Review: Pathology and Its Clinical Relevance of Mucinous Appendiceal Neoplasms and Pseudomyxoma Peritonei

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Abstract

Until recently, many classifications existed for the terminology and histopathologic classification of appendiceal mucinous neoplasms, mucinous appendiceal adenocarcinomas, and pseudomyxoma peritonei (PMP). A major accomplishment was achieved by consensus-based histopathologic classifications on behalf of the Peritoneal Surface Oncology Group International regarding mucinous appendiceal tumours and PMP. As different classifications were used over the years and also owing to the rare nature of these tumors, many clinicians are not familiar with the terminology and the impact on patient management. Hence, an overview concerning mucinous appendiceal neoplasms, mucinous appendiceal adenocarcinomas, and PMP is provided to serve as an introduction into the basic morphology of these tumors with tentative recommendations for management.

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Introduction

Appendiceal epithelial tumors are scarce. In comparison, the incidence of colorectal cancer is approximately 100-fold higher.[1] As appendiceal neoplasms and colorectal cancer exhibit a distinctly different clinical and tumor behavior, these tumors are classified separately in the various tumor classifications.[2] Most appendiceal neoplasms are found during surgery or postoperatively in appendectomy specimens. However, the percentage of appendiceal tumors that is incidentally discovered preoperatively by imaging is increasing over time.[3,4] A clinical diagnosis is challenging due to a variable symptomatology in patients, ranging from an asymptomatic course to vague acute or chronic abdominal complaints, even with symptoms mimicking acute appendicitis.[4-6]

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Pathology is of prognostic significance in patients with appendiceal cancer.[2] Adenocarcinoma is the most common histologic malignant subtype, accounting for more than one-half of the cases.[6-8] Other malignant subtypes of appendiceal cancer include lymphomas, sarcomas, grade 1 and 2 neuroendocrine tumors (NETs), and goblet cell tumors/carcinomas (previously called goblet cell carcinoids).[3,6] Goblet cell tumors are a remarkable group of tumors, occurring almost exclusively in the appendix. Recent insights have shown that goblet cell tumors are lesions composed of several cell types, including neuroendocrine cells, Paneth cells, and goblet cells. These tumors show a continuum with adenocarcinomas, and the prognosis is dependent of the dominant morphologic component of the goblet cell tumor.[9,10]

A subgroup of epithelial tumors, including those with uncertain malignant potential and adenocarcinomas, are known for their extensive mucus production and therefore, belong to the group of mucinous appendiceal neoplasms. Mucinous appendiceal neoplasms are the leading cause of pseudomyxoma peritonei (PMP), a unique clinical condition characterized by progressive accumulation of mucinous ascites and peritoneal implants with fatal outcome.[1,11-13] The terminology and histopathologic classification of mucinous appendiceal neoplasms, mucinous appendiceal adenocarcinomas, and PMP has been subject to diverse consensus-based changes over time. The aim of this general overview is to provide an introduction into the basic morphology of these tumors with tentative recommendations for management of these various neoplasms.

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Pathology

Mucinous appendiceal neoplasms are a frequently discussed item within the group of appendiceal tumors, but the classification might still be experienced as confusing by clinicians.[9-12,14-18] Mucinous appendiceal neoplasms are distinguished in 3 different categories according to the latest consensus-based classification by the Peritoneal Surface Oncology Group International (PSOGI), consisting of true premalignant lesions, tumors of uncertain malignant potential, and malignant lesions.[11,16] Serrated polyps and tubular, villous, and tubulovillous adenomas all belong to the group of premalignant lesions. Meanwhile, tumors of uncertain malignant potential, also known as low-grade appendiceal mucinous neoplasms (LAMNs) and high-grade appendiceal mucinous neoplasms (HAMNs), share some histologic features with adenomas, but these lesions have the capacity to proliferate out of the appendix in a malignant fashion. Finally, the malignant lesions can be subdivided into mucinous adenocarcinomas, with or without a signet ring cell component, and signet ring cell carcinomas. The premalignant lesions do not have the potential to cause PMP, which is not the case for the other 2 categories.[12,19]

