72]. Deciding whether a patient needs regional lymphadenectomy depends on the risk of nodal metastasis, which current guidelines often base solely on tumor size; however, a more accurate predictive tool is offered by a newer model combining depth of invasion and tumor size [73], underscoring the critical role of pathological factors beyond size alone, while the core debate over RHC versus simple appendectomy for tumors sized between 1-2 cm remains central [71]. IHC plays a useful role in diagnosis and molecular classification, with the expression of specific markers, such as PCSK2 (prohormone convertase 2), having been evaluated for its utility in a panel approach to distinguish between foregut and midgut NETs [74]. Furthermore, specific transcription factor IHC, such as SATB2, has been shown to distinguish Islet1 positive rectal NETs from pancreaticoduodenal NETs, a principle that aids in establishing the lower GI tract origin of appendiceal NETs [75]. However, the role of advanced imaging post-resection is limited; retrospective analyses have shown that routine early postoperative 68-Ga-DOTATATE PET/CT has a low yield in incidental appendiceal NETs [76]. The determination of whether to perform oncological completion surgery remains a critical challenge, with studies evaluating the reliability of proposed risk criteria by comparing histopathological findings with disease-free survival [77]. The clinical utility of SATB2 has been verified in an extensive tissue microarray study analyzing thousands of tumors [78]. The foundation of the workup is the pathological report, which classifies aNETs—the most common neoplasm of the appendix—and provides the critical size, LVI, and pT category data [79]. The necessity for careful pathological review is further highlighted by the complexity of rare entities, such as appendiceal collision tumors, which require adherence to the oncological principles of the component tumor types (neuroendocrine and mucinous neoplasms) [35]. The principal histopathological patterns, diagnostic markers, and prognostic features of aNENs are outlined in Table 2.

Table 2 Key histopathological features, diagnostic markers, and prognostic criteria of aNENs. This table summarizes the main histological patterns, diagnostic markers, molecular features, and prognostic factors that guide the classification and management of aNENs

Category	Key Features (based on the article)
WHO/ENETS classification	• Well-differentiated NETs (G1-G3) based on Ki-67 index and mitotic rate. • Poorly differentiated NECs as a distinct, highly aggressive category.
Typical location	• Most aNENs arise at the appendiceal tip and are often incidental findings after appendectomy.
Morphological patterns	• Wide spectrum resembling midgut NETs: solid, insular, nest, trabecular, acinar patterns.
IHC	• Classical NET markers: chromogranin A, synaptophysin. • Highly specific nuclear marker: INSM1 (strong expression in WDNETs). • SATB2 strongly expressed in lower GI NETs, useful for determining site of origin. • Additional markers under investigation: PCSK2, CXCR4.
Molecular features	• NETs of appendix show chromosomal and methylation alterations (e.g., 18LOH). • Distinct GPCR gene methylation profiles including somatostatin gene alterations. • Emerging biomarkers: microRNAs miR-96, miR-133a.
Aggressive histological variants	• MiNENs/MANECs: mixed adeno-neuroendocrine carcinomas requiring distinct management. • Goblet cell adenocarcinomas: biologically aggressive, molecularly distinct from classical NETs.
Prognostic pathological features	• Tumor size. • Depth of invasion, especially mesoappendiceal invasion. • LVI and PNI. • Margin status (R0 vs. R1), influencing need for completion surgery.
Utility of pathology in surgical decision-making	• Determines need for RHC. • Novel tools include nomograms combining depth of invasion + size to stratify nodal metastasis risk.
Diagnostic challenges	• Preoperative imaging often non-diagnostic due to non–mass-forming growth. • Some variants show atypical IHC profiles (e.g., AdexGCC with weak classical markers but INSM1-positive subclusters).
Role of advanced techniques	• Targeted next-generation sequencing, useful for identifying genetic signatures in WDNETs. • 68Ga-DOTATATE PET has limited postoperative utility in incidental aNENs.

aNENs, appendiceal neuroendocrine neoplasms; WHO, World Health Organization; NET, neuroendocrine tumor; Ki-67, proliferation index marker Ki-67; NEC, neuroendocrine carcinoma; IHC, immunohistochemistry; INSM1, insulinoma-associated protein 1; WDNET, well-differentiated NET; GI, gastrointestinal; SATB2, special AT-rich sequence-binding protein 2; PCSK2, proprotein convertase subtilisin/kexin type 2; CXCR4, C-X-C chemokine receptor type 4; GPCR, G-protein coupled receptor; MiNEN, mixed neuroendocrine–non-neuroendocrine neoplasm; MANEC, mixed adeno-neuroendocrine carcinoma; LVI, lymphovascular invasion; PNI, perineural invasion; RHC, right hemicolectomy; AdexGCC, adenocarcinoma ex-goblet cell carcinoid

