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Review

Appendiceal Tumors: A Narrative Review

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Abstract

Appendiceal tumors (ATs) are classified by the World Health Organization's (WHO) 5th edition of their categorization of digestive system tumors into four subtypes: mucinous neoplasms, adenocarcinomas, serrated lesions, polyps, and neuroendocrine neoplasms (NENs). Due to their rarity and the lack of data from randomized controlled studies, ATs can be challenging to differentiate in medical practice. Specimens obtained during appendectomies for clinically acute appendicitis typically contain ATs. Most ATs in the European population affect women over 50 years. Neuroendocrine tumors (NETs) are the most common histological type, comprising 54.6%, followed by cystic, mucinous, and serous neoplasms (26.7%) and adenocarcinoma not otherwise defined (NOS) (18.6%). Most findings of ATs on pathologic investigation are benign lesions or small NENs that do not require additional treatment. The development of pseudomyxoma peritonei (PMP), a complicated situation of peritoneal carcinomatosis, may result from the presence of appendiceal mucinous neoplasm (AMN). Over the past few decades, multimodal treatment for abdominal cancers has advanced; however, ATs' clinical diagnosis and management are still debated. This review aims to outline the diagnostic options, molecular-based diagnosis, staging, treatment, and prognostic markers related to ATs.

Keywords: Chemotherapy, appendiceal cancer, gastrointestinal stromal tumors, targeted therapy, appendiceal surgery, review.

Introduction

Appendiceal tumors (ATs) are classified into four major types according to the World Health Organization's (WHO) 5th edition: serrated lesions and polyps, mucinous neoplasms, adenocarcinomas, and neuroendocrine neoplasms (NENs) (1, 2). Due to its rarity and the lack of information from randomized controlled studies involving large, heterogeneous patient populations, AT differential diagnosis can still be challenging in clinical practice (1). Specimens collected after appendectomies performed for clinically acute appendicitis, are typically found to have

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ATs (3). The majority of ATs in the European population (65%) affect women over 50 years of age (56.8%). Histologically, neuroendocrine tumors (NETs) comprise 54.6%, followed by cystic, mucinous, and serous neoplasms (26.7%) and adenocarcinoma not otherwise defined (NOS) (18.6%) (4).

There are 1.2-1.63 cases of appendix cancer of primary origin (PAC) for every 100,000 individuals in the U.S. population (5, 6). The histologic nature of the PAC determines the 5-year overall survival (OS). According to data from a study by Wang *et al*. (6), five-year survival rates for colonic-type adenocarcinoma, mucinous adenocarcinoma (MAC), NET, signet ring cell carcinoma (SRCC), and malignant carcinoid are, respectively, 90.8%, 92.9%, 84.6%, 63.2%, and 96.6%. Additional factors that affect the 5-year OS include the patient's race, age at diagnosis, tumor size, staging, grading, and chemotherapy (CTH) treatment.

Acute appendicitis is the most frequent clinical manifestation of ATs, characterized by nonspecific abdominal pain in the right lower quadrant, anorexia, weight loss, fever, vomiting, intestinal obstruction from intussusception, and asthenia (7). These symptoms typically necessitate appendectomy in clinical practice (8).

Most pathologic analysis results are benign lesions or small NENs that don't need additional treatment. There are various categories of appendix serrated lesions among the benign masses observed on pathology after appendectomy. These are categorized as hyperplastic polyps, sessile serrated lesions with dysplasia, and sessile serrated lesions without dysplasia (1, 2). Inflammatory alterations in the appendix may result in a development resembling a polyp. Differentiating reactive proliferation from hyperplastic lesions is the primary diagnostic issue. For more conclusive treatment, however, repeat surgery to obtain a radical surgical margin, cytoreductive surgery (CRS), or CTH may be necessary if lymphoma or a bigger NEN is found. The absence of data from existing studies has led to a lack of knowledge to direct treatment strategies in the cases of mucinous tumors and appendiceal adenocarcinoma (9).