LAMN

A subgroup of mucinous appendiceal lesions can be classified as LAMNs. Historically, cystadenoma and mucocele were used as synonyms for LAMN, but these terms were abandoned based on consensus, owing to their incomplete and misleading nature.[10-12,15] The histologic criteria for LAMN are summarized in Table 1. The most important and distinctive feature of LAMN is the low-grade cytologic atypia without signs of invasive infiltration in the appendiceal wall. In almost all cases of LAMN, there is loss of the normal mucosal architecture of the appendix, at least focally, with loss of the lamina propria and muscularis mucosa with lymphoid follicle atrophy associated with fibrosis of the submucosa.[16] LAMNs are the main cause of PMP. These lesions generally do not cause nodal or distant extraperitoneal metastases.[11]

In case of a suspected LAMN, accurate pathologic examination of the total appendix is essential, as some features are associated with potential intraperitoneal tumor spread, which worsens the natural disease course and the prognosis of the patient. Worrisome features of LAMN include appendiceal rupture (including microperforation), a background of appendiceal inflammation, the presence of extra-appendiceal mucin, or extensive dissecting mucin pools within the appendiceal wall. LAMNs with these ominous features are prone to develop into PMP.[4,11,20,21] A LAMN in an intact appendix and without other risk factors is considered as benign with only very small risk to evolve to PMP.

Patients with LAMN show different characteristics, clinical course, and survival than patients with a mucinous adenocarcinoma. Patients are generally young, with a median age of approximately 53 years, and with a slightly female predominance (~60%).[15,20,22] Among all mucinous appendiceal neoplasms without peritoneal spread, it has the most favorable prognosis. In patients with completely resected LAMNs or with low-volume peritoneal disease, a 5-year recurrence-free survival and overall survival rate of 95.2% and 100%, respectively, were observed.[23]

HAMN

The term HAMN was added in the latest classification for mucinous neoplasms, but these tumors are extremely rare and therefore still poorly understood.[11] These lesions display the same architectural features of a LAMN but with high-grade cytology (Table 1).[11,16] It might be hypothesized that HAMNs form an intermediate group between LAMNs and mucinous adenocarcinomas. In a small study by Misdraji et al, HAMNs had a more aggressive clinical course than LAMNs.[15] Information on prognosis is lacking for patients with HAMNs.

Table 1 Classification and Grading of Mucinous Epithelial Lesions of the Appendix (Adapted from Carr et al[11])

Terminology	Grading	Histologic Features
Serrated polyp	Without or with low-/high-grade dysplasia	Lesion with serrated featured, confined to the mucosa and intact muscularis mucosae. In case of dysplasia, it can be classified as low or high grade.
Adenoma	Low-/high-grade dysplasia	Adenoma with tubular, tubulovillous of villous features, resembling usual colorectal type. Confined to mucosa and intact muscularis mucosae.
LAMN	Low	Mucinous neoplasm with low-grade cytologic atypia and without invasive infiltration but with any of the following features: • Loss of muscularis mucosae • Fibrosis of submucosa • 'Pushing invasion' (expansile or diverticulum-like growth) • Dissection of acellular mucin in the appendiceal wall • Undulating or flattened epithelial growth • Rupture of the appendix • Mucin and/or cells outside the appendix
HAMN	High	Mucinous neoplasm with the architectural features of LAMN but with high-grade cytologic atypia.
Mucinous adenocarcinoma	Well/moderately/poorly differentiated	Mucinous neoplasm, comprising of >50% extracellular mucin, with infiltrative invasion.
Mucinous adenocarcinoma with signet ring cells	Poorly differentiated	Mucinous adenocarcinoma, comprising up to 50% signet ring cells.
Signet ring cell adenocarcinoma	Poorly differentiated	Adenocarcinoma, comprising of >50% signet ring cells

Abbreviations: HAMN = high-grade appendiceal mucinous neoplasm; LAMN = low-grade appendiceal mucinous neoplasm.