Outcome

aNENs generally have a favorable prognosis; however, their outcomes depend on accurate risk stratification and appropriate surgical planning, with the central debate concerning the necessity of colon resection (RHC) [80]. A systematic review and meta-analysis focusing on the histopathological diagnosis of aNENs evaluated the specific criteria that should mandate an RHC [81]. The established risk factors for nodal metastasis (N+) that require RHC include tumor size, histological grade and LVI, particularly when the tumor size exceeds 2 cm, or if LVI is present [59,81]. Since LVI is often difficult to detect and is associated with a worse prognosis, its presence is a significant marker; studies have shown that LVI is highly associated with lymph node involvement, even in small appendiceal NETs 1-2 cm, regardless of histology (typical, goblet cell, or composite) [82]. The surgical management of tumors within the disputed 1-2-cm diameter range has been thoroughly investigated: a large database analysis compared the clinical outcomes of simple appendectomy to RHC in this cohort, and concluded that RHC generally does not confer a significant survival advantage for most 1-2 cm tumors, suggesting that appendectomy may be sufficient in the absence of other high-risk factors [83]. In contrast, a comparative study, assessing whether colon resection truly enhances outcomes across a diverse patient population, found that simple appendectomy with negative resection margins was associated with overall survival (OS) comparable to RHC [80]. However, the pathological assessment remains vital, as prognostic features such as tumor size, depth of invasion (e.g., mesoappendiceal invasion), and angio- and neuro-invasion are essential for identifying the minority of patients who truly require an RHC [59,80]. The prognostic factors that guide surgical decision-making encompass various microscopic features [84]. Specifically, regarding well-differentiated neuroendocrine (carcinoid) tumors of the appendix, the clinical importance of small vessel invasion in addition to size has been shown to be a useful feature associated with metastatic disease [84]. Further stratification is necessary for very small tumors, as low-stage tumors smaller than 5 mm appear to be overwhelmingly indolent and may merit a separate designation, challenging the conventional cutoffs for risk assessment [85]. A 10-year audit of clinical characteristics and results confirmed that, while appendectomy is mostly curative in the majority of cases, guidelines recommend RHC for those with specific high-risk features, despite the absence of definitive data supporting a survival benefit from the RHC itself [86]. When analyzing the management of 1-2-cm carcinoid tumors specifically using the National Cancer Data Base (NCDB), a retrospective cohort study found that RHC failed to provide a statistically significant OS advantage compared to primary resection alone [87]. Lymph node status remains the primary predictor of disease recurrence, making the adequate surgical sampling of lymph nodes crucial [88]. A study analyzing the role and prognostic significance of mesenteric lymphadenectomy in well-differentiated aNENs identified the risk of lymph node metastases as a function of tumor size, supporting the practice of nodal evaluation in higher-risk patients [88]. Lastly, a large retrospective, Europe-wide, pooled cohort study focusing on the surgical management of aNETs sized 1-2 cm reinforced this conservative approach, concluding that RHC is limited primarily to cases with incomplete tumor resection or high-grade G2 or G3 aNENs [89]. The controversy regarding the surgical relevance of lymph node involvement and RHC on OS in aNENs remains central [90]. A comparative analysis of primary NETs and non-NET appendiceal cancers in the US found that NENs occurred at a younger age, and were less prone to present with metastatic disease, yet for both groups surgical resection was the cornerstone of treatment [91]. This same study showed that non-NET appendiceal cancers (such as adenocarcinoma) were often treated similarly to colon cancers, while NETs had a higher OS [91]. Retrospective cohort studies characterizing the trends in RHC utilization found that the rate of RHC for NEN decreased over time, while RHC failed to demonstrate a significant OS benefit for localized NENs [25]. A comprehensive characterization of aNEN patients referred to a European NET Center of Excellence confirmed that tumor size and Ki-67 index were strongly associated with adverse outcomes, guiding their surgical approach [92]. Further studies evaluating the necessity of RHC in high-risk aNENs determined that, while guidelines suggest RHC for high-risk features, its association with disease-free survival is not always conclusive [93]. Negative factors that negatively affect survival outcomes include tumor grade, age, and extent of disease, with Black patients in 1 study showing a statistically significant higher rate of advanced disease at presentation [94]. Metastatic spread to sites such as the liver has also been reported [94]. The overall treatment and follow-up algorithms for aNENs continue to change in light of new guidelines and our evolving understanding of disease progression [95]. This retrospective analysis confirms that ANETs are the most common appendiceal tumors, often detected incidentally during emergency appendectomy, underscoring the challenge in preoperative diagnosis and the continuous evolution in management strategies [95]. The necessity for comparing surgical options is further emphasized in aggressive variants, where the management of appendiceal MiNENs involves an ongoing comparison of RHC versus appendectomy to determine whether RHC confers a significant survival advantage for this aggressive entity [36]. Finally, the treatment of appendiceal tumors that result in peritoneal surface malignancies requires specialized care; while the difficulties in deciding upon cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal metastases are known, it remains an established treatment for peritoneal metastases arising from appendiceal tumors [96].

Surgical risk stratification is summarized in Fig. 2, while Table 3 summarizes the key management recommendations for aNENs across major international guidelines, highlighting areas of consensus and the persisting controversy in the 1-2 cm subgroup.

Table 3 Management recommendations for aNENs across major international guidelines. This table compares the main surgical and management recommendations for aNENs provided by ENETS, NANETS, ESMO and AIOM, highlighting areas of consensus and the key differences in the 1-2 cm tumor subgroup

Tumor category	ENETS 2023	NANETS	ESMO 2020	AIOM 2022
<1 cm, well-differentiated NET, R0 resection	Appendectomy only; no further surgery regardless of additional features	Appendectomy sufficient	Appendectomy sufficient	Appendectomy sufficient
1-2 cm without high-risk features (no LVI, no mesoappendiceal invasion >3 mm, negative margins, G1)	Appendectomy acceptable; RHC not routinely indicated	Strongly favors appendectomy alone; RHC rarely beneficial	Individualized decision; appendectomy acceptable	Appendectomy acceptable; evaluate HRFs case-by-case
1-2 cm with high-risk features (LVI, mesoappendiceal invasion >3 mm, G2, positive/uncertain margins)	Consider RHC; discuss in multidisciplinary setting	Appendectomy acceptable in many cases; RHC only for selected high-risk situations	RHC may be considered depending on patient factors and HRFs	RHC recommended when ≥1 HRF is present
>2 cm	RHC recommended in view of high risk of nodal metastasis	RHC recommended	RHC recommended	RHC recommended
Poorly differentiated NEC (any size)	Oncologic colectomy + staging; treat as high-grade NEC	Treat as high-grade NEC; RHC usually required	Formal oncologic colectomy and systemic therapy	Systemic therapy; oncologic colectomy per colorectal protocol
MANEC/MiNEN/GCC	Manage as aggressive adenocarcinoma; RHC mandatory	Treat as adenocarcinoma; RHC	Colorectal cancer approach; RHC + oncology evaluation	RHC + adjuvant therapy based on stage
Positive/uncertain margins (R1)	Completion RHC recommended if feasibility and patient suitability allow	Individual decision; RHC reasonable but not mandatory for small G1 tumors	RHC considered	RHC recommended
Surveillance after low-risk appendectomy	Often no routine imaging needed; follow-up individualized	Observation; no imaging for low-risk <2 cm	Minimal surveillance for low-risk disease	Follow-up generally not required for <1 cm; individualized thereafter

