Review Article

Narrative review of appendiceal pseudomyxoma peritonei

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Background and Objective: In the US, the overall incidence of appendiceal neoplasm is 2.8/1,000,000 per year and is present in <2% of all appendectomy specimens. The rarity of this disease is arduous for clinicians as there are few randomized controlled trials to offer evidence-based approaches to care. Previously, there were inconsistencies in terminology and classifications for appendiceal neoplasms, but there have been significant contributions from multiple societies to reduce the confusion. The objective of this review is to discuss appendiceal tumors histologically, pathologically, and discuss treatment options.

Methods: A narrative review was conducted in the month June 2022. A search on PubMed and MEDLINE were done containing the search terms "HIPEC", "appendiceal", and "neoplasm" was used. The articles were reviewed independently and then discussed in a collaborative group setting to discuss which articles would be included in this review.

Key Contents and Findings: We detail the various histologic entities of appendiceal tumors that can result in pseudomyxoma peritonei (PMP), discuss potential pathophysiology, examine the underlying genetics of PMP, and present treatment options including cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemoperfusion (HIPEC).

Conclusions: Although the current available classification provides a framework for PMP diagnosis and treatment, there still lacks a comprehensive system that includes both the primary tumor and PMP. As such, the goal of this review was to provide further clarification on different histologic findings, genetics, diagnostic workup, and treatment for appendiceal neoplasm.

Keywords: Pseudomyxoma peritonei (PMP); appendiceal neoplasm; cytoreductive surgery (CRS); hyperthermic intraperitoneal chemoperfusion (HIPEC)

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Introduction

Appendiceal neoplasm was first identified in 1842 by Rokitansky in a description of mucous filled appendix, termed mucocele. Despite the early description of this singular entity, appendiceal neoplasms represent a heterogenous, yet unique, group of rare tumors with a wide spectrum of both benign and malignant behaviors. In the US, the overall incidence is 2.8/1,000,000 per year and is present in <2% of all appendectomy specimens (1,2). A recent population-based study examining the incidence of appendiceal malignancies in the United States and Canada demonstrated a significant increase during period of 2000–2016 (3). Nonetheless, appendiceal neoplasm remains rare and the associated risk factors remain incompletely

Table 1 Search parameters

Iterms	Specification
Date of search	6/28/2022
Databases	PubMed and MEDLINE
Search terms	HIPEC and/or appendiceal and/or neoplasm
Timeframe	2/1994–1/1/2022
Inclusion criteria	Only English articles were evaluated, and only information on appendiceal neoplasms were included
Selection process	Information was conducted independently by reviewers and discussed in a collaborative setting to adequately create a comprehensive review
Any additional considerations, if applicable	This is not a systematic review, as a result PRISMA guidelines were not used in this study

HIPEC, hyperthermic intraperitoneal chemoperfusion.

understood. Currently, it is hypothesized that the underlying mechanism of pathogenesis is thought to be multifactorial including age, obesity, lifestyle factors, and environment (1). The clinical presentation ranges from incidental findings on imaging to vague abdominal discomfort, to acute abdominal pain mimicking appendicitis. In advanced stages, patients can present with abdominal distention, bloating, and oral intolerance due to peritoneal mucinous tumor accumulation, also known as pseudomyxoma peritonei (PMP). This is a dreaded pathology which occurs in approximately in 20% of patients and is a result of either benign or malignant mucinous spread. Patient prognosis and treatment options are highly variable and dependent on multiple variables including underlying primary tumor histology, volume of PMP and location of mucinous deposits. The purpose of this review is to detail the various histologic entities of various appendiceal tumors that can result in PMP, discuss potential pathophysiology, review the genetics of PMP, and outline the diagnostic workup and treatment options. We present this article in accordance with the Narrative Review reporting checklist (available at https://dmr.amegroups.com/article/view/10.21037/dmr-22-46/rc).