Mucinous Adenocarcinoma (Including Signet Ring Cell Adenocarcinoma)

Appendiceal mucinous adenocarcinomas are defined as mucinous neoplasms comprised of > 50% extracellular mucin, with the presence of infiltrative invasion of the appendix.[11,16] According to the PSOGI classification, mucinous adenocarcinomas are classified as well, moderately, and poorly differentiated, although the histologic criteria for the different grading systems are not well-established.[11] The presence of signet ring cells in the lesion to whatever extent, indicates a poorly differentiated carcinoma. If more than 50% of the tumor consists of signet ring cells, the term signet ring cell carcinoma is used. Otherwise, if less than 50% of the cells have signet ring cell morphology, the tumor is classified as poorly differentiated adenocarcinoma with signet ring cells.[11]

Mucinous adenocarcinomas develop mainly from precursor lesions.[10,13] Patients are generally young, with a median age of 50 to 60 years, and many patients already present with synchronous metastatic disease, especially in the case of signet ring cell adenocarcinomas.[2,24,25] Nodal metastases are commonly seen, in contrast to patients with LAMNs. Mucinous and signet ring cell adenocarcinomas metastasize intra- and extraperitoneally, but usually intra-abdominal dissemination occurs first. Survival is strongly dependent of histologic grade.[2,13,24,26] Among appendiceal adenocarcinomas, mucinous adenocarcinoma has the most favorable prognosis, with a median overall survival of over 60 months. Like colorectal cancer, patients with signet ring cell appendiceal adenocarcinoma have the worst overall survival among all morphologies, with a reported median overall survival of approximately 20 to 25 months and a 5-year survival rate of 22% to 38%.[2,8,13,24]

Peritoneal Disease

PMP is a heterogeneous clinical disease, for which a uniform and comprehensive definition is still lacking. It is distinguished from usual peritoneal metastases of other gastrointestinal cancers by the presence of excessive amounts of mucin in the peritoneal cavity.[12] However, as the extent of mucinous ascites to be classified as PMP is not clarified, the exact cutoff point between (mucinous) peritoneal metastases and PMP is unclear. As already stated by Carr et al, PMP should only be used for the macroscopic appearance of mucinous ascites, as it is not a histologic diagnosis.[12] Mucinous appendiceal neoplasms are the leading cause of PMP.[11]

PMP can be divided into several categories based on histologic features of the peritoneal disease with its clinical consequences and prognostic value, including acellular PMP, low-grade PMP, high-grade PMP, and high-grade PMP with signet ring cells. It is of importance to describe and subdivide the histologic grade of both peritoneal disease and the primary tumor, as morphology can be discordant in rare cases. For instance, patients with LAMN may present with high-grade PMP, whereas invasive adenocarcinomas could cause low-grade PMP. This discordance may in some cases be explained by sampling error or incorrect diagnosis. However, the histologic grade of the peritoneal disease outweighs its primary appendiceal lesion in terms of prognosis.[11,12,27]

Acellular PMP

The separated entity of acellular mucin in the overarching group of PMP is characterized by the absence of epithelial cells in the mucin within the peritoneal cavity. In case of appendiceal origin, this acellular mucin usually results from LAMNs with low-volume peritoneal disease, mostly located in the right lower quadrant of the abdomen.[22] Patients with acellular mucin comprise a small group within the spectrum of PMP and have the most favorable clinical outcome, owing to the relatively indolent course of disease.[15,22]

Low-grade PMP

Low-grade PMP is the most common variant of PMP. Other terms used for low-grade PMP are low-grade mucinous carcinoma peritonei and disseminated peritoneal adenomucinosis (DPAM).[12] All histologic features associated with low-grade PMP are described in Table 2. The main cause of low-grade PMP are LAMNs.[27]

High-grade PMP

Peritoneal disease with high-grade cytologic atypia is also known in literature as high-grade mucinous carcinoma peritonei, peritoneal mucinous carcinomatosis (PMCA), and high-grade PMP. High-grade PMP is in the majority of cases caused by mucinous adenocarcinomas.[11,12] Further details are listed in Table 2. It remains to be seen whether HAMNs will cause high- or low-grade PMP or even an intermediate form. A continuum is present between high-grade PMP and non-mucinous peritoneal metastases in which the presence of a large amount of mucin points to PMP instead of non-mucinous peritoneal metastases.[12]

High-grade PMP With Signet Ring Cells

High-grade PMP with signet ring cells is classified separately from high-grade PMP without signet ring cells, as the presence of signet ring cells is a powerful negative prognostic factor for survival in patients with PMP.[11,13] All further criteria for high-grade PMP also apply for high-grade PMP with signet ring cells.

