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Unmasking the Hidden Tumours: Clinical and Pathological Insights into Appendicular Neoplasms

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Abstract: Appendicular neoplasms, although rare, represent a diverse group of tumours arising from the appendix, including adenocarcinomas, carcinoid tumours, and mucinous neoplasms. This review aims to synthesize current knowledge on the epidemiology, diagnostic approaches, and treatment options for appendicular neoplasms. We conducted a comprehensive literature search across multiple databases, identifying key studies that elucidate the incidence, clinical presentation, and histopathological characteristics of these tumours. The epidemiological data highlight a slight male predominance and variability in incidence across different populations. Clinical symptoms often mimic acute appendicitis, leading to potential diagnostic challenges. Advanced imaging techniques, including ultrasound and computed tomography, play a critical role in diagnosis, often supplemented by histological analysis. Treatment typically involves surgical resection, with chemotherapy considered for advanced or high-grade tumours. Prognosis varies significantly depending on tumour type and stage at diagnosis, underscoring the need for early detection and tailored management strategies. This review identifies critical gaps in the literature and suggests directions for future research to enhance understanding and treatment of appendicular neoplasms.

Keywords: *Epidemiology, Adenocarcinomas, Carcinoid Tumours, Mucinous Neoplasms, Clinical Presentations.*

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I. INTRODUCTION

Appendiceal neoplasms are rare gastrointestinal tract tumors that can cause palpable masses, right lower quadrant discomfort, or appendicitis symptoms, which may prompt imaging or surgery. [1] The majority of appendiceal masses are neuroendocrine tumors (NETs) and primary epithelial neoplasms. Because of their bigger size and tendency for peritoneal spread and metastatic illness, mucinous and non-mucinous epithelial neoplasms are more frequently seen during imaging than NETs. When mucin is found during radiologic and pathologic investigation, it is a characteristic of epithelial mucinous neoplasms. In appendiceal mucinous neoplasms, the two most frequent cross-sectional imaging findings are a mucocele or pseudomyxoma peritonei from epithelial mucinous tumors. Non-mucinous epithelial tumors are less frequent and resemble masses of the colonic type. Because of their modest size and nonaggressive nature, NETs are frequently identified after an appendectomy. Acute appendicitis and primary appendiceal tumor imaging results might be similar. Acute appendicitis can also result from an appendiceal mass, hiding the underlying lesion. It is uncommon to find other neoplasms such as lymphoma, sarcoma, mesenchymal and nerve sheath tumors, or subsequent malignant involvement of the appendix. [2]

Appendiceal neoplasms are rare tumors that account for approximately 1% of all cancers [2]. They are mos1tly found incidentally in an appendectomy specimen [2,3]. They can also be found during abdominal imaging or during colonoscopy, as only 30–50% of patients exhibit clinical manifestations such as acute appendicitis of these tumors [4,5]. They represent a unique and clinically significant category of tumours arising from the appendix. They are rare tumours, with an age-adjusted annual incidence of six cases per 1,000,000 people in recent years. [1] These neoplasms

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encompass a variety of histological types, including adenocarcinomas, carcinoid tumours, and mucinous neoplasms, each with distinct biological behaviours and clinical implications. While the incidence of appendicular neoplasms is low, their diagnosis often poses challenges due to their ability to present similarly to acute appendicitis, leading to potential delays in appropriate treatment. [6] Epidemiological studies suggest a slight male predominance and variable incidence rates across different populations, with certain tumour types exhibiting unique demographic characteristics. Understanding the epidemiology of these neoplasms is crucial for recognizing risk factors and improving early detection. There are several risk factors reported for underlying malignant disease of the appendix that should be considered in patients with suspected acute appendicitis: age, multiple comorbidities, atypical presentation, complicated appendicitis, absence of leucocytosis, and diameter of the appendix on ultrasound of > 13 mm. [7,8,9] However, when limited to the appendix, primary appendiceal tumours are challenging to identify preoperatively. About 1% of appendectomy specimens had tumours, and patient presentations frequently mimic acute appendicitis. [10] During surgery, the diagnosis is frequently unclear. Inflammation may prevent a conclusive intraoperative diagnosis, even if the surgeon suspects cancer. As a result, the majority of appendiceal cancer cases are discovered after surgery.