aNENs, appendiceal neuroendocrine neoplasms; ENETS, European Neuroendocrine Tumor Society; NANETS, North American Neuroendocrine Tumor Society; ESMO, European Society for Medical Oncology; AIOM, Associazione Italiana di Oncologia Medica; LVI, lymphovascular invasion; RHC, right hemicolectomy; HRFs, high-risk features; NEC, neuroendocrine carcinoma; MANEC, mixed adeno-neuroendocrine carcinoma; MiNEN, mixed neuroendocrine–non-neuroendocrine neoplasm; GCC, goblet cell carcinoma

Special populations

NENs in children and adolescents represent an exceedingly rare population, with an estimated prevalence of approximately 2.8 cases per million [97]. In this rare population, among all GEP-NENs, the appendix remains the most frequent primary site, with diagnoses often occurring incidentally after appendectomy for suspected appendicitis [97].

Pediatrics

Pediatric aNETs typically exhibit a positive clinical prognosis, and are usually small (median size 0.9 cm [98] or 8 mm [99]). Such good characteristics have been widely confirmed: both the German MET registry (662 cases) and the Danish national cohort (205 cases) reported no tumor-related mortality or recurrence [100,99]. The management of aNETs in children remains controversial, as guidelines have historically been extrapolated from adult data, which recommend aggressive procedures, such as completion RHC, for tumors above certain size thresholds or with high-risk features [97]. However, extensive pediatric data strongly argue against this approach. Even in the presence of lymphovascular spread, lymph node metastases, or tumor size ≥1.5 cm, the prognosis remains excellent, with risk factors showing no impact on outcome [100]. Accordingly, additional surgical procedures offer no therapeutic advantage, according to consistent reports from multiple single-center experiences and cohorts [101]. This consensus supports the position that appendectomy alone is sufficient and curative for most pediatric aNETs [98,101]. The presence of multifocal aNETs (2-5 tumors) is also rare, but a case series suggests this pattern does not predict local advanced or metastatic disease and, therefore, does not warrant more aggressive treatment [102]. Occurrence of aNETs alongside genetic conditions, such as a *de novo* MLH1 gene pathogenic variant causing Lynch Syndrome (LS) [103], or with parasitic bowel infections such as *Enterobius vermicularis* [104], has been reported, raising the intriguing, though unproven, hypothesis

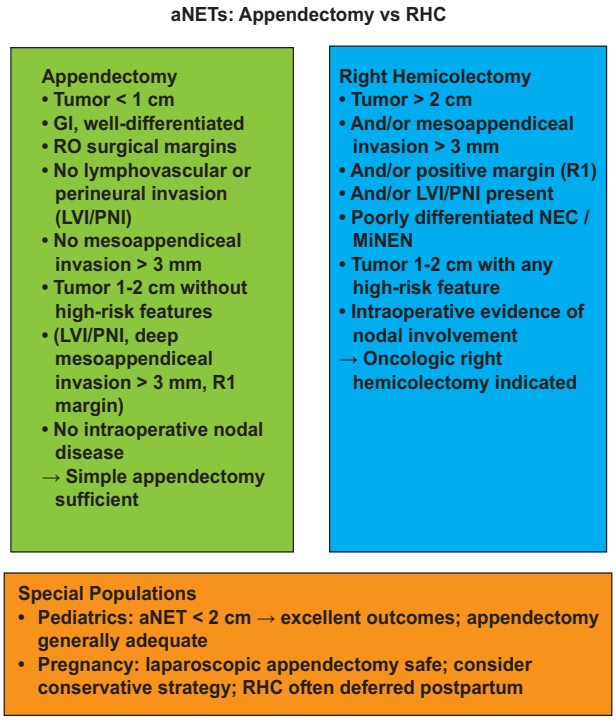

Figure 2 Surgical management of appandiceal neuroendocrine tumors: appendectomy vs right hemicolectomy.
Summary of current criteria guiding the choice between appendectomy and RHC in aNETs. Appendectomy is appropriate for tumors <1 cm and for 1-2 cm lesions lacking high-risk features (lymphovascular or perineural invasion, deep mesoappendiceal invasion, positive margin, or intraoperative nodal disease). RHC is recommended for tumors >2 cm and for 1-2 cm tumors with any adverse feature, as well as for poorly differentiated NEC/MiNEN. Management in pediatric and pregnant patients generally favors appendectomy, with RHC often deferred in pregnancy
aNET/aNETs, appendiceal neuroendocrine tumor/tumors; RHC, right hemicolectomy; R0, microscopically margin-negative resection; R1, microscopically margin-positive resection; LVI, lymphovascular invasion; PNI, perineural invasion; NEC, neuroendocrine carcinoma; MiNEN, mixed neuroendocrine–non-neuroendocrine neoplasm; ENETS, European Neuroendocrine Tumor Society; G1, grade 1; cm, centimeters; mm, millimeters; vs, versus