Table 2 Classification of Pseudomyxoma Peritonei (Adapted from Carr et al[11,12])

Terminology	Histologic Features
Acellular PMP	Mucin within the peritoneal cavity without neoplastic epithelial cells.
Low-grade PMP	• Low-grade or minimal cytologic atypia • Epithelial component typically scanty • Strips, gland-like structures, or small clusters of cells • Not more than occasional (sporadic) mitoses • 'Pushing' invasion into underlying organs
High-grade PMP	• High-grade cytologic atypia • High cellularity • Cribiform growth • Numerous mitoses • Destructive infiltrative invasion of underlying organs
High-grade PMP with signet ring cells	Any lesion with a component of signet ring cells.

Abbreviation: PMP = pseudomyxoma peritonei.

Management

LAMN

For patients without extra-appendiceal disease, appendectomy and follow-up is recommended. Right hemicolectomy should not be performed, because it provides no survival benefit for patients with LAMNs, as these lesions usually do not cause nodal metastases.[13,28] In patients with positive margins, additional surgery like cecectomy may be considered, although several data suggest no survival benefit after further resection.[4,29] Although the exact duration and prognostic value of follow-up is unknown, long-term follow-up of 5 to 10 years is recommended, because peritoneal dissemination can occur lately after the primary lesion.[11,16] Currently, follow-up is recommended to start annually, including an abdominal computed tomography (CT) scan and determination of serum tumor markers (carcinoembryonic antigen, cancer antigen 19.9, and cancer antigen-125).[11] Especially in patients with worrisome prognostic signs, such as elevated tumor markers, positive resection margins or the presence of mucin beyond the appendix, close and extended follow-up is advised.[11,20] Whether patients with a radically resected and intact appendix with LAMN without worrisome features need close and frequent follow-up is debatable, as it is considered as a lesion with an indolent behavior and a low potential to develop PMP.[4] In the study of Guaglio et al, a 5-year recurrence-free rate of 95.2% and no patient deaths were found in patients with radically resected LAMNs or low-volume peritoneal disease.[23]

HAMN

As the term HAMN was introduced recently, limited literature regarding the management of this lesion is present. Moreover, the diagnosis of HAMN is exclusively made after surgery by pathologic examination of the appendix, in which the surgeon has already performed an appendectomy, cecectomy, or right hemicolectomy. Due to the rareness of the tumor, it is still unknown whether local removal of the tumor is sufficient or a more extended tumor resection is needed. Long-term follow-up is advised, because patients with HAMNs might have an increased risk to develop peritoneal disease.[16]

Mucinous Appendiceal Adenocarcinoma

In patients with mucinous adenocarcinomas, a right hemicolectomy with lymph node dissection should be performed in locoregional disease, due to an increased risk of lymph node invasion and improved survival rates compared with appendectomy only.[13,21,30] The value of adjuvant chemotherapy is unknown, as no randomized controlled trials have been conducted due to the rarity of the appendiceal adenocarcinomas. In a retrospective cohort study of Asare et al, the role of adjuvant systemic therapy on overall survival was evaluated and showed a survival benefit for treated patients with mucinous and non-mucinous morphology.[25] However, in this study, information about the systemic regimens used were lacking, and adjuvant chemotherapy was administrated in all locoregional stages (I-III). In all patients with appendiceal mucinous adenocarcinomas, follow-up is recommended according to the guidelines of colorectal cancer, because recurrence and distant metastases are frequently observed, comparable with other gastrointestinal mucinous adenocarcinomas.[11]

Peritoneal Disease

Cytoreductive Surgery With Hyperthermic Intraperitoneal Chemotherapy (CRS + HIPEC). In peritoneal dissemination, CRS + HIPEC is recommended for all types of PMP, although different criteria apply for low- and high-grade PMP. For all peritoneal malignancies, the extent of the peritoneal disease is assessed by the peritoneal cancer index (PCI). The PCI comprises a score between 1 to 39, composed of a scoring system in which the peritoneal cavity and small bowel are divided into 13 regions, in which the tumor burden is assessed through a score of 1 to 3.[31] For example, in peritoneal metastases of colorectal origin, CRS + HIPEC is usually not performed if PCI $\geq$ 20, as radical resection of the peritoneal tumor is nearly impossible, and the morbidity caused by CRS + HIPEC outweighs the potential minimal beneficial effect on survival.[32]