Diagnostic modalities have advanced significantly, with imaging techniques such as ultrasound and computed tomography (CT) playing pivotal roles in identifying appendicular masses. [11,12] But depending on the entity of appendiceal malignancies some sonographic features such as enlarged or small inner luminal diameter, thick and irregular appendix wall, loss of layer pattern of the appendix wall, and even hypo-echogenicity are described. [12] In addition, infiltration of the peri-appendiceal fat or even abscess formation with suspicion of appendix perforation may be seen in cases of appendiceal malignancies. [12] Findings in abdominal CT scans are again depending on the underlying type of malignancy and reach from hyperenhancement, nodular wall thickening, calcification, mucocele, lymphadenopathy, peri-appendiceal fat infiltration, or tumour mass. [13] Histopathological examination remains essential for definitive diagnosis and classification, guiding treatment decisions. [13]

A multidisciplinary strategy adapted to the kind, size, and stage of the neoplasm is used in the modern treatment of appendicular neoplasms, which include both benign and malignant tumours of the appendix. Usually, surgery is the primary course of therapy; for benign tumours or early-stage cancers, an appendectomy is enough. To remove the appendix together with the surrounding colon and lymph nodes, a right hemicolectomy may be necessary for bigger or more aggressive cancers. To identify the kind of tumour and direct future therapy, pathological analysis of the excised tissue following surgery is essential. Adjuvant treatments like chemotherapy or targeted therapy may be used in situations with malignant tumours to lower the chance of recurrence. Combining hyperthermic intraperitoneal chemotherapy (HIPEC) with cytoreductive surgery has become a viable treatment option for advanced mucinous malignancies. Monitoring recurrence and controlling any therapeutic side effects require routine follow-up. All things considered, improvements in surgical methods and available treatments have greatly enhanced the prognosis of patients with appendicular tumours. [14]

II. METHODOLOGY

To conduct this comprehensive review of appendicular neoplasms, we employed a systematic approach to gather and analyse relevant literature. The following steps outline our methodology:

- *Inclusion and Exclusion Criteria:*

Inclusion criteria for the review encompassed studies that concentrated on the epidemiology, diagnosis, treatment, and outcomes of appendicular neoplasms, allowing for a comprehensive perspective through clinical and experimental studies, reviews, and case reports. Conversely, exclusion criteria involved omitting articles that did not specifically address appendicular neoplasms or that pertained to unrelated conditions. Additionally, studies lacking sufficient data or methodological rigor were excluded to ensure the quality and relevance of the included research.

- *Data Extraction:*

Relevant data were extracted from the selected articles, including study design, population characteristics, diagnostic methods, and treatment approaches. Special attention was given to the histological types of appendicular neoplasms and their clinical implications.

- *Synthesis of Findings:*

The extracted data were synthesized to identify patterns, discrepancies, and knowledge gaps in the current understanding of appendicular neoplasms. This synthesis formed the basis for the subsequent discussion on epidemiology, diagnosis, treatment, and future research directions.

By utilizing this systematic approach, we aimed to provide a comprehensive overview of appendicular neoplasms, contributing to the existing body of knowledge and informing clinical practice.

III. EPIDEMIOLOGY AND RISK FACTORS

The incidence of appendicular neoplasms is low, with epidemiological data indicating variability across different populations. Factors such as age, gender, and geographic location may influence the prevalence of specific tumour types. [15] For instance, carcinoid tumours tend to occur more frequently in younger individuals, while adenocarcinomas are more common in older adults. The identification of risk factors remains an area of ongoing research, as the pathogenesis of these tumors is not yet fully understood. Future studies should focus on delineating genetic and environmental contributors to enhance early detection and prevention strategies.

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➢ *Clinical presentation*

Appendicular neoplasms typically present with abdominal pain, often starting as vague discomfort near the umbilicus and localizing to the right lower quadrant. Patients may also experience nausea, vomiting, and a decreased appetite, along with low-grade fever if inflammation or infection is present. A palpable mass might be detected during a physical exam, and some individuals may notice changes in bowel habits, weight loss, or signs of intestinal obstruction, such as distension and severe pain. In more advanced cases, symptoms like ascites can develop, and specific tumor types, like carcinoid tumors, may lead to additional systemic effects. Prompt evaluation through imaging and diagnostic procedures is crucial for determining the nature of the neoplasm. [16]

➢ *Diagnostic Challenges*

Diagnosing appendicular neoplasms presents unique challenges, primarily due to their clinical presentation, which often mimics acute appendicitis. Advanced imaging techniques, such as CT and MRI, have improved diagnostic accuracy but may not always definitively differentiate between neoplastic and non-neoplastic conditions. Histopathological evaluation remains the gold standard for diagnosis, but delays in obtaining tissue samples can hinder timely treatment. There is a need for improved diagnostic protocols and potentially the development of biomarkers that could aid in early detection. [17]