of inflammation-related carcinogenesis [104]. Nevertheless, the appendiceal NEN associated with LS was found to exhibit proficient mismatch repair expression, indicating the tumor was not related to the germline MLH1 deletion [103]. Additional diagnostic challenge arises when aNETs coexist with other rare abdominal pathologies, such as intestinal malrotation and Fitz-Hugh-Curtis syndrome, complicating the differential diagnosis of chronic intermittent abdominal pain [98]. NENs originating outside the appendix and pancreas are significantly rarer. Well-differentiated NENs from other GI sites (e.g., stomach and colorectum) present in 31.3% of cases with distant metastases, a high rate for pediatrics, but lower than in adults [101]. Nevertheless, these patients demonstrate a favorable prognosis (3-year OS of 93.3%) following treatment involving comprehensive operative excision [105]. Conversely, poorly differentiated GEP-NECs are highly aggressive, with the 5-year OS being 85.4% [106]. The principal prognostic indicator is the original site, since pancreatic GEP-NECs yield the lowest longevity (56.0% after 5 years), whereas non-metastatic illness across all regions displays a superior clinical survival rate (97.7%) relative to juvenile patients suffering from metastatic overall disease (52.7%) [106]. The rarity and biological aggressiveness of GEP-NECs require individualized management within a dedicated multidisciplinary team [106]. Finally, distant metastatic dissemination—particularly to the liver—has been reported even among younger patients, underscoring the need for early recognition and optimized therapeutic strategies [103].

Pregnancy

Regarding aNENs in women, diagnosis during pregnancy is extremely rare, occurring most commonly within the third trimester [107,99]. Evaluation of cases diagnosed during gestation found favorable pregnancy outcomes and excellent long-term prognosis, suggesting that a conservative management approach may be considered, with RHC often postponed to the postpartum period [107]. The rarity of appendiceal NETs can lead to challenging or delayed diagnosis, as symptoms may be nonspecific, mimicking conditions such as appendicitis or pyelonephritis [108].

Concluding remarks

The future management of aNETs is rapidly evolving towards a precision model that incorporates advanced technological and biological insights. Artificial intelligence (AI) is set to become a useful tool, particularly in radiomics and digital pathology, important for improving risk stratification and refining surgical planning, and useful for guiding the choice between appendectomy and RHC [109]. At the same time, significant therapeutic progress has been focused on optimizing peptide receptor radionuclide therapy (PRRT), through combination studies involving radiosensitizers, or the exploration of next-generation alpha emitters, which promises to expand PRRT's efficacy even to higher-grade NETs [110]. A key emerging research frontier is the host-tumor metabolic interaction. In particular, prospective multicenter analyses are critically needed to systematically study the "obesity paradox"—where a higher body mass index correlates with better outcomes in certain GI malignancies—to determine its relevance and underlying mechanisms in aNETs [111]. Clarifying whether chronic inflammation or altered adipokine profiles influence the tumor microenvironment might redefine risk assessment, and potentially introduce metabolic modulation or lifestyle modification as an adjuvant therapeutic strategy [112].

In conclusion, the ultimate goal is to shift the management paradigm entirely from size-based algorithms to robust predictive models shaped by the integration of molecular, imaging (AI), and personalized patient metabolic data, ensuring optimal oncological safety balanced with therapeutic restraint.