In patients with low-grade PMP, CRS + HIPEC should always be considered irrespective of the PCI. If complete cytoreduction could be achieved, CRS + HIPEC is still a curative option in patients with high peritoneal tumor load.[1,33,34] The great impact of CRS + HIPEC on survival in low-grade PMP is reflected in a reported median overall survival of 7.7 to 12.3 years and a 5-year and 10-year survival rate of 84% and 48%, respectively, in case of complete cytoreduction.[1,26,27,35] In case of incomplete cytoreduction, the 5-year survival rate decreased to 63%.[27] Even in patients with very extensive disease, with a PCI ranging from 31 to 39, long-term survival was achieved with 5- and 10-year survival rates of 73% and 68%, respectively, in the study of Chua et al.[1] These results might indicate an increased survival for a selected group of patients, if referred to a specialized center.[1]

In contrast, the PCI may be considered to select patients with high-grade PMP for CRS + HIPEC, as a high PCI is associated with significant poorer survival. After achieving complete cytoreduction, a median overall survival of 2.8 to 5.3 years and a 5-year and 10-year survival rate of, respectively, 48% and 40% are reported.[1,26,27,35,36] However, after incomplete cytoreduction, the 5-year overall survival decreases to only 23%.[27]

CRS + HIPEC can be considered in patients with high-grade PMP with signet ring cells, although a positive impact of CRS + HIPEC on survival is less clear. Several studies showed a poor prognosis after CRS + HIPEC for patients with high-grade PMP with signet ring cells, with a median overall survival of only 9 to 31 months and a 5-year survival rate varying from 0% to 22%.[26,35,36] As patient selection by clinicians already occurred in these studies, the use of CRS + HIPEC for high-grade PMP with signet ring cells might be limited in daily practice, especially given the small gain in survival and the major morbidity up to 50% in treated patients caused by CRS + HIPEC.[26,30]

Systemic Therapy

Neo-adjuvant Setting. Several studies investigated the effect of neoadjuvant chemotherapy prior to CRS + HIPEC. Only in the study of Milovanov et al, in a small group of 18 patients with high-grade PMP with signet ring cells, a benefit in progression-free survival and overall survival was observed with preoperative systemic therapy, followed by complete cytoreduction.[37] However, it should be noticed that many different chemotherapeutic regimens and

targeted therapies were used.[37] No other studies found a survival gain for patients treated with neoadjuvant or perioperative chemotherapy in low- or high-grade PMP.[1,38-43]

Adjuvant Setting. No evidence exists for a beneficial effect of the subsequent use of adjuvant systemic therapy after CRS + HIPEC in patients with PMP of any type.[40,44]

Palliative Setting. Palliative systemic therapy can be considered in patients with irresectable or recurrent (high-grade) PMP who are not suitable for CRS + HIPEC. Generally accepted reasons for surgical ineligibility include short progression-free survival (often < 1 year to prior CRS + HIPEC), residual disease after prior CRS + HIPEC, and extensive comorbidities.[45,46] No randomized controlled trials have been performed for palliative systemic therapy in patients with PMP. Commonly, chemotherapy regimens by analogy of colorectal cancers are used, like fluoropyrimidine-based regimens, either fluorouracil/capecitabine monotherapy, or oxaliplatin- or irinotecan-based combination therapy.[41,46] In the series of Choe et al, addition of targeted therapy to palliative chemotherapy was used in 50% of the cases, mainly with a doublet chemotherapeutical regimen.[45] Owing to the rarity of the tumor, most of the performed studies were of retrospective design and conducted in the same single tertiary institution. Besides, different patient inclusion criteria and chemotherapy regimens were used in most studies.

Despite different regimens used in diverse studies, it was suggested that palliative systemic therapy could provide a survival benefit in selected patients not suitable for CRS + HIPEC. In the treated group of patients, the median progression-free survival and median overall survival was around 8 months and 26 to 56 months, respectively.[41,46-48] Overall response rate (ORR) varied between 20% and 60%, depending on the definition of ORR and the regimens used.[41,46-48] The use of the biologic agent bevacizumab, an anti-vascular endothelial growth factor (anti-VEGF) antibody, in 95% of the cases in addition to combination chemotherapy, was associated with an ORR of 87% and a gain in progression-free and overall survival in a selected group of patients of 5 months and 34 months, respectively.[45]

Among patients treated with palliative chemotherapy, a moderately to poorly differentiated tumor, including signet ring histology, was associated with poorer survival than patients with a well-differentiated tumor, which reflects the more aggressive biological behavior of the higher grade tumors.[46] However, the administration of palliative chemotherapy provides a benefit in progression-free survival and overall survival for selected patients with high-grade PMP. In these patients, with primary moderately or poorly differentiated tumors (including signet ring cells), the overall survival improved for moderate and poor differentiation from 20 to 36 months and 12 to 19 months, respectively.[25] The use of anti-VEGF therapy was associated with prolonged progression-free survival and overall survival in all histologic subtypes, but especially in high-grade PMP.[45] Although the number of patients included in the studies were small and selection bias probably played a significant role, these results favor the use of palliative chemotherapy and targeted therapy in selected patients with irresectable or recurrent high-grade PMP.