Pseudomyxoma peritonei (PMP) may result from appendiceal mucinous neoplasm (AMN) (10). Peritoneal carcinomatosis, which is defined by the spread of intra-abdominal ascites on the peritoneum's surface, is a feature of PMP. Several neoplasms, such as intraductal papillary neoplasm of the bile duct, ovarian tumors, and AMN, can cause PMP (11-13). Despite its widespread nature, high post-surgery recurrence rate, limited treatment efficiency, and high risk of comorbidities, co-occurrence of PMP with PAC is regarded as a poor prognostic factor (10).

The clinical workup and treatment of ATs are still challenging, even though multimodal therapy techniques for abdominal malignancies have improved over the past few decades (14). Thus, the purpose of this review is to outline the most recent diagnostic options, molecular-based diagnosis, staging, variations during treatment, and prognostic variables for ATs.

Methods of Search

We searched PubMed for full-text articles from 2017 to January 31, 2025, using the Keywords chemotherapy, appendiceal cancer, gastrointestinal stromal tumors, targeted therapy, appendiceal surgery. The full-text articles found were carefully examined. In addition, all abstracts presented at international conferences between January 2020 and January 2025 were examined.

Genetic Characteristics

Tumor molecular subtypes have been linked to responsiveness to CTH, metastatic load, and survival of patients with PAC (15). Tumor samples from 703 cases of appendiceal neoplasms were studied by Ang *et al*. (16). Of the specimens, 17.5% were primary tumors, 75.0% were intraperitoneal metastases, and 7.5% were distant metastases. According to the study, colorectal cancer (CRC) and appendiceal neoplasms exhibit distinct molecular profiles. Specifically, TP53 and APC changes were substantially less common in all appendiceal subtypes than in CRC (χ^2 p<0.001). Mutation frequencies

(%) in five major histopathologic subtypes were noted in MAC, 77% *KRAS*, 52% *GNAS*, 33% *TP53*, 23% *SMAC4*, 8% *ARID1A*, 6% *APC*, 3% *ERBB2*, 2% *RB1*, and 1.4% microsatellite instability-high (MSI-H); in adenocarcinoma (Ad), 56% KRAS, 47% TP53, 25% GNAS, 18% SMAC4, 17% APC, 11% ARID1A, 3.2% MSI-H, 3% RB1, and 3% ERBB2; in PMP, 81% KRAS, 72% GNAS, 11% SMAC4, 7% TP53, 6% ARID1A, 4% ERBB2, 2% APC, 0% RB1, and 0.0% MSI-H; in SRCC, 43% TP53, 35% KRAS, 30% SMAC4, 11% APC, 8% GNAS, 5% ERBB2, 3% ARID1A, 3.2% MSI-H, and 0% RB1; and in goblet cell carcinoma (GCC), 33% TP53, 19% SMAC4, 15% ARID1A, 13% KRAS, 6% GNAS, 4% RB1, 2% APC, 2% ERBB2, and 2.8% MSI-H.

A typical gain-of-function pattern was shown by the fact that GNAS mutations were confined to codon 201 and *KRAS* mutations were primarily found at codon 12. However, *TP53* mutations were distributed widely throughout the gene and included many frameshift mutations that are consistent with loss of function. GCCs were not included in co-mutation and mutual exclusivity analyses due to their unique mutation profile in comparison to other histological types. GNAS and *TP53* were found to be mutually exclusive, whereas GNAS and *KRAS* were found to exhibit significant co-mutation exclusively. Signaling pathways were then used to classify genetic abnormalities. The most frequently altered signaling pathway in epithelial appendix tumors was the RAS/RAF pathway, which includes BRAF, HRAS, KRAS, and NRAS. It was more than 80% prevalent in MACs and PMP, 60% in Ads, and only 33% in GCCs. Over 50% of all subtypes had changes in homologous recombination deficit genes, with SRCC having the highest incidence at 80%. These results emphasize the predictive importance of *GNAS* and *TP53* mutant statuses and indicate significant molecular differences across different appendix cancer subtypes.