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References

1. Pavel M, Öberg K, Falconi M, et al. Gastroenteropancreatic neuroendocrine neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2020;**31**:844-860.
2. Associazione Italiana di Oncologia Medica (AIOM), It.a.net. Linee guida neoplasie neuroendocrine. Edizione 2018.
3. Andrini E, Lamberti G, Alberici L, Ricci C, Campana D. An update on appendiceal neuroendocrine tumors. *Curr Treat Options Oncol* 2023;**24**:742-756.
4. 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**:150.
5. Bednarczuk T, Zemczak A, Bolanowski M, et al. Neuroendocrine neoplasms of the small intestine and the appendix: update of the diagnostic and therapeutic guidelines (recommended by the Polish Network of Neuroendocrine Tumours). *Endokrynol Pol* 2022;**73:** 549-583.
6. Mohamed A, Wu S, Hamid M, et al. Management of appendix neuroendocrine neoplasms: insights on the current guidelines. *Cancers (Basel)* 2022;**15**:295.
7. Kaltsas G, Walter T, Knigge U, et al. European Neuroendocrine Tumor Society (ENETS) 2023 guidance paper for appendiceal neuroendocrine tumours (aNET). *J Neuroendocrinol* 2023;**35**:e13332.
8. Associazione Italiana di Oncologia Medica (AIOM), It.a.net. Linee guida neoplasie neuroendocrine. Aggiornamento 2022.
9. Volante M, Grillo F, Massa F, et al. Neuroendocrine neoplasms of the appendix, colon and rectum. *Pathologica* 2021;**113**:19-27.
10. Holmager P, Langer SW, Kjaer A, et al. Appendiceal neuroendocrine neoplasms: an update for 2023. *Curr Oncol Rep* 2024;**26**:114-120.
11. Halfter K, Schubert-Fritschle G, Klauschen F, et al. The other colon cancer: a population-based cohort study of appendix tumour trends and prognosis. *Colorectal Dis* 2023;**25**:943-953.
12. Wu P, He D, Chang H, Zhang X. Epidemiologic trends of and factors associated with overall survival in patients with neuroendocrine tumors over the last two decades in the USA. *Endocr Connect* 2023;**12**:e230331.
13. Liu M, Wei L, Liu W, et al. Trends in incidence and survival in patients with gastrointestinal neuroendocrine tumors: a SEER database analysis, 1977-2016. *Front Oncol* 2023;**13**:1079575.
14. White BE, Rous B, Chandrakumaran K, et al. Incidence and survival of neuroendocrine neoplasia in England 1995-2018: a retrospective, population-based study. *Lancet Reg Health Eur* 2022;**23**:100510.
15. Wyld D, Wan MH, Moore J, Dunn N, Youl P. Epidemiological trends of neuroendocrine tumours over three decades in Queensland, Australia. *Cancer Epidemiol* 2019;**63**:101598.
16. Masui T, Ito T, Komoto I, Uemoto S; JNETS Project Study Group. Recent epidemiology of patients with gastro-entero-pancreatic neuroendocrine neoplasms (GEP-NEN) in Japan: a population-based study. *BMC Cancer* 2020;**20**:1104.
17. Ribeiro S, De Maeyer F, De Man M, et al. Lessons learned about appendiceal neuroendocrine neoplasms from data analysis of the Belgian Cancer Registry 2010-2015. *Acta Gastroenterol Belg* 2021;**84**:458-466.
18. Alkhayyat M, Saleh MA, Coronado W, et al. Epidemiology of neuroendocrine tumors of the appendix in the USA: a population-based national study (2014-2019). *Ann Gastroenterol* 2021;**34**: 713-720.
19. Gobishangar S, Gobinath S, Thevamirtha C, Sarmila S, Kasthuri S, Paramanathan S. Prevalence of neuroendocrine tumours (NET) in patients undergoing appendicectomy for acute appendicitis: a tertiary care study. *Cureus* 2023;**15**:e50783.
20. Harman Kamali G, Ulusoy C, Nikolovski A, Eğin S, Kamalı S. Uncommon causes of acute appendicitis: retrospective analysis of 6785 histopathological findings in a tertiary center. *Ulus Travma Acil Cerrahi Derg* 2022;**28**:1708-1715.
21. Limaiem F, Arfa N, Marsaoui L, Bouraoui S, Lahmar A, Mzabi S. Unexpected histopathological findings in appendectomy specimens: a retrospective study of 1627 cases. *Indian J Surg* 2015;**77**:1285-90.
22. Tartaglia D, Bertolucci A, Galatioto C, et al. Incidental appendectomy? Microscopy tells another story: a retrospective cohort study in patients presenting acute right lower quadrant abdominal pain. *Int J Surg* 2016;**28**:149-52.
23. 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**:461-466.
24. Bazarbashi S, Aseafan M, Elgazzar T, et al. Characteristics and treatment results of patients with gastroenteropancreatic neuroendocrine tumors in a tertiary care centre. *BMC Endocr Disord* 2023;**23**:74.
25. Marks VA, Kerekes D, Butensky S, et al. Role of colectomy in the management of appendiceal tumors: a retrospective cohort study. *BMC Gastroenterol* 2023;**23**:398.
26. Russell B, White BE, Rous B, et al. Second primary malignancies in patients with a neuroendocrine neoplasm in England. *Neuroendocrinology* 2023;**113**:811-821.
27. Brathwaite S, Yearsley MM, Bekaii-Saab T, et al. Appendiceal mixed adeno-neuroendocrine carcinoma: a population-based study of the surveillance, epidemiology, and end results registry. *Front Oncol* 2016;**6**:148.
28. Song H, Yang S, Zhang Y, et al. Comprehensive analysis of mixed neuroendocrine non-neuroendocrine neoplasms (MiNENs): a SEER database analysis of 767 cases. *Front Oncol* 2022;**12**:1007317.
29. Lin DL, Wang LL, Zhao P, et al. Gastrointestinal goblet cell adenocarcinomas harbor distinctive clinicopathological, immune, and genomic landscape. *Front Oncol* 2021;**11**:758643.
30. Byun S, Affolter KE, Snow AK, et al. Differential methylation of G-protein coupled receptor signaling genes in gastrointestinal neuroendocrine tumors. *Sci Rep* 2021;**11**:12303.

