Appendiceal cancer : a review of the literature

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Abstract

Primary appendiceal cancer is rare and most commonly found incidentally on a surgical specimen after appendectomy for acute appendicitis.

This small organ gives rise to different subtypes which are histological and biological distinct. Historically the classification of these tumors has been confusing because of the different nomenclature that is used. This review has broadly classified them into four subgroups : colonic-type adenocarcinoma, mucinous neoplasm, goblet cell carcinoma and neuroendocrine neoplasm. Signet ring cells is not considered as a distinct subgroup but as a histologic feature that can be present in colonic-type adenocarcinoma and mucinous neoplams.

As staging and management of appendiceal tumors depends on these subtypes, an adequate classification of them is important. This review aimed to give an overview of the epidemiology, grading and staging, management and prognosis of these neoplasms. Despite its rarety specific staging systems and treatment guidelines exist for some subtypes. For other subtypes staging systems and management is extrapolised from colorectal cancer because of the lack of randomised, prospective trials. (Acta gastroenterol. belg., **2020**, 83, **441-448**).

Key words : colonic-type adenocarcinoma, mucinous neoplasm, goblet cell carcinoma, neuroendocrine carcinoma.

Introduction

Primary cancer of the appendix is rare with an incidence of approximately 1,2 cases per 100000 people per year in the United States (1). Most often it is found incidentally in a appendectomy specimen that was obtained because of acute appendicitis. Sometimes it can be found incidentally on imaging of the abdomen or during colonoscopy or surgery. When symptoms are present most often the disease is advanced and there can be weight loss and pain and abdominal distention due to peritoneal dissemination.

There are different histologic subtypes and classification of these tumors is historically confusing. In this review they will be classified into four subtypes : colonic-type adenocarcinoma, mucinous neoplasm, goblet cell carcinoma (GCC) and neuroendocrine neoplasm. The presence of signet ring cells is considered as a histologic feature and can be present in colonic-type adenocarcinoma and mucinous neoplasms.

Colonic-type adenocarcinoma

Epidemiology

Colonic-type adenocarcinoma is thought to be the most common type of primary appendix cancer, comprising 60% of all cases. Because of its rarity, it still constitutes less than 0,5% of all gastrointestinal tract neoplasm (1). Similar to colorectal adenocarcinomas, they arise from preexisting adenomas (2) and present at a mean age of 62 to 65 years, with a slight male predominance (1,3).

Grading and staging

There is no specific staging system or guideline for colonic-type adenocarcinoma arising in the appendix. The workup, staging and treatment mirror that of colon cancer. The American Joint Commission on Cancer (AJCC) staging system and the National Comprehensive Cancer Network (NCCN) or European Society for Medical Oncology (ESMO) guideline for colon cancer can be used.

Management

As is true for all appendiceal neoplasms, colonic-type adenocarcinoma is most often found incidentally following appendectomy for appendicitis and T-stage information will be immediately available which will guide further treatment.

Patients with Tis tumors resected with negative margins are cured with appendectomy alone. It is not always easy to differ between Tis and T1. For T1 tumors with favorable characteristics (grade 1 or 2, no vascular or lymph vessel invasion and negative section margins) appendectomy alone may be sufficient. Patients with unfavorable T1 tumors (G3, vascular or lymph vessel invasion and/or positive section margins) should be considered for right hemicolectomy for adequate staging and resection. For patients with T2 or greater tumors right hemicolectomy is recommended with 12 or more lymph nodes typically considered adequate for accurate staging. The rate of lymph node involvement in the colonic-type adenocarcinoma subtype was 30% in the largest population-based study of primary appendix cancer (1). For these patients with stage III disease adjuvant systemic chemotherapy is recommended, in analogy with colon cancer, although specific studies for

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Table 1. — **Diagnostic terminology for appendiceal mucinous neoplasia based on AJCC Eighth Edition (4,5)**