Methods

A narrative review was conducted in the month June 2022. A search on PubMed and MEDLINE were done containing the search terms "HIPEC", "appendiceal", and "neoplasm" was used. The articles were reviewed independently and then discussed in a collaborative group setting to discuss which articles would be included in this comprehensive review. Only English articles were evaluated and information only dealing with appendiceal neoplasms were included (*Table 1*).

PMP

PMP is a clinical syndrome that results from the intraperitoneal deposition and spread of mucinous ascites from the primary appendiceal mucinous neoplasms within the abdominopelvic cavity. This incredibly rare syndrome has an incidence of approximately 0.2 per 100,000 per year (4). Patients typically present with abdominal fullness, discomfort, early satiety, constipation, and at times with intestinal obstruction. A wide differential diagnosis includes non-gastrointestinal (GI) causes such as gynecologic malignancies and GI causes such as the appendix, colon, urachus, and pancreas. On diagnostic imaging, the patient may exhibit "omental caking" which is a result of excessive mucin accumulation on the omentum (5-9). Due to the fluid distribution within the peritoneal cavity, mucinous deposits are often observed along the subphrenic, subhepatic, hepatorenal, perisplenic, perigastric, periportal, mesenteric, or pelvic regions. Moreover, the excessive accumulation can result in mucin-filled umbilical or inguinal hernias. Overall, PMP is defined according to several notable characteristics: (I) the presence of mucinous ascites; (II) the predictable redistribution of the tumor within the abdominal cavity; (III) typically of an appendiceal origin, including low-grade appendiceal mucinous neoplasm (LAMN), high-grade appendiceal mucinous neoplasm (HAMN), or mucinous adenocarcinoma (MACA) (7,10-12).

The process of appendiceal PMP development is a result of mucinous neoplasm perforation, rupture, or

Table 2 Comparison of 2016 PSOGI consensus guidelines (16), 2017 AJCC staging system, 8th edition (17), and 2019 WHO classification of tumors, 5th edition (19)

2016 consensus PSOGI	2017 AJCC staging system, 8th edition (TNM)	2019 WHO, 5th edition
Acellular mucin	M1a	PM1a
Low grade mucinous carcinoma peritonei	M1b, G1, well differentiated	PM1b, grade 1
High grade mucinous carcinoma peritonei	M1b, G2 or G3, moderately or poorly differentiated	PM1b, grade 2
High grade mucinous carcinoma peritonei with signet-ring cells	M1b, G3, poorly differentiated PMCA-S	PM1b, mucinous tumor deposits with signet-ring cells

PSOGI, Peritoneal Surface Oncology Group International; AJCC, American Joint Committee on Cancer; WHO, World Health Organization; TNM, tumor, lymphnodes, metastasis; G, grade; PMCA-S, peritoneal mucinous carcinomatosis with signet ring cells.

metastasis. The released epithelial cells or metastasis of malignant cells are commonly deposited in the omentum and along the peritoneal linings. Exfoliation of the cells from these initial deposits further accumulates throughout the abdominal cavity via "redistribution phenomenon" (13). Redistribution explains that in particular predetermined sites of the abdominal cavity, there may be more tumor burden as compared to other sites. Physiologic mechanisms responsible for the striking contrast in distribution include peritoneal fluid flow patterns, sites of fluid reabsorption, and gravity in conjunction with the non-adhesive properties of the primary tumor epithelial cells.

Stemming from multiple causes of PMP from both non-GI and GI in origin, PMP is classified through multiple competing systems. The classification systems consist of Ronnett three-tier system (8), the Bradley two-tier system (14), and the World Health Organization (WHO) two-tier system (15). These systems represent diverse clinical interpretations, variable pathological characteristics, and elusive nature. Unfortunately, the use of multiple tier systems has proven disadvantageous for PMP diagnosis for several reasons. For example, Ronnet's three-tier system includes non-appendiceal PMP, while the Bradley and WHO systems do not include signet ring cell histology and its associated prognosis (8,14,15). Discrepancies such as this are responsible for heterogeneity between results from different research centers rendering comparison of similar or identical studies non-conducive. The result is a significant variation in diagnosis, treatment and patient prognosis.