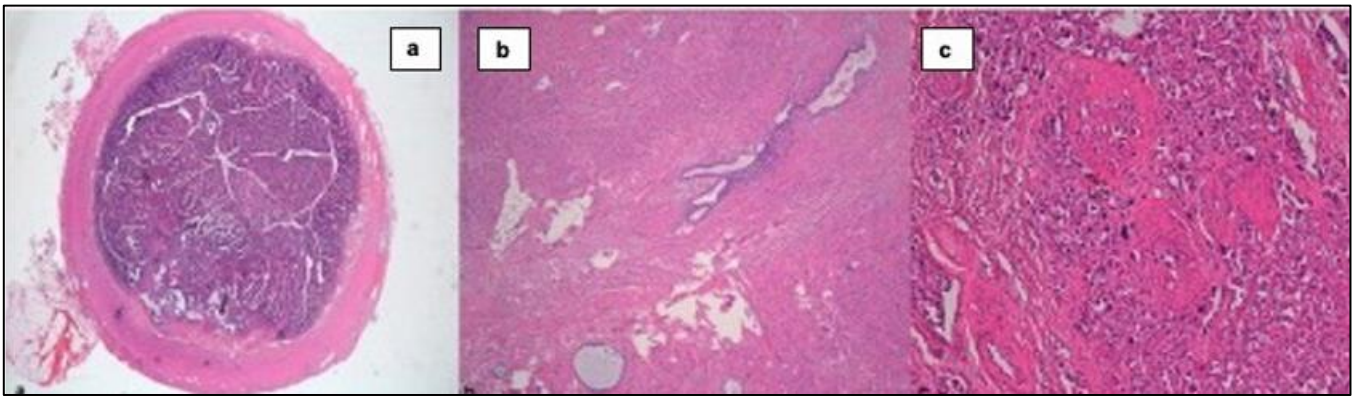

Fig 1 – Appendicular Neoplasms [Adenocarcinoma, Mucinous Tumour, Neuroendocrine Tumour]

[a] In a typical appendiceal adenocarcinoma, an epithelial proliferation of aberrant cells that form glands and focally penetrate the wall occupies the light. (HE × 20). [b] Mucinous adenocarcinoma: a kind of epithelial proliferation of atypical cells that form glands that are focally infiltrated into the wall and exhibit well-differentiated mucus production in the presence of light. (HE x 40). [c] Neuroendocrine carcinoma: infiltration of vascular structures that in immunohistochemistry studies tested positive for neuroendocrine markers (chromogranin and synaptophysin) and vague proliferation of a high degree without glandular differentiation in the appendix wall (HE × 100).

➢ *Treatment Approaches*

The treatment of appendicular tumours, which can include both benign and malignant neoplasms, primarily revolves around surgical intervention, but the approach can vary significantly based on the type, stage, and characteristics of the tumour. Here's a detailed overview: The treatment of appendicular neoplasms begins with diagnosis and staging, utilizing imaging techniques like ultrasound, CT scans, or MRI to assess the tumour's size, location, and potential metastasis, followed by biopsy for histopathological confirmation. Surgical treatment is the cornerstone of management, with appendectomy being the primary approach for benign tumours, such as appendiceal carcinoids, while right hemicolectomy is indicated for larger or aggressive tumours, like high-grade adenocarcinomas. Surgical methods can be laparoscopic or open, depending on various factors. Adjuvant therapies, including chemotherapy for malignant tumours with metastatic potential and, in rare cases, radiation therapy for palliative care, may also be employed. Postoperative follow-up is essential for early detection of recurrence, involving regular imaging and blood tests, along with long-term care plans addressing potential complications. Specific tumour types require tailored approaches: carcinoid tumours may need simple appendectomy unless they are large or metastatic, adenocarcinomas often necessitate extensive surgical intervention and chemotherapy, while mucinous tumours may require significant surgical debulking to manage associated conditions like pseudomyxoma peritonei. [17,18]

➢ *Prognosis and Future Directions*

The prognosis for patients with appendicular neoplasms is highly variable and is influenced by factors such as tumor type, grade, and stage at diagnosis. While carcinoid tumors generally have a favorable prognosis, high-grade adenocarcinomas are associated with poorer outcomes. Enhanced understanding of the molecular characteristics of these tumors could pave the way for more personalized treatment approaches and improved prognostic models. Future research should prioritize large-scale, multicenter studies to establish more robust epidemiological data, refine diagnostic protocols, and evaluate the efficacy of emerging therapies. Additionally, there is a critical need for increased awareness among clinicians regarding the potential for appendicular neoplasms, which may facilitate earlier diagnosis and intervention. In conclusion, appendicular neoplasms represent a complex interplay of factors that

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challenge both diagnosis and treatment. By synthesizing current knowledge and identifying areas for further research, this review aims to contribute to a deeper understanding of these rare tumors and their management.