When it is unclear whether the low-grade mucinous tumor is originating from the appendix or the ovary, next-generation sequencing (NGS) can aid diagnosis. Low-grade appendiceal mucinous neoplasm (LAMN) is the most likely diagnosis when *KRAS* and *GNAS* mutations coexist (17).

Regarding AMN, oncogenes such as *KRAS*, *GNAS*, *TP53*, and *RNF43* are mutated at comparable rates in both LAMNs, high-grade appendiceal mucinous neoplasm (HAMN), and MAC. However, each AMN subtype has a unique pattern of mutations. It is also possible that LAMN could progressively change into MAC through HAMN, although further study is required on this subject (18).

Foote *et al*. distinguished three different molecular subtypes: an aggressive, highly aneuploid *TP53*-mut predominant subtype, a CTH-resistant GNAS-mut predominant subtype, and a clinically indolent *RAS*-mut/*GNAS*-wt/*TP53*-wt subtype. Regardless of its histological nature, each subtype displayed distinct clinical behavior (15).

Appendiceal Tumor Grading and Staging

The current staging procedures for appendix neoplasms are based on the 8th edition of the American Joint Commission on Cancer (AJCC), although the 9th edition was recently published (19, 20). Adenocarcinomas (and their variations), GCC, mucinous neoplasms, and small-cell and large-cell (poorly differentiated) neuroendocrine carcinomas are all included in the staging scheme for appendix carcinomas (Table I) (21, 22). For well-differentiated neuroendocrine tumors, the appendix's 8th AJCC protocol for NET can be used. When evaluating NET staging, the ENET standards can be applied interchangeably (23). GIST is the sole recipient of the eighth AJCC protocol. It is hard to create a uniform standards classification because of the varied nature of ATs, which also presents a diagnostic problem (20).

Mucinous tumors. Serrated lesions with or without dysplasia and hyperplastic polyps, LAMN, HAMN, and MAC are the several types of AMN according to the International Agency for Research on Cancer (IARC)/WHO, 2019 (1).

Serrated lesions and polyps have intact muscularis mucosae and a serrated architecture of the crypt lumen, either with or without atypia. Characteristic histologic features of LAMN include low-grade cytology, rare non-atypical mitotic activity, filiform villi, undulating or flat architecture, a pushing type of invasion (21), dissection of acellular mucin within the wall, and submucosal fibrosis (24).

Table I. *The 8th edition of the American Joint Commission on Cancer (AJCC) staging system for carcinomas of the appendix.*

T-primary tumor
TX: The assessment of the primary tumor is not feasible
T0: No indication of a primary tumor
Tis: Carcinoma in situ (intramucosal carcinoma, with the invasion of the lamina propria or extension into the muscularis mucosae, without penetration through it)
Tis (LAMN): Low-grade appendiceal mucinous neoplasm confined by the muscularis propria. Infiltration of acellular mucin or the mucinous epithelium into the muscularis propria can occur. The T1 and T2 classifications are not applicable to low-grade appendiceal mucinous neoplasm (LAMN). If a cellular mucin or the mucinous epithelium extends into the subserosa, it should be categorized as T3, and if it reaches the serosa, it should be classified as T4a
T1: The tumor infiltrates the submucosa by penetrating through the muscularis mucosa but without extending into the muscularis propria
T2: The tumor infiltrates the muscularis propria
T3: The tumor infiltrates through the muscularis propria into the subserosa or the mesoappendix
T4: The tumor infiltrates the visceral peritoneum, incorporating acellular mucin or the mucinous epithelium that affects the serosa of the appendix or mesoappendix, or directly invades nearby organs or structures
T4a: The tumor penetrates through the visceral peritoneum, encompassing the presence of acellular mucin or the mucinous epithelium involving the serosa of the appendix or the serosa of the appendix
T4b: The tumor directly infiltrates or adheres to adjacent organs or structures
N-regional lymph nodes (including ileocolic nodes)
Nx: Assessment of regional lymph nodes is not feasible.
N0: There is no evidence of metastasis to regional lymph nodes
N1: One to three regional lymph nodes exhibit positivity, indicated by the presence of a tumor in the lymph nodes, measuring >0.2 mm, or the existence of tumor deposit(s) alongside negative lymph nodes
N1a: A single regional lymph node is positive
N1b: Two or three regional lymph nodes are positive
N1c: No regional lymph nodes are positive, but there are tumor deposits in the subserosa or mesentery
N2: Four or more regional lymph nodes are positive
M-distant metastasis (in cases where specimens comprise acellular mucin without identifiable tumor cells, if additional tissue is available, it should be submitted to comprehensively assess for the presence of tumor cells)
M0: No distant metastasis
M1: Distant metastasis
M1a: Intraperitoneal acellular mucin, without identifiable tumor cells in the disseminated peritoneal mucinous deposits
M1b: Intraperitoneal metastasis only, including peritoneal mucinous deposits containing tumor cells
M1c: Metastasis to sites other than the peritoneum