A consensus on the classification and diagnostic terminology of PMP is imperative, as it will elucidate its diagnosis, prognosis, and treatment options. In 2016, the Peritoneal Surface Oncology Group International (PSOGI) published a written consensus on the diagnostic terminology and classification of PMP (16). PSOGI classifies PMP into four different categories: (I) acellular mucin; (II) low-grade mucinous carcinoma peritonei (LMCP); (III) high-grade mucinous carcinoma peritonei (HMCP); (IV) high-grade mucinous carcinoma peritonei with singlet ring cells (HMCP-S). Acellular mucin is defined as mucin lacking neoplastic epithelium and may be distant from or confined to the organ surface. LMCP has low-grade cytology, few tumoral mucinous epithelium (<20% of tumor volume), and rare mitoses. Conversely, HMCP presents with high-grade cytology, metastatic and invasive nature, and contains neoplastic mucinous epithelium (>20% of tumor volume). Lastly, HMCP-S is recognized as tumor with signet ring cell component (≥10%). Due to PSOGI classification system's inclusion of mucin histology and subsequently its role in patient prognosis, it is widely utilized by specialists managing patients with PMP. The 8th edition American Joint Committee on Cancer (AJCC) staging system distinguished between the dissemination of acellular mucin as M1a and cellular mucin as M1b in 2017 (17). M1b is further categorized into a well-differentiated grade (G1), moderately differentiated (G2), and poorly differentiated (G3). Of note, histology should be obtained from the peritoneal disease, not the primary itself. Following AJCC, in 2019 the World Health Organization published a similar classification system as PSOGI and a similar grading system to AJCC (18) (*Table 2*).

Pathology

There are multiple, yet distinct appendiceal histologic entities that contribute to PMP. For the purposes of this review, we will discuss the pathologic characteristics of low-grade and high-grade mucinous neoplasms, MACA, and goblet cell carcinoma (GCC), utilizing prognosis-based

classification systems including PSOGI histopathologic classification, AJCC 8th edition, and the Tang classification system (20).

Low-grade appendiceal mucinous neoplasms (LAMNs)

LAMN represents an indolent and benign overgrowth of intraluminal mucinous cellular proliferation (3). Histologically, LAMN exhibit cellular atypia with a monolayer of cells with small, basally-located nuclei, abundant cytoplasmic mucin, and rare mitosis (3). These features are exemplary of "low-grade" cytology. Macroscopically, the appendix may be normal or have cystic dilation due to increased intraluminal pressure from mucin accumulation. The effacement of lamina propria is frequently observed with occasional obliteration of the muscularis mucosa (3). The result is a thin, fibrous wall with calcification, which is often visualized in cross sectional imaging. The excessive dilation from the accumulated mucin can result in dissection of the mucin through the appendiceal wall (7). Serosal surfaces of the appendix containing mucinous deposits are associated with neovascularization, in which mucin notably contains many capillaries containing luminal red-blood cells (7). With the dilated weakened walls, appendiceal rupture may occur with subsequent spread of mucinous deposits on the visceral peritoneum (21). The examination of the mucin typically reveals acellularity. However, the presence of the extra-appendiceal neoplastic epithelium is indicative for worse prognosis.

Genetic assessment of LAMN revealed frequent somatic mutations in the proto-oncogene Kirsten rat sarcoma virus (*KRAS*) and guanine nucleotide binding protein, alpha stimulating activity peptide (*GNAS*) genes, in approximately 50% of examined specimen (22). Despite the traditional role of KRAS in various cellular processes including proliferation and differentiation through the mitogen-activated protein kinase (MAPK) pathway and of GNAS association with mucin production, the role of these genes in LAMN development remains unclear (4). Interestingly, few studies exist examining the correlation of these mutations with peritoneal dissemination and to treatment response. These studies failed to demonstrate the mechanistic roles of *KRAS* or *GNAS* in peritoneal spread but rather suggested the mutation as a marker of early tumorigenesis. As such, several recent studies utilizing next-generation sequencing techniques including deep-sequencing have identified additional mutations in LAMN, including *CTNNB1*, *NOTCH1*, *NOTCH4*, *APC*, *MET*, and *PIK3CA* (23-25). However, further molecular studies are lacking to truly understand to the mechanism of tumorigenesis.