Diagnostic terminology	Histologic criteria
Serrated polyp with or without dysplasia	Serrated crypt profiles confined to the mucosa with intact muscularis mucosae.
LAMN	Mucinous neoplasm with low-grade cytology and any of the following :
	-loss of the lamina propria and muscularis mucosae
	-fibrosis of the submucosa
	-'pushing' diverticulum-like growth into the wall
	-dissection of acellular mucin in the wall
	-mucin and/or neoplastic cells outside of the appendix
HAMN	Mucinous neoplasm with high-grade cytology present (at least focally) and lacking infiltrative invasion
Mucinous adenocarcinoma	Mucinous neoplasm with infiltrative invasion. Patterns of infiltrative invasion include :
	-infiltrative glands, incomplete glands, or single infiltrative tumor cells associated extracellular mucin and desmoplastic stroma
	-'small cellular mucin pool' pattern characterized by small dissecting pools of mucin containing floating nests, glands, or single neoplastic cells
Mucinous adenocarcinoma with signet ring cells	Mucinous neoplasm with signet ring cell component accounting for ≤50% of the tumor cells
Mucinous signet ring cell carcinoma	Mucinous neoplasm with a signet ring cell component accounting for >50% of the tumor cells

appendiceal adenocarcinomas are not available. As for colon adenocarcinoma, adjuvant chemotherapy should also be considered for stage II tumors with high risk features. The rate of distant metastases at presentation is not well known but has been reported at 23 to 37% (1,3). Most often there is peritoneal dissemination and for these patients complete cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) should be considered if complete resection can be achieved. As is true for colorectal cancer, surgical resection including metastasectomy of limited liver and lung lesions, is reasonable for selected patients with appendix adenocarcinoma.

Mucinous neoplasm

Epidemiology

The appendiceal mucinous neoplasm is a biologically and histologically distinct entity from colorectal cancer and from colonic-type adenocarcinoma of the appendix. A concurrent colorectal adenocarcinoma should be ruled out because of the association between this two entities. The mean age of presentation is 60 years and there is no clear sex prediliction and there are no known risk factors for this disease (1,3).

Grading, staging and prognosis

The grading and staging of appendiceal mucinous neoplasms is challenging and often confusing, but has critical prognostic and therapeutic implications.

Mucinous neoplasms exhibit a wide spectrum of clinical behavior, ranging from neoplasms which are relatively slow-growing but with considerable risk for recurrence and possible fatal outcome and those neoplasms that are highly agressive with increased likelyhood of early death.

Despite the fourth edition of the World Health Organisation (WHO) Classification of Tumors of the Digestive System that differentiated low-grade from high-grade disease, there was a persistent lack of uniform diagnostic terminology. Recently the eighth edition of the AJCC Staging Manual was published and expands on current WHO diagnostic terminology. The eighth edition of the AJCC Staging Manual now uses a 3-tiered approach instead of a 2-tiered. It uses the descriptive terminology well-differentiated, moderately and poorly differentiated in parallel with the alphanumeric grades (G1, G2 and G3, respectively) and where G1 tumors are classified as low-grade and where G2 and G3 tumors are classified as high-grade. Based on the AJCC eight edition appendiceal mucinous neoplasms can be classified into serrated polyp with or without dysplasia, low-grade appendiceal mucinous neoplasm (LAMN), high-grade appendiceal mucinous neoplasm (HAMN), mucinous adenocarcinima with (50% or less of cells are signet cells) or without signet ring cells and mucinous signet ring cell carcinoma (more than 50% of cells are signet cells). Table 1 shows an overview of this classification and their histologic criteria (4,5).

LAMNs lack infiltrative invasion that characterize mucinous adenocarcinoma. According to the eighth edition of AJCC LAMNs are well differentiated (G1, low-grade).

HAMNs are extremely rare and defined as a mucinous neoplasm with high-grade cytology but lack infiltrative invasion within the appendix like LAMNs. It should be noted that if HAMN is identified, great care should be taken to exclude the presence of associated invasive adenocarcinoma. According to the eighth edition of AJCC HAMNs are moderately differentiated (G2). A neoplasm with mucinous deposits on the visceral peritoneal surface containing neoplastic mucinous epithelium with high-grade cytology should not be classified as HAMN and is best considered a mucinous adenocarcinoma because

of the high risk of developing disseminated peritoneal disease like described by Yantis et al (6).