31. Soltani H, Ahmadinejad M, Shafiee A, et al. Expression rate and comparison of immunohistochemistry biomarkers in appendiceal neuroendocrine and other epithelial cell neoplasms: systematic review and meta-analysis. *Rare Tumors* 2025;**17**:20363613251330179.
32. Aldera AP, Govender D, Locketz ML, Mukhopadhyay S, McHugh K, Allende D. Combined use of INSM1 and synaptophysin is the most sensitive and specific panel to detect neuroendocrine neoplasms in the digestive tract. *Am J Clin Pathol* 2020;**154**:870-871.
33. Munari G, Businello G, Mattiolo P, et al. Molecular profiling of appendiceal serrated lesions, polyps and mucinous neoplasms: a single-centre experience. *J Cancer Res Clin Oncol* 2021;**147**: 1897-1904.
34. Tan HL, Tan GHC, Teo M. Two rare cases of appendiceal collision tumours involving an appendiceal mucinous neoplasm and carcinoid. *BMJ Case Rep* 2016;**2016**:bcr2015213938.
35. Sholi AN, Gray KD, Pomp A. Management and outcome of an appendiceal collision tumour composed of neuroendocrine and mucinous neoplasms. *BMJ Case Rep* 2019;**12**:e229414.
36. Hou Y, Tan Z. Mixed adenoneuroendocrine carcinomas of the appendix: is there a survival advantage to right hemicolectomy over appendectomy? *Eur J Surg Oncol* 2025;**51**:109356.
37. Ciarrocchi A, Pietroletti R, Carlei F, Necozione S, Amicucci G. Propensity adjusted appraisal of the surgical strategy for appendiceal carcinoids. *Tech Coloproctol* 2015;**19**:35-41.
38. Mandal R, Hardin H, Baus R, Rehrauer W, Lloyd RV. Analysis of miR-96 and miR-133a expression in gastrointestinal neuroendocrine neoplasms. *Endocr Pathol* 2017;**28**:345-350.
39. Diwaker C, Shah RK, Patil V, et al. 68Ga-DOTATATE PET/CT of ectopic Cushing syndrome due to appendicular carcinoid. *Clin Nucl Med* 2019;**44**:881-882.
40. Lendzion R, Phan-Thien KC. Synchronous small intestinal and appendiceal neuroendocrine tumours: a rare case. *ANZ J Surg* 2017;**87**:E159-E160.
41. Yilmaz S, Bolukbasi H. Appendiceal neoplasms: suspected findings and reports of 14 cases. *Indian J Cancer* 2023;**60**:331-336.
42. Süleyman M, Senlikci A, Durhan A, et al. Incidental presentation of appendix neuroendocrine tumor: long-term results from a single institution. *Ulus Travma Acil Cerrahi Derg* 2023;**29**:972-977.
43. Al-Darwish AS, Alsubaie WR, AlShammari W, AlaSheikh M, AlRashed M. Neuroendocrine tumor of the appendix masquerading as acute appendicitis with a mucocele on CT scan: a rare finding. *Surg Case Rep* 2024;**10**:65.
44. Watanabe HA, Fujimoto T, Kato Y, Sasaki M, Ikusue T. Acute appendicitis with a neuroendocrine tumor G1 (carcinoid): pitfalls of conservative treatment. *Clin J Gastroenterol* 2016;**9**:203-7.
45. Turaga AH. Incidental detection and management of a neuroendocrine carcinoid tumor of the appendix in a young male patient. *Cureus* 2023;**15**:e44386.
46. Gao T, Xu W. An unusual case of appendicitis due to appendiceal neuroendocrine tumor in a patient: a case report. *Exp Ther Med* 2022;**24**:531.
47. Şenel F, Karaman H, Demir H. Neuroendocrine tumors detected in appendectomy specimens: ten-year single-center experience. *Turk J Med Sci* 2018;**48**:68-73.
48. Sarici B, Akbulut S, Piskin T. Appendiceal carcinoid tumor within Amyand's hernia: a case report and review of the literature. *Turk J Emerg Med* 2019;**19**:73-75.
49. Lai YC, Hung MS, Chen YH, Chen YC. Comparing AIMS65 score with MEWS, qSOFA score, Glasgow-Blatchford score, and Rockall score for predicting clinical outcomes in cirrhotic patients with upper gastrointestinal bleeding. *J Acute Med* 2018;**8**:154-167.
50. Basukala S, Bhusal U, Sharma S, Tamang A, Gurung S. An incidental finding of ANET in a patient with perforated appendix: a case report. *Int J Surg Case Rep* 2021;**89**:106625.
51. Meeks MW, Grace S, Chen Y, et al. Synchronous quadruple primary neoplasms: colon adenocarcinoma, collision tumor of neuroendocrine tumor and Schwann cell hamartoma and sessile serrated adenoma of the appendix. *Anticancer Res* 2016;**36**:4307-11.
52. AlAli MN, AlWadani ST, Amer SM, et al. Appendiceal neuroendocrine tumors: a case series and literature review. *J Surg Case Rep.* 2025;**2025**:rjaf237.
53. Gardner BM, Haymov A, Jones R. When appendicitis masks a malignancy: a case of appendiceal goblet cell adenocarcinoma. *Cureus* 2025;**17**:e89868.
54. Schmidt V, Blum R, Möhrenschlager M. Sudden onset of multiple seborrhoeic keratoses in a patient with well-differentiated neuroendocrine tumours of the gut. *Gut* 2023;**72**:1254-1354.
55. Zouki J, Dharmawardhane A. An Amyand hernia with concurrent appendicitis secondary to a neuroendocrine neoplasm: a case report. *Cureus* 2024;**16**:e54894.
56. Cakar E, Bayrak S, Bektaş H, et al. Carcinoid tumor of the cecum presenting with acute appendicitis: a case report. *Chirurgia (Bucur)* 2015;**110**:171-4.
57. Onyemkpa C, Davis A, McLeod M, Oyasiji T. Typical carcinoids, goblet cell carcinoids, mixed adenoneuroendocrine carcinomas, neuroendocrine carcinomas and adenocarcinomas of the appendix: a comparative analysis of survival profile and predictors. *J Gastrointest Oncol* 2019;**10**:300-306.
58. Hajjar R, Dubé P, Mitchell A, Sidéris L. Combined mucinous and neuroendocrine tumours of the appendix managed with surgical cytoreduction and oxaliplatin-based hyperthermic intraperitoneal chemotherapy. *Cureus* 2019;**11**:e3894.
59. Alexandraki KI, Kaltsas GA, Grozinsky-Glasberg S, ChatzellisE, Grossman AB. Appendiceal neuroendocrine neoplasms: diagnosis and management. *Endocr Relat Cancer* 2016;**23**:R27-41.
60. Moris D, Tsilimigras DI, Vagios S, et al. Neuroendocrine neoplasms of the appendix: a review of the literature. *Anticancer Res* 2018;**38**:601-611.
61. Koyuncuer A, Canbak T, Acar A, Şahin O. Evaluation of immunohistochemical expression of novel neuroendocrine marker INSM1 and histological tumor growth pattern in well-differentiated neuroendocrine tumors of the appendix: 15-year single tertiary center experience. *Indian J Pathol Microbiol* 2024;**67**:282-288.
62. Mete O, Dodington DW, Shen DL, Asa SL. The clinicopathological significance of tumor cell subtyping in appendiceal neuroendocrine tumors: a series of 135 tumors. *Endocr Pathol* 2024;**35**:107-112.
63. Shibahara Y, Krzyzanowska M, Vajpeyi R. Appendiceal well-differentiated neuroendocrine tumors: a single-center experience and new insights into the effective use of immunohistochemistry. *Int J Surg Pathol* 2023;**31**:252-259.
64. Park HY, Kwon MJ, Kang HS, et al. Targeted next-generation sequencing of well-differentiated rectal, gastric, and appendiceal neuroendocrine tumors to identify potential targets. *Hum Pathol* 2019;**87**:83-94.
65. Bellizzi AM. SATB2 in neuroendocrine neoplasms: strong expression is restricted to well-differentiated tumours of lower gastrointestinal tract origin and is most frequent in Merkel cell carcinoma among poorly differentiated carcinomas. *Histopathology* 2020;**76**:251-264.
66. Yang C, Gonzalez I, Zhang L, et al. Neuroendocrine markers insulinoma-associated protein 1, chromogranin, synaptophysin, and CD56 show rare positivity in adenocarcinoma ex-goblet cell carcinoids. *Gastroenterology Res* 2019;**12**:120-127.
67. Popa O, Täban SM, Dema ALC, et al. Immunohistochemical expression of chemokine receptor in neuroendocrine neoplasms (CXCR4) of the gastrointestinal tract: a retrospective study of