High-grade mucinous neoplasms (HAMNs)

HAMNs exhibit cytologic atypia with loss of polarity with full-thickness nuclear stratification, hyperchromatic and enlarged nucleus, and numerous mitotic figures. However, they are classified as neoplasms due to lack of infiltrative invasion (7). Similar to LAMN, HAMN exhibit loss of normal mucosal architecture including loss of lamina propria, muscularis mucosa and submucosa fibrosis (8). The changes to the appendiceal wall and the architecture distortion parallel that of LAMN (4). High-grade mucinous deposits containing neoplastic epithelium on the visceral peritoneum should be considered MACA, not HAMN (8). Unfortunately, there are limited number of published studies that clearly distinguish this particular entity from adenocarcinoma. The examination of the discordance in diagnostic terminology from a high-volume center revealed potential inaccurate pathologic assessment resulting in diagnosis of LAMN or MACA. Cases that present with such neoplasms lining the visceral peritoneum are likely a consequence of MACA and warrant a thorough evaluation of the appendix for perforation and invasive adenocarcinoma (26).

Due to difficulty in histologic differentiation of LAMN and HAMN, genetic studies conducted identified an increasing incidence of tumor protein 53 (*TP53*) and ataxia-telangiectasia mutated (*ATM*) in HAMN (14). Despite these differential genetic mutations, the role of either *TP53* or *ATM* in contribution to high-grade cytology or prognosis remains inconclusive.

Mucinous appendiceal adenocarcinoma (MACA)

MACA is differentiated from LAMN and HAMN due to its invasion potential and infiltrative capacity similar to other carcinomas with extracellular mucin comprising greater than 50% of the histologically examined area. Microscopically, there is evidence of basement membrane destruction by the infiltrative tumor cells. The tumor cells demonstrate high-grade cytology with exhibition of features such as decreased nuclear polarity, enlarged nuclei with full-thickness stratification, increased mitotic figures, and prominent nucleoli. Histologically, MACA can be separated into three categories of well-, moderately-, or poorly-differentiated based on the degree of nuclear atypia and

gland formation (20). In addition, poorly-differentiated MACA can exhibit further aggressive biologic behavior by containing signet ring cells. If less than 50% of the cells are signet cells, the tumor is classified as poorly differentiated adenocarcinoma with signet ring features. On the other hand, if there are greater than 50% of the cells are signet cells, the tumor is classified as mucinous signet ring cell carcinoma.

Similar to their non-invasive counterparts, MACA frequently exhibit mutations in *KRAS* and *GNAS*. Further molecular studies in comparison of LAMN to MACA have identified *MYC* amplification, *TP53* mutation, and loss of SMAD4 expression (24,27,28). Interestingly, SMAD4 loss was dependent on loss of heterozygosity of chromosome 18 with a correlation between loss of heterozygosity and worse overall survival (OS) in these patients. Davison *et al.* previously studied the role of the SMAD4 protein, a major component of the TGF-β pathway, in low- and high-grade appendiceal neoplasms. Through this study, SMAD4 expression was found to be associated with poor prognosis of carcinomas of the GI tract. Their results show that SMAD4 protein expression is significantly correlated with overall tumor-grade (P<0.0003) (28). Notably, they discovered that all tumors lacking SMAD4 expression were cytologically high-grade, whereas all tumors with preserved SMAD4 protein expression were low-grade (28).