Mucinous adenocarcinoma of the appendix is defined by the presence of infiltrative invasion in a mucinous neoplasm. In contrast to the 'pushing' pattern of LAMN, infiltrative invasion refers to destructive stromal invasion into the wall of the appendix. The presence of any signet ring cell differentiation in a mucinous neoplasm is also indicative of infiltrative mucinous adenocarcinoma. If the tumor is composed of ≤50% signet ring cells it is considered as a mucinous adenocarcinoma with signet ring cells. If the tumor is composed of >50% signet ring cells the tumor is considered as a mucinous signet ring cell carcinoma.

Appendiceal mucinous neoplasm are often localised to the appendix but can also be advanced with peritoneal dissemination. Pseudomyxoma peritonei is a condition that has been characterized as a localised or generalized accumulation of thick, gelatinous material in the abdomen and/or pelvic peritoneal cavity. Most cases develop as a result of appendiceal mucinous neoplasia, however other primary sites of origin including pancreas (7,8,9), urachus of the bladder (10,11,12) and ovarian teratoma (13) give rise to pseudomyxoma peritonei. Given this, pseudomyxoma peritonei is best used as a clinical, radiologic or even syndromic descriptor and should not be used as a histopathologic diagnosis (5). Figure 1 shows a CT scan of a patient with an appendiceal mucinous adenocarcinoma with pseudomyxoma peritonei. Distant metastasis through lymphatics or hematogenous spread is uncommon but can occur in high-grade disease.

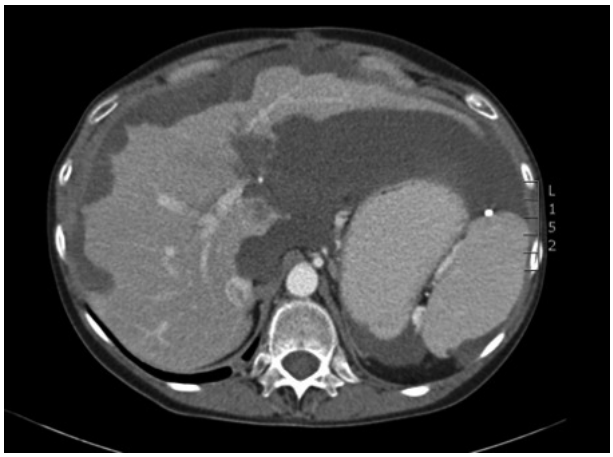

Figure 1. — CT scan of a female patient with mucinous adenocarcinoma of the appendix with pseudomyxoma peritonei and extreme gelateneous deposits leading to liver compression, while maintaining the liver function.

Table 2. — **AJCC Eighth Edition Staging of mucinous neoplasm (4)**

T – primary tumor	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ (intramucosal carci-noma ; invasion of the lamina propria or extension into but not through the muscularis mucosae)
Tis(LAMN)	Tumor confined by the muscularis propria ; acellular mucin or mucinous epithelium mayinvadeinto themuscularis propria
T1	Tumor invades the submucosa (through the muscularis mucosa but not into the muscularis propria)
T2	Tumor invades the muscularis propria
T3	Tumor invades through the muscularis propria into the subserosa or the mesoappendix
T4a	Tumor invades the visceral peritoneum, including the acellular mucin or mucinous epithelium involving the serosa of the appendix or mesoappendix
T4b	Tumor directly invades or adheres to adjacent organs or structures

Note : T1 and T2 are not applicable to LAMN ; acellular mucin or mucinous epithelium that extends into the subserosa or serosa should be classified as T3 or T4a, respectively.