Applicable to Ads (and variants), GCC, mucinous neoplasms, and small-cell and large-cell (poorly differentiated) neuroendocrine carcinoma.

The anatomic characteristic of pTis LAMN is focal obliteration or loss of the muscularis mucosa and lamina propria. The subserosa is not penetrated by acellular mucin (24). There are two types of LAMN: type I, where the tumor is inside the appendix lumen, and type II, where the tumor epithelium and/or mucin extend into the appendix wall, submucosa, and/or surrounding tissues, possibly leading to perforation (25). The tumor should be categorized as pT3 when mucinous epithelium or acellular mucin are observed in the subserosa or mesoappendix but do not reach the visceral peritoneal surface (21, 24). pT4a should be used to identify invasion of the visceral peritoneum, including localized mucin or the mucinous epithelium involving the mesoappendix or serosal surface. The tumor is categorized as pT4b when it directly invades or attaches to nearby organs and structures (24). High-grade cytology with noticeable atypia and frequent, typically unusual mitotic activity are the histologic characteristics that differentiate HAMN from LAMN (21).

The infiltrative invasion type of MAC contains infiltrative glands, incomplete glands, or solitary infiltrative tumor cells linked to desmoplastic stroma and extracellular mucin. A "small cellular mucin pool" represents another form of infiltrative invasion, characterized by small

dissecting mucin pools containing floating nests, glands, or isolated cancer cells.

Mucinous SRCC is distinguished from MAC with signet ring cells when the signet ring cell component comprises more than 50% of the tumor cells, and MAC with signet ring cells when it comprises equal to or less than 50%. The WHO has classified AMN into the following grades: MAC-G2, HAMN-G2, LAMN-G1, and MAC with signet ring cells-G3 (21).

A particular clinical condition, like PMP, is linked to the spread of AMN in the peritoneum. Dissemination might occur because of recurrence or be found during an appendectomy. Mucosal deposits that are implanted in the abdominal cavity, pelvis, intraperitoneal organs, and visceral peritoneum are what define PMP. There are other sources of PMP besides the appendix. Pancreas, intestine, and ovaries are additional primary sources that have been documented (10, 23, 26).

Based on the methylation patterns in their promoters, PMP can be divided into two different groups: unique methylation epigenotype (UME) and normal-like methylation epigenotype (NLME). PMP may emerge as a result of the involvement of genes related to synaptic transmission and neuronal development (27). Like AMN, the most common genetic abnormalities in PMP include mutations in *KRAS*, *GNAS*, *TP53*, *ATM*, *ERBB2, FBXW7*, *NRAS*, and *SMAD4* (27, 28). Furthermore, PMP may have heterogeneous histologic characteristics; for instance, specimens may exhibit an epithelium with both low-grade and high-grade cytologic atypia. Additionally, the specimens may have signet ring cells and may be rich or poor in cells. Tumor grading can be carried out using these characteristics (21, 28).