Appendiceal GCC

Appendiceal GCC represents a distinct subtype of appendiceal neoplasms with infiltrative and invasion capacity that exhibit both exocrine and endocrine phenotypes. Microscopically, the tumors are comprised of infiltrating tubular glands containing goblet cells with a variable number of endocrine and Paneth cells. The cells demonstrate small compressed nuclei with intracytoplasmic mucin. Detailed immunohistochemistry assessments for GCC are helpful to differentiate this particular entity from other appendiceal neoplasms. Particularly, GCC are usually positive for markers which suggest a lower GI origin such as CK19, CK20, CDX2, and carcinoembryonic antigen (CEA) (29). GCC also have increased CK7 expression compared to other appendiceal neoplasms. Moreover, GCC can be positive for chromogranin A and synaptophysin, specifically in neuroendocrine cells (30). Unique to GCC is the Tang classification. This system is utilized to further categorize these tumors into three classes: (I) group A tumors that are characterized by well-defined goblet cell morphology, clustered cellular or cohesive linear arrangement, minimal architectural distortion, and minimal cytologic atypia; (II) group B carcinomas are characterized by presence of signet ring cells with significant cellular atypia, an irregular, large clustered-cell arrangement, desmoplasia, obliteration of the appendiceal wall and lack of confluent sheets of cells; (III) group C adenocarcinomas are defined by poorly differentiated histology with at minimum focal evidence of goblet cell morphology which may present as gland formation, undifferentiated carcinoma or confluent sheets and or signet ring cells (30-32). Particularly for stage IV disease, Tang classification corresponded with patient prognosis with matched 5-year survival of 100%, 38%, and 0% for groups A, B, and C, respectively (32).

GCC are genetically distinct from LAMN, HAMN, and MACA, with rare *KRAS*, *GNAS*, and *SMAD4* mutations. Interestingly, *TP53* mutations are observed at higher rates (31%) in comparison to other genes (29). Moreover, *ARID1A*, *ARID2*, *CHD1*, *RHNP2*, and *MLL2* mutations were among the most prevalent. Nonetheless, comprehensive genetic profiling and accompanying molecular studies for these tumors are lacking and are needed to further understand their tumorigenesis.

Overall, these are distinct primary appendiceal tumors that have the potential to cause PMP. Despite the current pathologic and genetic understanding of these tumors, further work is needed understand the underlying molecular mechanism of tumorigenesis and PMP development.

Diagnosis and workup

Stemming from wide range of histologic subtypes to disease progression, comprehensive patient assessment is essential. Thorough histological assessment of the resected primary specimen or biopsied tumors should be evaluated by an experienced pathologist at an experienced, high-volume center. Additionally, cross sectional imagining is important to assess the location and the burden of disease. Contrast-enhanced computed tomography (CT) of the chest, abdomen and pelvis and/or magnetic resonance imaging (MRI) is required to assess the location and burden of disease. CT remains the mainstay imaging modality due to accessibility and ease of interpretation. Reported sensitivities of CT scan detecting lesions <5 cm is 59–94% to 19–28% for lesions <1 cm and only 11–28% identifying lesions <0.5 cm (33). With increased accessibility and prevalence of MRI, MRI is an acceptable alternative to CT. Uniquely, MRI is able to utilize the main component of PMP, mucin,

and is able to highlight the detection in T2 weighted and diffusion sequences (33). Protocolized peritoneal MRI scans use key elements of fat suppression on T2 weighted imaging and high spatial resolution to improve tumor and mucin detection. Recent studies have demonstrated significant capacity of MRI in evaluation in subtle tumors along the small bowel and mesentery or in the hepatic hilar region, allowing preoperative determination of surgical resectability without the need for an exploratory operation (34-36). More importantly, MRI does not subject the patient to added radiation, which is a benefit in contrast to CT.

Although not diagnostic, tumor markers play a potential role in utilization of neo-adjuvant therapy, intra-operative decision making and post-treatment surveillance. Tumor markers including CEA, CA19-9 and carbohydrate antigen-125 (CA-125) can be helpful when expressed. For example, normalization of pre-operative CEA and CA19-9 was demonstrated to be correlated with improved patient OS following complete surgical resection (36,37).