IV. DISCUSSION

A recent comprehensive study by Bastiaenen et al. [19] found that 0.71% of cases were appendiceal neoplasms. Similarly, Lohsiriwat et al. [20] discovered a tumor rate of 0.97% in an examination of 4545 appendectomy components. Other studies, however, have reported neoplasm occurrences as high as 2.5% [15,16]. According to the literature, the incidence of appendiceal tumors has increased by up to 54% in recent decades [21]. One risk factor for appendiceal cancers is the patients' mean age of 63 years (IQR 52–75) [15,22]. Recent investigations including data from as many as 3293 individuals have even indicated a three-fold increase in the probability of appendiceal neoplasm and appendiceal diameter more than 10 mm as detected by CT [23]. Since many of these tumors are small and asymptomatic, it is plausible that slight differences in their prevalence could be linked to varying rates of blank appendectomy. This is because it is more likely that pauci-symptomatic appendiceal tumors will be discovered in institutions with a higher rate of blank appendectomy. Similarly, Orchard et al. showed a higher rate of appendectomies concurrent with an increase in the frequency of appendiceal neoplasms, however they did not specifically address the number of blank appendectomies [24].

Neuroendocrine tumors are less common than low-grade appendiceal neoplasms (LAMN) in the histologic distribution of neoplasms. This discovery validates the recent shift in epidemiology, where neuroendocrine tumors—previously referred to as carcinoids—are no longer the most common [25]. During the time period examined by Marmor et al. [21], there was a rise in epithelial tumors but no decline in the frequency of neuroendocrine ones. With almost 3000 cases registered, Naar et al. [23] recently verified a shift in the trend toward epithelial neoplasms. An appendectomy with a free margin is typically used to treat LAMN. Those who had a ruptured appendix before to surgery or who had an intraoperative finding of peri-appendiceal free mucus are among the patient subgroups where the contrary has been found. They often had a low recurrence risk following appendectomy. An appendix rupture has been linked to a recurrence rate of up to 65%, whereas those that did not rupture had a recurrence rate of 17%. In situations of ruptured LAMNs, some writers have even suggested intraperitoneal hyperthermic chemotherapy and cytoreductive surgery [17]. According to recent data, LAMNs have an excellent prognosis overall, with 5-year survival rates of about 93% [26].

The appendectomy alone is adequate therapy for NETs that are less than 1 cm and have a free margin. A right hemicolectomy would be recommended for tumors 1-2 cm in size without multifocality, vascular invasion, or a free meso-appendiceal border more than 3 mm [18]. A minor patient with a grade 2 neuroendocrine tumor in our research did not exhibit the aforementioned traits and consented to adequate treatment, which included an appendectomy and close monitoring. A right hemicolectomy is advised for NETs larger than 2 cm or grade 3 [17]. There was no correlation between the surgeon's macroscopic observations and the tumors' anatomopathological reports. Only three out of thirty instances of appendiceal neoplasms in the study by Bolmers et al. [27] had an accurate intraoperative diagnosis, suggesting that the preceding finding is not an uncommon one. Two out of twenty patients in another retrospective research with a sample of 3554 appendectomies had a true suspicion of appendiceal tumor [25].

Only one of the seven studies that examined this criterion in the study by Bastiaenen et al. [19] showed a proper correlation between the pathologist's and surgeon's findings; in the other trials, none of the neoplasia had an intraoperative suspicion. An appendectomy is usually enough to treat the discovered malignancies. Only eight of the patients in our research required a second operation, and these were primarily due to metastases, locally progressed tumors, or malignant tumors such adenocarcinomas. Marmor et al.'s study [17] revealed that 74% of patients with appendiceal carcinomas had either distant metastases (35%) or regional local metastases (39%) at the time of diagnosis, indicating that mucinous carcinoma and signet ring cell adenocarcinoma were the most likely types. Similarly, individuals with distant metastases (33%) and regional metastases (60%) had a markedly worse 5-year survival rate. A 5-year survival rate of 83% for mucinous adenocarcinoma and 62% for non-mucinous adenocarcinoma was reported in another recent study of Japanese provenance; the majority of patients did not exhibit lymphatic or distant metastases. The prognosis was considerably worse in the presence instance, and patients' 5-year survival rates decreased from up to 52% in mucinous adenocarcinomas and 25% in non-mucinous ones [26]. Signet ring cell adenocarcinoma is the histologic subtype with the worst prognosis, with 5-year survival rates below 30% [17,18], and it accounted for two of the four instances of death in our investigation. It would be wise to conduct more research in this area, primarily to determine what hazards and dietary or environmental exposure agents have changed and caused a subsequent shift in the histology of this type of tumor from neuroendocrine to epithelial, which has an implicit impact on the prognosis of patients and may lead to changes in treatment [28,29].