N – regional lymph nodes	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1a	One 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	
M0	No 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 peritoneum

Except for the adaption in terminology and grading, the AJCC eighth edition initiated significant changes to the staging of appendiceal mucinous neoplasms, in particular for low-grade tumors (Table 2). It created a new T category specifically for LAMN, termed the Tis(LAMN). Tis(LAMN) refers to LAMN confined to the muscularis propria. The pT1 and pT2 designation do not apply to LAMN because of a number of challenges unique to LAMN that do not allow for staging using conventional criteria used elsewhere in the gastrointestinal tract. First, LAMN significantly distorts the architecture of the appendix. In this setting, assessing involvement of the lamina propria, muscularis mucosae and submucosa is not possible, and the pT1 designation cannot be applied to LAMN.

Second, LAMN often exhibits a 'pushing' diverticulum-like growth into the muscularis propria. However, studies evaluating outcome in LAMN have determined that this 'pushing' pattern of extention into the appendiceal wall is not associated with tumor recurrence (14,15,16). Thus, the pT2 designation does not apply to LAMN.

Finally, both acellular mucin and neoplastic mucinous epithelium can extend through the muscularis propria to involve the appendiceal subserosa or mesoappendix or be present on the appendiceal visceral peritoneal surface. In contrast to other sites of the luminal gastrointestinal tract, acellular mucinous deposits present outside of the appendix carries risk for tumor recurrence. Thus, both the extent of acellular and cellular mucin should be considered in these neoplasms. Acellular mucin only extending to the muscularis propria is classified as Tis(LAMN). Dissecting cellular mucinous deposits into the subserosa or muscularis propria are not typical for LAMN, and their presence should promp consideration for an infiltrating mucinous adenocarcinoma for wich the pT1 or pT2 designation do apply. If acellular mucin or neoplastic mucinous epithelium penetrates the visceral peritoneal surface, the tumor is designated pT4a. If this acellular mucin or neoplastic mucinous epithelium directly invades adjacent structures, it is designated pT4b.

LAMNs pT4a with acellular mucin present on the visceral peritoneal surface have a better prognosis compared to LAMNs pT4a with neoplastic mucinous epithelium and are associated with a small risk of recurrence (3% (2 of 58 patients (14,16)). This likely reflects the difficulty in identifying microscopic foci of neoplastic mucinous epithelium within the mucin deposits (5). LAMN pT4a with cellular mucin deposits present on the visceral peritoneal surface are associated with a significant risk for the development of subsequent full-blown disseminated disease (36% (5 of 14 patients (14,16)).

The AJCC eighth edition has also updated the M category for appendiceal mucinous neoplasms. The M1 category has been expanded to include 3 options instead of 2 detailed in the seventh edition. It now defines M1a as intraperitoneal acellular mucin. In a study by Pai et al (14) and Davison et al (17), 2 and 5 patients respectively, with acellular intraperitoneal disease were followed with neither patient developed recurrence. In the study by Young et al (18), 5 patient had long-term follow up and 1 patient developed recurrence after 18 years. This limited literature data suggest that these patients have a decreased risk of recurrence compared with patients with cellular disease and support the inclusion of a separate M category. The M1b category is defined as intraperitoneal metastasis only, and the M1c category refers to metastasis to sites other than the peritoneum.

For patients with disseminated mucinous appendiceal neoplasms, pathologic grade has repeatedly been shown to be an independent prognostic factor. Patients with high-grade (G2 or G3) mucinous adenocarcinoma have a significantly worse overall survival in comparison to patients with disseminated low-grade (G1, well differentiated) mucinous neoplasms. The overall 5-years survival for patients with disseminated low-grade (G1, well differentiated) mucinous neoplasm ranges from 60% to 90% with an estimated 10-year overall survival of 50% (15,19-25). The overall 5-year and 10-year survival for patients with high-grade (G2, moderatly differentiated) mucinous adenocarcinoma ranges from 30% to 60% and 20% to 30%, respectively (17,24,25). The overall 5-year and 10-year overall survival for patients with high-grade (G3, poorly differentiated) mucinous adenocarcinoma with signet ring cells ranges from 10% to 40% and 10% to 20%, respectively (17,24,25).