Patients with low-grade PMP derive less to no benefit from palliative chemotherapy compared with higher grade tumors.[25,45] Asare et al even showed a worse overall survival for patients treated with palliative chemotherapy compared with non-treated patients.[25] A clinical relevant gain of 7 months in progression-free survival was observed in patients with low-grade PMP after the administration of anti-VEGF therapy.[45] Perhaps this might indicate a role for this targeted agent in symptomatic patients with low-grade PMP not suitable for CRS + HIPEC. However, the generally indolent behavior of irresectable or recurrent low-grade PMP challenges both clinicians and patients to decide between an active management or observation.

Discussion

The classification and nomenclature of mucinous appendiceal neoplasms and PMP have been adapted several times over the years.[11,12] However, these classifications are based on experiences and theoretic assumptions of experts in the field, and are not totally evidence-based. Future research is needed to determine the accuracy and clinical relevance of the most recent consensus-based classification.

Despite the increased knowledge and insights concerning appendiceal mucinous neoplasms in recent years, there is still much to be investigated and clarified. For instance, exact information on the incidence and natural course of LAMNs and HAMNs is lacking. Besides, it is difficult to distinguish between the true benign and the premalignant lesions with their potential to cause PMP within the subgroup of LAMNs, which might affect management and surveillance decisions. Especially the subgroup of HAMNs is currently poorly understood, as this subgroup is extremely rare, and it is unknown whether the biological behavior differs significantly from other subgroups, also in their potential to cause peritoneal disease.[11,16]

No strict guidelines exist for the management of mucinous appendiceal neoplasms, especially LAMNs and HAMNs, and PMP. In patients with PMP, CRS + HIPEC should be considered in all types of PMP, taking the potential benefits and harms into account for the histologic subtypes.[1,26,27,33-36] For instance, in patients with the aggressive high-grade PMP with signet ring cells, the value of CRS + HIPEC is limited. However, selected patients could still have a clinical benefit from CRS + HIPEC in high-grade PMP with signet ring cells, but this has to be studied in a larger subset of patients.

There seems to be no indication for standard neo-adjuvant or adjuvant systemic therapy in PMP. However, it is theoretically possible that selected patients with high-grade PMP with irresectable disease due to a high degree of tumor burden could benefit from neo-adjuvant chemotherapy.[1,38-44] On an individual level, the administration of neo-adjuvant chemotherapy could result in a situation of resectable peritoneal disease, after which CRS + HIPEC could be performed. Palliative systemic therapy can be considered in patients with irresectable or recurrent PMP, especially in patients with high-grade PMP. The administration of palliative chemotherapy could result in a prolonged survival in patients with high-grade PMP, but probably not in patients with low-grade PMP.[25,41,46-48] There are indications that patients with both

low- and high-grade PMP could possibly benefit from the use of targeted therapy.[45] However, it should be noted that the obtained evidence on patient management is mainly based on the experience of a few tertiary centers.

Moreover, the present insights into appendiceal mucinous neoplasms including LAMNs are largely derived of collected samples by hospitals and pathology archives.[20] Data on lesions that were previously assumed to be non-malignant lesions are usually not recorded by cancer registries. For example, in the Netherlands Cancer Registry only in case of PMP, data on the primary appendiceal lesions as LAMNs and HAMNs are registered. In addition, due to the new classification of mucinous appendiceal neoplasms, the available data of these tumors might be contaminated, as some LAMNs were probably classified as well-differentiated mucinous adenocarcinomas, resulting in incorrect survival rates in retrospective or population-based studies. However, if collected properly, population-based data could be of value for future research in reflecting the clinical course of the disease and the use and effect of treatments in daily practice.

Disclosure

The authors have stated that they have no conflicts of interest.

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