Neuroendocrine neoplasm. As an appendiceal epithelial neoplasm that is well-differentiated, NEN typically has a favorable prognosis and a nearly 100% 5-year OS. Both adult and pediatric patients have been documented to have appendiceal NEN, which is usually located at the appendix's tip (23, 29). Appendiceal NENs are usually discovered incidentally during evaluation for appendicitis. Rarely, tumors may cause carcinoid syndrome, which is associated with metastasis. To verify the neuroendocrine origin of NEN, immunohistochemical staining for synaptophysin and chromogranin A is required (30). Since the WHO grading categorization of NEN is based on these criteria, it is also necessary to record the Ki-67 index and the mitotic count per 10 high-power fields (HPF) (23).

Gastrointestinal stromal tumors (GISTs) of the appendix. Rarely detected in appendix tissues, GISTs are mesenchymal tumors that typically stain positive for CD117 (C-Kit), CD34, and/or DOG-1 (31). Although aggressive activity (invasion and perforation of adjacent intestine) has been documented, the majority of appendiceal GISTs are indolent (32).

According to Hu *et al*., there were 27 cases of appendiceal GISTs, with a male-to-female ratio of 1:2 and a median patient age of 68 years (range=34-83 years) (33). The tumor was discovered by chance during endoscopic or imaging tests or intra-abdominal surgery for another cause in 85% of patients who had no symptoms. Appendicitis symptoms were seen in 15% of the remaining individuals. No tumor showed any indications of tumor necrosis, and all had a spindle-shaped cell structure. Two tumors were subjected to molecular analysis; one had a loss in KIT exon 11, while the other showed no alterations in PDGFRA, NF1, or KIT. None of the specimens had germline mutations. Following appendectomy, none of the patients showed signs of disease progression. However, bigger group investigations are needed to have a better understanding of this class of ATs (33).

Globet cell carcinoma. Globet cell carcinoma (GCC) comprises 15% of PAC (5). Due to its extensive infiltration of the appendix wall, a typical tumor may not form a mass that may be detected by radiological or macroscopic inspection of the samples. Depending on the stage, the clinical presentation can resemble appendicitis in cases of low-grade GCC (34). Rarely, high-grade GCC might emerge as acute appendicitis. Metastases, which are typically seen in the peritoneum, are more frequently linked to symptoms (34, 35). The most frequent cause of death unique to a

disease is peritoneal spreading (36). For G1 (low grade), G2 (intermediate grade), and G3 (high grade), the percentage of tumors with a low-grade tubular/clustered growth pattern (%) is >75%, 50-75%, and <50%, respectively, according to the WHO grading system for GCC. The primary tumor and peritoneal/ovarian metastases may be graded differently for stage IV cancers. The grade of the metastatic lesion should be assigned by established procedure (37, 38). According to the histologic criteria used to classify GCC, the pattern is typified by a traditional circular, tubular growth structure that is mainly made up of goblet-like mucinous cells, with a smaller percentage of Paneth-like and endocrine-like cells.

The five main patterns of high-grade GCC are extracellular mucin pools with round tubules or cohesive clusters, including ruptured tubules, are frequently found in low-grade GCC. Pathological patterns of high-grade GCC are characterized by single-row infiltrating cords of tumor cells with high-grade nuclei, or glandular adenocarcinomas, often exhibiting a microglandular growth pattern. Another pathological pattern is characterized by a diffuse infiltration of signet-ring or goblet-shaped cells, either as single cells or in tubules. Finally, clusters of cells may be observed, resulting in the formation of large, anastomosed structures with solid growth that exhibit minimal or no intracytoplasmic mucin. Compared to low-grade GCC, high-grade GCC exhibits more cytologic and architectural atypia, more mitotic activity, and the potential to cause necrosis and a desmoplastic reaction (38). Staining is usually only localized, but synaptophysin and chromogranin expression in GCC can be extensive and strongly positive (34). Although their usefulness is limited, the Ki67 index and immunohistochemical markers including CDX2, SATB2, CK7, and CK20 may have prognostic and diagnostic significance in GCC (38).