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Table 1 – Literature Review about Appendicular Neoplasm [30-40]

Authors	M/F	Age	Clinical features	Appendectomy	MIS	Right hemecolectomy	Pathology	Recurrance	Death
Tan et al.	F	59	Yes	Yes	Yes	No	MA	No	No
	M	52	No	Yes	Yes	No	LAMN	No	No
Baena-del-valle	F	49	No	Yes	No	-na-	LAMN	No	No
	M	45	Yes	Yes	-na-	-na-	LAMN	Yes	-na-
Dellaportas et al.	F	57	Yes	Yes	Yes	Yes	MC	No	No
Singh	M	52	Yes	No	No	Yes	A	Yes	Yes
Rossi et al.	F	35	Yes	Yes	No	Yes	A	No	No
Sholi	F	23	Yes	Yes	No	Yes	LAMN	No	No
Ekinci	M	60	Yes	Yes	-na-	No [Patient refused surgery]	LAMN	No	No
Sugarbaker	F	39	Yes	Yes	No	Yes	LAMN	Yes	No
	M	32	Yes	Yes	No	Yes	LAMN	No	No
Cafaro et al.	F	35	Yes	Yes	No	No	LAMN	No	No
Villa et al.	F	31	Yes	Yes	Yes	Yes	LAMN	No	No

F = Female; M = Male; na = not available LAMN = Low grade appendiceal mucinous neoplasm; A = Adenocarcinoma; MA = Mucinous adenoma; MC = Mucinous cystadenoma

This table summarizes clinical data from multiple studies on Appendicular neoplasm, focusing on factors such as patient demographics, clinical features, treatments, pathology, recurrence, and survival outcomes. The patients, aged 23 to 60 years, were treated for Appendicular neoplasm, with the majority exhibiting common clinical features such as abdominal distension and pain. Most underwent appendectomy, a standard procedure. Right hemicolectomy was done in some cases, particularly when the disease involved the colon, while minimally invasive surgery (MIS) was used in a few instances. The pathology results revealed that Low-Grade Appendiceal Mucinous Neoplasm (LAMN) was the most common diagnosis, associated with a better prognosis and lower recurrence rates. More aggressive tumors, like Adenocarcinoma (A) and Mucinous Cystadenoma (MC), were linked to higher recurrence and death. The majority of patients with LAMN survived without recurrence, whereas those with adenocarcinoma faced poorer outcomes, including recurrence and death.

The earlier research has a number of useful ramifications. First of all, it has been demonstrated that the great majority of patients who had an appendiceal tumor discovered by accident were treated with an appendectomy alone, without the need for any additional, more involved resection. In the event that emergency surgery is necessary, this should also be considered in order to prevent more dangerous procedures, such as appendectomy, which is seldom recommended after the final specimen analysis is completed. Appendicular neoplasms are complicated, with a wide range of epidemiologies, diagnostic difficulties, and therapeutic options highlighted in this thorough overview. Since these tumors are very uncommon, knowing their features is crucial to enhancing patient outcomes.

V. CONCLUSION

Appendicular neoplasms, although infrequently encountered, present significant challenges in terms of diagnosis and management. This review has highlighted the diversity of tumor types, including adenocarcinomas, carcinoid tumors, and mucinous neoplasms, each with distinct epidemiological characteristics and clinical implications. The diagnostic process often mimics acute appendicitis, necessitating a high index of suspicion and the use of advanced imaging techniques complemented by histopathological confirmation. Surgical intervention remains the primary treatment modality, but the approach must be tailored to the specific tumor type and stage. Prognosis varies widely, with factors such as tumor grade and extent of disease playing critical roles in patient outcomes. As our understanding of the molecular biology of these tumors advances, there is potential for more personalized treatment strategies that could improve survival rates. Future research should focus on addressing the current gaps in knowledge, including the identification of risk factors, the development of reliable biomarkers for early detection, and the exploration of novel therapeutic options. By fostering collaboration among researchers, clinicians, and patients, we can enhance the understanding and management of appendicular neoplasms, ultimately leading to better outcomes for affected individuals. In summary, a concerted effort is needed to raise awareness of appendicular neoplasms within the medical community, improve diagnostic accuracy, and optimize treatment protocols to ensure timely and effective care.

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