71 cases. *Rom J Morphol Embryol* 2021;**62**:151-157.
68. Panarelli N, Tyryshkin K, Wong JJM, et al. Evaluating gastroenteropancreatic neuroendocrine tumors through microRNA sequencing. *Endocr Relat Cancer* 2019;**26**:47-57.
69. Shaib W, Krishna K, Kim S, et al. Appendiceal neuroendocrine, goblet and signet-ring cell tumors: a spectrum of diseases with different patterns of presentation and outcome. *Cancer Res Treat* 2016;**48**:596-604.
70. Ghani R, O'Connor A, Sajid I, Johnson G, Ullah S. Diagnostic accuracy of ultrasound in the paediatric population with acute right iliac fossa pain, our District General Hospital experience. *Ulster Med J* 2022;**91**:26-29.
71. Panidis D, Bartsch DK. Right hemicolectomy vs. appendectomy in patients with appendiceal NENs 1-2 cm in size. *Chirurgie (Heidelb)* 2024;**95**:157-158.
72. Sana L, Saber M. Incidental neuroendocrine tumor of the appendiceal base less than 20 mm in diameter: is appendectomy enough? *Pan Afr Med J* 2015;**22**:102.
73. Mosquera C, Fitzgerald TL, Vora H, Grzybowski M. Novel nomogram combining depth of invasion and size can accurately predict the risk for regional nodal metastases for appendiceal neuroendocrine tumors (A-NET). *J Surg Oncol* 2017;**116**:651-657.
74. Ladenheim A, Zheng JX, Teklu A, Matsukuma K. PCSK2 can be useful in a panel approach to distinguish foregut and midgut neuroendocrine tumors. *Int J Surg Pathol* 2025;**33**:76-84.
75. Mohanty SK, Tiwari A, Bhardwaj N, et al. Positivity for SATB2 distinguishes Islet1 positive rectal neuroendocrine tumours from pancreaticoduodenal neuroendocrine tumours. *J Clin Pathol* 2021;**74**:582-588.
76. Pauvert E, Larcos G. Postoperative ^{68}Ga-DOTATATE positron emission tomography has a low yield in incidental appendiceal neuroendocrine tumours. *ANZ J Surg* 2024;**94**:2185-2188.
77. Wächter S, Panidis D, Jesinghaus M, et al. Retrospective analysis of criteria for oncological completion surgery of neuroendocrine tumors of the appendix. *Langenbecks Arch Surg* 2025;**410**:46.
78. Dum D, Kromm D, Lennartz M, et al. SATB2 expression in human tumors: a tissue microarray study on more than 15 000 tumors. *Arch Pathol Lab Med* 2023;**147**:451-464.
79. Navale P, Gonzalez RS. Well-differentiated neuroendocrine tumors of the appendix: diagnosis, differentials, and disease progression. *Semin Diagn Pathol* 2024;**41**:236-242.
80. Crown A, Simianu VV, Kennecke H, et al. Appendiceal neuroendocrine tumors: does colon resection improve outcomes? *J Gastrointest Surg* 2020;**24**:2121-2126.
81. Ricci C, Ingaldi C, Alberici L, et al. Histopathological diagnosis of appendiceal neuroendocrine neoplasms: when to perform a right hemicolectomy? A systematic review and meta-analysis. *Endocrine* 2019;**66**:460-466.
82. Blakely AM, Raoof M, Ituarte PHG, Fong Y, Singh G, Lee B. Lymphovascular invasion is associated with lymph node involvement in small appendiceal neuroendocrine tumors. *Ann Surg Oncol* 2019;**26**:4008-4015.
83. Ahmed FA, Wu VS, Kakish H, et al. Surgical management of 1- to 2-cm neuroendocrine tumors of the appendix: appendectomy or right hemicolectomy? *Surgery* 2024;**175**:251-257.
84. Kleiman DA, Finnerty B, Beninato T, et al. Features associated with metastases among well-differentiated neuroendocrine (carcinoid) tumors of the appendix: the significance of small vessel invasion in addition to size. *Dis Colon Rectum* 2015;**58**:1137-43.
85. Noor M, Huber AR, Cates JMM, Gonzalez RS. Risk factors for progression of appendiceal neuroendocrine tumours: low-stage tumours <5 mm appear to be overwhelmingly indolent and may merit a separate designation. *Histopathology* 2021;**79**:416-426.
86. Storan D, Swan N, Swan K, et al. Clinical features and outcomes of appendiceal neuroendocrine tumours: 10 year audit from the Irish NET Centre of Excellence. *J Neuroendocrinol* 2023;**35**:e13329.
87. Nussbaum DP, Speicher PJ, Gulack BC, et al. Management of 1- to 2-cm carcinoid tumors of the appendix: using the National Cancer Data Base to address controversies in general surgery. *J Am Coll Surg* 2015;**220**:894-903.
88. Raoof M, Dumitra S, O'Leary MP, et al. Mesenteric lymphadenectomy in well-differentiated appendiceal neuroendocrine tumors. *Dis Colon Rectum* 2017;**60**:674-681.
89. Nesti C, Bräutigam K, Benavent M, et al. Hemicolectomy versus appendectomy for patients with appendiceal neuroendocrine tumours 1-2 cm in size: a retrospective, Europe-wide, pooled cohort study. *Lancet Oncol* 2023;**24**:187-194.
90. Alabraba E, Pritchard DM, Griffin R, et al. The impact of lymph node metastases and right hemicolectomy on outcomes in appendiceal neuroendocrine tumours (aNETs). *Eur J Surg Oncol* 2021;**47**:1332-1338.
91. Alese OB, Kim S, Chen Z, et al. Management and outcomes of hospitalized patients with primary neuroendocrine tumor and non-neuroendocrine tumor appendiceal cancers in the United States. *World J Oncol* 2015;**6**:349-354.
92. Holmager P, Willemoe GL, Nielsen K, et al. Neuroendocrine neoplasms of the appendix: characterization of 335 patients referred to the Copenhagen NET Center of Excellence. *Eur J Surg Oncol* 2021;**47**:1357-1363.
93. Canbak T, Erdem O, Acar A, Başak F. Evaluating the necessity of right hemicolectomy in high-risk appendiceal neuroendocrine tumors: a retrospective analysis. *BMC Surg* 2025;**25**:320.
94. Nagesh VK, Aguilar IK, Elias D, et al. Factors affecting survival outcomes in neuroendocrine tumor of the appendix over the past two decades. *Diseases* 2024;**12**:96.
95. Gumuşoglu AY, Donmez T, Kabuli HA, et al. Management of appendiceal neuroendocrine tumors in the light of new guidelines. *Ir J Med Sci* 2022;**191**:1133-1137.
96. Brandl A, Zielinski CB, Raue W, Pratschke J, Rau B. Peritoneal metastases of rare carcinomas treated with cytoreductive surgery and HIPEC: a single center case series. *Ann Med Surg (Lond)* 2017;**22**:7-11.
97. Lin W, Zhu Z, Shang Y. Gastroenteropancreatic neuroendocrine carcinoma in children and adolescents: a population-based study. *J Cancer Res Clin Oncol* 2024;**150**:4.
98. Vandevelde A, Gera P. Carcinoid tumours of the appendix in children having appendicectomies at Princess Margaret Hospital since 1995. *J Pediatr Surg* 2015;**50**:1595-9.
99. Kuhlen M, Kunstreich M, Pape UF, et al. Lymph node metastases are more frequent in paediatric appendiceal NET ≥1.5 cm but without impact on outcome: data from the German MET studies. *Eur J Surg Oncol* 2024;**50**:108051.
100. Karges K, Kunstreich M, Abele M, et al. Gastrointestinal neuroendocrine neoplasms in children and adolescents: data from the German MET studies (1997–2024). *Neuroendocrinology* 2025;**116**:1-12.
101. Hasan F, Davoodi A, Bordogna A, et al. A case of appendiceal neuroendocrine tumor with metastatic spread in a young patient. *SAGE Open Med Case Rep* 2025;**13**:2050313X251369764.
102. Twito O, Akirov A, Rosenblum RC, et al. Clinical and pathologic characteristics of appendiceal neuroendocrine neoplasms diagnosed during pregnancy. *Front Endocrinol (Lausanne)* 2023;**14**:1013638.
103. Virgone C, Cecchetto G, Besutti V, et al. Bowel parasitosis and neuroendocrine tumours of the appendix. A report from the Italian TREP project. *Epidemiol Infect* 2015;**143**:1552-5.
104. Cusimano A, Abdelghany AM, Donadini A. Chronic intermittent abdominal pain in young woman with intestinal malrotation, Fitz-Hugh-Curtis syndrome and appendiceal neuroendocrine tumor: a rare case report and literature review. *BMC Womens*