Management

Prognosis and treatment of appendiceal mucinous neoplasms depends on the grading and staging of the disease. Patients with Tis(LAMN) are typically cured by complete resection of the appendix with no risk for recurrent disease. Given the uncertainty regarding the risk of peritoneal dissemination of patients with T3 LAMN they should be considered to have close follow-up to evaluate for the development of peritoneal disease. Intraperitoneal recurrence can develop many years after the initial presentation suggesting that prolonged clinical follow-up (10 y) may be necessary. The exact duration and role and frequency of imaging is not well established. For patients with LAMN T4a with acellular mucin on the visceral peritoneal surface close follow-up is recommended similar to patients with LAMN T3. For patients with LAMN T4a with cellular mucin deposits on the visceral peritoneal surface some centers have counseled patients to have HIPEC therapy given the relatively high rate of peritoneal recurrence. Though the role of additional surgery and/of HIPEC therapy are uncertain.

Patients with HAMN are extremely rare and there is limited literature data regarding the natural history of HAMN. The management of patients with HAMN and the role of additional surgery are uncertain. For sure, patients with HAMN should have an appendectomy with negative margins and should have long-term follow-up.

Since mucinous adenocarcinomas of the appendix are clinically agressive and are frequently disseminated to the peritoneum, an oncologic resection with right hemicolectomy and evaluation for lymph node involvement is recommended. An oncologic treatment regimen similar to colorectal carcinomas is often followed (14).

Patients with disseminated low-grade (G1, well-differentiated) neoplasms are most commonly treated with CRS and HIPEC (17,26,27). Systemic chemotherapy is not effective in patients with stage IV low-grade mucinous neoplasms, underscoring the importance of tumor grade assessment in therapeutic management (28). In contrast, for patients with stage IV G2 or G3 mucinous adenocarcinoma, systemic chemotherapy has been shown to improve overall survival. These patients are often given systemic chemotherapy in an attempt to reduce tumor volume with the option for CRS and HIPEC after assessment of tumor respons to systemic chemotherapy (26,29,30). Patients with unresectable high-grade (G2 or G3) adenocarcinoma are often treated with systemic chemotherapy alone (31).

Goblet cell carcinoma

Epidemiology

Goblet cell adenocarcinoma is a rare but distinct entity of appendiceal tumors accounting for approximately 14-19% of primary appendix cancers (1,32). GCC is a heterogenous neoplasm that exhibit unique pathologic and clinical features. It is a mixed tumor consisting of both epithelial (glandular) and neuroendocrine elements containing goblet cells. The prognosis of GCC lays intermediate between appendiceal neuroendocrine tumors (NET) and primary appendiceal adenocarcinoma (1,33). The mean patient age is 52 years and there is no sex prediliction and there are no established risk factors (34,35).

Grading and staging

Multiple classification systems exist to describe GCC. Due to its heterogenicity, it is the combination of these different classification systems that should guide further therapy. The 2010 WHO classification for tumors of the appendix classifies GCC under the category of neuroendocrine neoplasms based on differentiation and histologic grading (36). Both the seventh and eighth AJCC staging system are based on the tumor size, nodal status and metastatic disease (37,4). And Tang et al proposed a system of classification specific for GCC of appendix based on histologic features of the tumor at the primary site including the arrangement of the goblet cells, degree of atypia and desmoplasia. They classified them in three groups: typical GCC (group A) and adenocarcinoma ex GCC that was further divided into signet ring cell type (group B) and poorly differentiated adenocarcinoma type (group C). Group A and B tumors shared a similar immunoprofile, which included generally focal immunoreactivity for neuroendocrine markers and a normal intestinal type mucin glycoprotein profile. The proliferative index was relatively low in these tumors and slightly increased from group A to B tumors and both b-cathenin and E-cadherin exhibited a normal membranous staining pattern. Group C, the poorly differentiated adenocarcinoma ex GCC, demonstrated abnormal p53 and b-catenin immunoreactivity. Patients in group C almost always have metastatic disease. This suggest that GCCs display a spectrum of histologic features and possess the potential to transform to an aggressive adenocarcinoma phenotype (38).