Therapy. Due to their rarity, as a result, the lack of a gold-standard method, appendix tumors pose several obstacles when it comes to therapy selection (14). Preoperative computed tomography (CT) evaluation of ATs is beneficial because it allows for the estimation of mass size, the detection of possible metastases, and occasionally the identification of tumor type. Making an informed judgment regarding the best surgical strategy for a particular case is aided by this evaluation (39).

Because serrated appendix lesions are benign, endoscopic ablation or minimally invasive appendectomy is still the preferred course of treatment. When lesions are discovered by mistake during an endoscopic examination, this treatment can help provide a histological diagnosis or, if there are no symptoms of appendicitis, a less stressful option for the patient. According to the local colon cancer screening programs, follow-up should be conducted (40, 41). Appendectomy alone is a sufficient treatment for LAMN if sufficient resection is obtained during the procedure and there is no concomitant perforation, PMP, or mucinosis (42). Meanwhile, research shows the benefits of combining appendectomy with CRS and hyperthermic intraperitoneal chemotherapy (HIPEC) when LAMN occurs in the context of perforation, diffusion of cellular mucin into the peritoneal cavity, or PMP (43-45). Although there are no set rules for a chemotherapeutic regimen, the recommended cytostatic drugs during HIPEC include mitomycin and oxaliplatin. However, mitomycin may be a better choice for patients with prior CTH and thrombocytopenia because of its somewhat higher hematologic toxicity and less detrimental effect on quality of life when compared to oxaliplatin in HIPEC. However, patients with leukopenia may benefit more from mitomycin (46). In conjunction with neoadjuvant CTH (NAC), Chen *et al*. assessed CRS+HIPEC treatment for PMP coexisting with other forms of ATs (not LAMN/HAMN). An independent factor linked to a noticeably worse OS was found to be NAC (47). The development and investigation of radical exenteration and transplantation methods is a promising direction for future PMP therapy research. This is demonstrated by the noted improvement in the patient's quality of life, which led to a 79% 1-year and a 55% 5-year survival rate, despite the difficulties caused by surgically linked comorbidities. Further research is necessary to maximize long-term efficacy and results, as seen by the noteworthy 91% rate of disease progression/recurrence in patients followed-up for more than six months (48). There is a lack of information on how to treat HAMN, and urgent

clinical practice frequently follows the same strategy for patients with LAMN (37).

The primary treatment for NEN <1 cm is surgery; surveillance is not necessary. Right colectomy with lymphadenectomy is advised for R1 resection or tumors near the base of the appendix (23). According to Nest *et al*., a right colectomy is not necessary following the complete resection of a 1-2 cm appendiceal NET with an appendectomy. In appendiceal NETs, regional lymph node metastases may not be clinically significant. Furthermore, it has been questioned whether additional postoperative exclusion of metastases and histological evaluation of risk factors are necessary (49). A right colectomy is indicated if the tumor is larger than 2 cm. In every case of NEN >1 cm (50), follow-up should be provided.

For appendiceal GISTs, there is insufficient data from high-quality randomized controlled trials to support any particular therapeutic approach. However, appendectomy alone seems to have positive results in the majority of cases (33, 51). Although research is still in progress, imatinib mesylate may be useful in malignant GISTs (32).

A right colectomy is linked to a higher 5-year survival rate for individuals with GCC tumors classified as stage pT3 or pT4. However, pT1-2 patients do not benefit from this. A favorable prognosis for stage III or higher-grade cancers has been linked to adjuvant CTH. The majority of studies support palliative CTH in cases of synchronous metastases. CRS + HIPEC shows encouraging potential for long-term survival attainment in patients with appendiceal GCC and limited peritoneal dissemination (52, 53).