Endoscopic evaluation with upper esophagogastroduodenoscopy or colonoscopy is highly recommended to ensure proper diagnosis of the primary tumor and to guide multimodal therapy. In addition, additional findings through the endoscopic assessment may potential guide surgical treatment. Multidisciplinary tumor board discussion is essential in treatment planning and sequencing. Following the completion of diagnostic workup, the treatment is stratified based on the histologic confirmation, location, and volume of disease.

Moreover, surgical exploration (laparoscopic or open) of the abdominal cavity can provide significant information regarding pathology, location, and burden of disease. There are two established staging systems for describing peritoneal carcinomatosis including the Gilly peritoneal carcinomatosis staging and the Peritoneal Cancer Index (PCI). The Gilly system was developed in Lyon, France in the 1990s as a reporting system for lesion sizes identified at the time of surgery and also to provide prognostic information. Although previously validated in a prospective multi-center EVOCAPE study, the Gilly system lost favor mainly due to inability to quantitate distribution of disease particularly in Gilly stage 3 or 4 disease (38,39).

In comparison, the PCI score established by Paul Sugarbaker assesses the severity of tumor burden intraoperatively by delineation of the abdomen into 9 sections and considers 4 additional sections of the small intestine (40). Each region is designated a legion-score (LS) of 0–3 with a total possible score of 39 points. A higher PCI score is an independent factor for poor prognosis. LS-0 corresponds to no visible tumor; LS-1 corresponds to tumor diameter ≤0.5 cm; LS-2 corresponds to tumor diameter of 0.5–5.0 cm; LS-3 indicates tumor diameter of >5.0 cm. PCI scoring helps identify specific areas within the abdominal cavity where the peritoneum may be stripped or removed and suggests whether effective cytoreductive surgery (CRS) is possible (41). Unfortunately, the PCI does have limitations in accurate assessment of mucinous tumors including PMP. As such, the field is still in search of better staging and prognostic tools to provide a more accurate staging workup and prognostic forecast.

Similarly, completeness of cytoreduction (CC) score is also an independent prognostic factor for PMP and serves as both an objective quantitative index and plays a significant role in the standardization of CRS. CC-0 corresponds with no residual tumor deposits after cytoreduction; CC-1 corresponds with residual tumor deposits of diameter <2.5 mm; CC-2 corresponds with residual tumor deposits of diameter between 2.5 mm to 2.5 cm; lastly CC-3 indicates presence of residual tumors with diameter >2.5 cm (42).

Treatment

LAMN

For localized LAMN with no evidence of peritoneal spread, a surgical exploration with an appendectomy is usually the only treatment required (43-45). Following appendectomy with negative margins and no perforation, the patient has completed treatment and surveillance. However, if there are positive margins, the current recommendation is for a cecetomy or ileocectomy to further clear the margins. A formal right hemicolectomy is not needed as there is no need for lymphatic staging due to the lack of invasive capacity. If there is evidence of peritoneal spread or extra-appendiceal mucin, consideration for CRS and hyperthermic intraperitoneal chemoperfusion (HIPEC) is required. Even in the setting of PMP, there is no role for systemic chemotherapy due to the lack of invasive potential.

HAMN

For HAMN, there lacks a clear recommendation for treatment. However, the consensus among the expert centers around the world is that HAMN should be treated like adenocarcinoma. As such, a simple appendectomy with negative margins, cecetomy or ileo-cecetomy is insufficient.

Table 3 Overview of treatment for appendiceal malignancies

Type of appendiceal cancer	Treatment
LAMN	Appendectomy unless positive margins in which patient will undergo ileocectomy or cecetomy
HAMN	Right hemicolectomy if it is localized disease. Patients with peritoneal spread will undergo CRS + HIPEC
Adenocarcinoma	In patients with high probability of complete resection, upfront CRS + HIPEC is recommended. Patients with high volume disease or has inoperable tumor, systemic chemotherapy for a duration of 3–6 months with re-staging for potential resection
GCC	Localized disease requires right hemicolectomy with/without adjuvant systemic therapy. For patients with Tang A disease can undergo CRS + HIPEC. Tang B or C classification usually requires upfront chemotherapy for 3–6 months followed by restaging for resectability

LAMN, low-grade appendiceal mucinous neoplasm; HAMN, high-grade appendiceal mucinous neoplasm; GCC, goblet cell carcinoma; CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemoperfusion.