Management and prognosis

Since many GCCs are found incidentally after appendectomy, the need for further right hemicolectomy is an important question that is still debated. Both the North American and European Neuroendocrine Tumor Societies recommend right hemicolectomy due to high risk of metastases and improvement in outcome (34,39). However, in several published analyses, there is evidence to suggest limited or no benefit of right hemicolectomy, primarily in patients with low grade disease and limited disease burden (38,40-42). Therefore, it is reasonable to consider appendectomy alone in those patients with tumor <2 cm with negative surgical section margins, with typical group A histology, and with pT1 or pT2 tumors (40).

Indication and selection of adjuvant treatment has been extrapoled from colorectal adenocarcinoma. All patients with stage III and selected patients with stage II disease have to be considered for adjuvant treatment with chemotherapy.

For patients with peritoneal metastatic disease there is a role for CRS and HIPEC. The 5-year overall survival data based on AJCC staging system is 100% for stage I, 76% for stage II, 22% for stage III and 14% for stage IV (37). Based on Tang's classification the 5-year overall survival is 100% in group A, 36% in group B and 0% in group C (38).

Neuroendocrine neoplasm

Epidemiology

Appendiceal neuroendocrine neoplasms are a relative frequent subgroup of NET with an approximate incidence rate of 0,15/100 000/year and with a slight female predominance in Western series (43). Mean age at diagnosis has been reported between 38 and 48 years (1,3).

Grading and staging

The histopathological characterization of appendiceal NET includes proof of the neuroendocrine tumor entity

Table 3. — **Grading classification of NET according to the WHO 2010 classification (44)**

Grading	Ki-67 index	Mitotic rate
G1 NET	≤2%	<2/10 HPF
G2 NET	3-20%	2-20/10 HPF
G3 NEC	>20%	>20/10 HPF

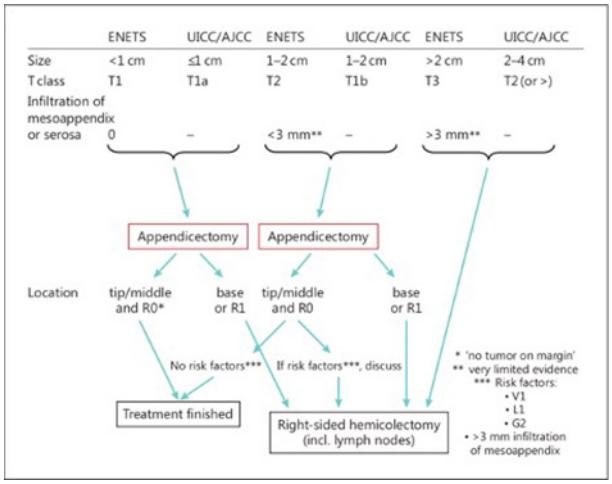

Figure 2. — Therapeutic alogrithm for small appendiceal NET suggested by ENET guidelines V1=vascular invasion; L1=lymphatic invasion; G2=grade 2 tumor (Ki-67:3-20%) (55).

by immunohistochemical staining for synaptophysin and chromogranine A as well as for Ki-67 to determine the proliferation capacity of the tumor (44-46). The Ki-67 index also determines the tumor grading according to the WHO classification (Tabel 3), NET of the appendix are usually G1 or G2 (44,46). Besides WHO grading the pathology report should also contain pTNM staging according to either AJCC classification or ENETS or both, vascular (V 0/1) and lymph (L 0/1) vessel involvement and a statement on mesoappendiceal infiltration (and the extent of the latter) (55). An invasion of the mesoappendix shows a higher rate of vascular and lymph vessel involvement than in cases without. An invasion depth of >3 mm has been suggested to reflect the agressiveness of the disease (T2 versus T3 according to the ENETS classification)(46,55).