Systematizing the instruments required for AT diagnosis, which is constantly challenging due to its intricacy and rarity, should be the fundamental goal of future studies on AT diagnosis and therapy. The inability to conduct extensive, randomized trials makes treating ATs challenging. Nonetheless, we should strive to standardize rules for all ATs given the large number of original reports.

Predictive Factors

The histological type and clinical manifestation of ATs influence the prognostic variables (54). Higher-grade tumors may have a worse prognosis and are frequently indicative of a more aggressive disease. While total cytoreduction with negative margins can improve results, the degree of peritoneal dissemination and staging can have a substantial impact on prognosis (5, 55). Poor survival is linked to AMN, especially in those with a high peritoneal cancer index (PCI) (55, 56). In 63 patients with PMP, Van Ruth *et al*. found a relationship between tumor size and levels of the carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9). Recurrence was significantly increased in patients with high initial or persistently non-normalizing levels of CA 19-9 (57). In a study by Carmignani *et al*. involving 532 patients with PMP, normal preoperative tumor markers were significantly associated with higher survival rates. CA 19-9 levels were not associated with outcomes, whereas higher CEA during recurrence was linked to a much worse prognosis (58). In patients with low-grade PMP receiving CRS and integrated palliative and oncology care (IPC), Kozman *et al*. found that the CA19-9/PCI ratio was an independent predictor of OS. Considering both tumor activity and volume at the same time, this innovative index served as a stand-in for tumor biology. It provided a valuable tool to help inform treatment choices in these patient groups. The detrimental impact on the OS seems to be exacerbated by an increased CEA/PCI ratio (59). Nummela *et al*. used immunohistochemistry to determine CEA tissue expression patterns in 91 appendiceal PMP cases. PCI and CEA serum levels were correlated, although there was no correlation between biomarkers and prognosis or histological subtype (60). In a cohort of 2,891 individuals, Wang *et al*. examined prognostic and survival variables for PAC. Among all age groups, patients aged ≥69 had the highest chance of dying, and Black patients were more likely to die than White patients. SRCC and poorly differentiated adenocarcinoma were markers of poor prognosis. The prognosis for patients with low-grade tumors was favorable. CTH did not result in a longer survival benefit for patients with distant metastases (6). Fleischmann *et al*. assessed how stage migration, OS, and cancer-specific survival (CSS) in appendiceal cancer were affected by regional lymph node (RLN) removal. Up to

approximately 10 retrieved RLNs, there was a correlation between the incidence of node-positive malignancy and the number of retrieved RLNs. However, the incidence of nodal metastases did not rise after 10 RLNs were recovered. The OS improved when 12 or more RLNs were retrieved (61). Similarly, in a study of 573 patients, Raoof *et al*. reported that tumors larger than 1 cm were associated with lower OS when 12 or fewer lymph nodes were retrieved (62).

Conclusion

The number of ATs is increasing, according to recent data. Current research on prognostic variables and treatment algorithms remains insufficient to establish uniform guidelines for disease management. Variations in staging procedures based on the histological type of cancer have significant prognostic implications and should guide the selection of patient-specific treatment strategies. In patients with ATs, achieving favorable short- and long-term outcomes continues to depend on the completeness of cytoreduction, which can be further enhanced by the use of HIPEC.

Conflicts of Interest

The Authors declare that they have no conflicts of interest in relation to this study.

Authors' Contributions

AC, VG and MRV collaborated on the article's conception and wrote the article. AC reviewed the article and approved the final version of the article to be published.

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During the preparation of this manuscript, a large language model (ChatGPT, OpenAI) was used solely for language editing and stylistic improvements in select paragraphs. No sections involving the generation, analysis, or interpretation of research data were produced by generative AI. All scientific content was created and verified by the authors. Furthermore, no figures or visual data were generated or modified using generative AI or machine learning-based image enhancement tools.

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