Health 2016;**16**:3.
105. Mahajan H, Gosselink MP, Di Re AM, Larcos G, P'ng CH, Ctercteko G. A multifocal pattern of neuroendocrine neoplasms along the appendix: a series of six cases. *Int J Surg Pathol* 2019;**27**:613-618.
106. Kartal İ. Childhood neuroendocrine tumors of the digestive system: a single center experience. *Medicine (Baltimore)* 2022;**101**:e28795.
107. Brignola C, Volorio S, De Vecchi G, et al. De novo germline pathogenic variant in Lynch syndrome: a rare event or the tip of the iceberg? *Tumori* 2024;**110**:69-73.
108. Yalçın B, Karnak, Orhan D, et al. Paediatric appendiceal neuroendocrine tumours: a review of 33 cases from a single center. ANZ J Surg 2022;92:742-746.
109. Balma M, Laudicella R, Gallio E, et al. Applications of artificial intelligence and radiomics in molecular hybrid imaging and theragnostics for neuro-endocrine neoplasms (NENs). *Life (Basel)* 2023;**13**:1647.
110. di Santo G, Santo G, Sviridenko A, Virgolini I. Peptide receptor radionuclide therapy combinations for neuroendocrine tumours in ongoing clinical trials: status 2023. *Theranostics* 2024;**14**: 940-953.
111. Abdel-Rahman O, Ghosh S, Morrish D. Impact of baseline body mass index on the outcomes of patients with neuroendocrine neoplasms. *J Endocrinol Invest* 2022;**45**:1683-1688.
112. Subedi BK, Bhimineni C, Modi S, Jahanshahi A, Quiza K, Bitetto D. The role of insulin resistance in cancer. *Curr Oncol* 2025;**32**:477.