Management

The surgical strategy (appendectomy versus right hemicolectomy) should be tailored to the individual situation. Figure 2 shows a therapeutic algorithm suggested by ENETS guidelines (55). For appendiceal NET <1 cm appendectomy alone is curative (if it is R0 resection). The only exception could be the rare situation when the NET is located in the base of the appendix or when a mesoappendiceal invasion of >3 mm is discovered. Under these circumstances, patients should be counseled for subsequent right hemicolectomy, although a worse prognosis has not been proven and a higher complication rate than with simple appendectomy has to be considered (47-55). For tumors >1 cm but <2 cm right hemicolectomy should be considered and be discussed with the patient if one or more of the following risk factors coexists because of the increased risk for lymph node or distant metastasis: G2, vascular or lymph vessel invasion and mesoappendiceal infiltration >3 mm. For appendiceal NET >2 cm right hemicolectomy with oncologic lymph node dissection is advised due to their clearly increased risk of lymph node metastasis and long-term recurrence and/or distant metastasis (56). Cases of higher tumor grade (G3) should, irrespective of the

Table 4. — **TNM staging for appendiceal NET according to either the ENETS guidelines or the UICC/AJCC classification (46,55)**

	ENETS guidelines	UICC/AJCC classification
T – primary tumor Tx	Primary tumor not assessed/assessable	
T0	No evidence of any primary tumor	
T1	Tumor ≤1 cm with infiltration of the submucosa and muscularis propria	
T1a		Tumor ≤1 cm
T1b		Tumor > 1 cm but ≤2 cm
T2	Tumor ≤2 cm with infiltration of the submucosa, muscularis propria and/or minimal (≤3 mm) infiltration of the subserosa and/or mesoappendix	Tumor > 2 cm but ≤4 cm or with extension into the cecum
T3	Tumor >2 cm and/or extensive (>3 mm) infiltration of the subserosa and/or mesoappendix	Tumor >4 cm or with extension into the ileum
T4	Tumor with infiltration of the peritoneum and/or other neighboring organs	Tumor with perforation of the peritoneum or invasion of other adjacent structures
N – regional lymp nodes Nx	Regional lymph nodes not assessed/assessable	
N0	No regional lymph node metastasis	
N1	Locoregional lymph node metastasis/-es	
M – distant metastasis Mx	Distant metastasis not assessed/assessable	
M0	No distant metastasis	
M1	Distant metastasis/-es	

tumor size, be treated with an oncological resection (55). In pediatric patients, outcome after appendiceal NET resection is more favorable and guidelines do not apply to this specific population (47,57,55).

Appendiceal NET <1 cm with R0 resection require no follow-up. For NET between 1 and 2 cm without risk factors as mentioned above there is not enough data for a clear-cut decision. For al other patients long-term follow-up is advised (55,58-60).

For the exceedingly rare cases of appendiceal NET with distant metastases, surgical treatment should be considered if lesions are limited and resectable. For unresectable disease or patients who are not fit for surgery, somatostatine analogues have been shown to improve progression-free survival (61). Everolimus and peptide receptor radionuclide therapy are other systemic options (39,58).

Conclusion

Primary appendix cancer is rare and most commonly found incidentally in an appendectomy specimen that was obtained for an unrelated condition. There are a lot of subtypes that are biological and histological divers and they can be broadly classified in colonic-type adenocarcinoma, mucinous neoplasm, GCC and NET. Depending on the subtype, grading and staging of the tumor further treatment will be guided. Simple appendectomy is often sufficient for early-stage appendiceal neoplasms except for mucinous adenocarcinomas. For these tumors and for more locally advanced tumors subsequent oncologic resection with right hemicolectomy and lymp node assessment is warranted. Patients with disseminated disease should be considered for CRS and HIPEC, with or without preoperative chemotherapy. Further trials evaluating novel therapies for patients who are not surgical candidates are needed.

Conflict of interest

None.

Reference

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