Therefore, HAMN requires a formal right hemi-colectomy even for a localized disease (33,46). In setting of peritoneal spread, careful review of the pathology is necessary to rule out any evidence of carcinoma. If the pathology confirms HAMN with PMP, CRS + HIPEC is recommended. Systemic chemotherapy for these patients is also reserved, similar to LAMN.

Appendiceal adenocarcinoma

Patients diagnosed with adenocarcinoma require a complete staging workup including tumor markers, diagnostic imaging, and colonoscopy. If there is no evidence of extra-appendiceal disease, a right hemicolectomy is recommended (47,48). Pending the staging of the disease from the final pathology, patients may require additional systemic chemotherapy, which is typically a 5-fluorouracil (5-FU) based regimen followed by surveillance. If there is evidence of peritoneal spread, the treatment strategy is further stratified based on histologic grade, volume and location of the disease. Well-differentiated adenocarcinoma is thought to be less aggressive in comparison to moderate or poorly differentiated cancer. As such, upfront CRS + HIPEC may be recommended in patients with high probability of complete resection. In patients with high volume disease or a disease location that is inoperable, consideration for systemic chemotherapy can be discussed in a multidisciplinary setting. For patients with moderate to poorly differentiated histology, systemic chemotherapy for duration of 3–6 months with interval re-staging for potential resection is recommended. In patients with progressive disease while on systemic therapy, 2nd line therapy or a clinical trial is usually preferred.

Appendiceal GCC

Similar to patients diagnosed with appendiceal adenocarcinoma, the treatment strategy for GCC is dependent on the stage of the disease. Localized disease, regardless of margin status on appendectomy specimen, requires right hemicolectomy with or without adjuvant systemic therapy, pending final pathologic staging (49). For patients with extraperitoneal disease, there is further stratification of treatment based on the Tang classification. For Tang A disease, patients with burden of disease are considered resectable, CRS ± HIPEC may be considered (50). Systemic therapy is reserved for a patient that is deemed unresectable as the prognosis for this particular histology is favorable. Unlike Tang A classification, patients with Tang B or C classification usually require upfront systemic chemotherapy for 3–6 months followed by a restaging workup for resectability (*Table 3*). If the patient has response to treatment or stable disease with favorable volume of disease, CRS ± HIPEC is recommended. In patients with progressive disease or unfavorable volume of disease, systemic therapy and/or clinical trial is recommended.

CRS + HIPEC

CRS + HIPEC is a two-step operation that entails surgical removal of macroscopic tumors and intraperitoneal perfusion of chemotherapy to eradicate microscopic disease. CRS entails surgical resection of visible tumors and associated intraabdominal organs or structures with

goal of complete removal. Following complete removal of disease, HIPEC is performed through surgically placed catheters and instillation of heated chemotherapy [typically mitomycin C (MMC) at 42 ℃] using a perfusion machine for 90–100 minutes.

Many studies report an impact on OS and disease-free survival (DFS) in PMP patients treated with the now widely accepted CRS + HIPEC (13,43,51,52). Vaira *et al.* published another 12-year study analyzing the results of 53 PMP patients treated with CRS + HIPEC, their OS, and disease-free survival. They found OS of 5 and 10 years to be 94% and 84.6% respectively. Disease free survival was 80% and 70% for 5 and 10 years respectively (53). Another large study conducted in 1999 by Sugarbaker cites the results of CRS + HIPEC on 385 patients with peritoneal surface spread of appendiceal malignancy. Patient morbidity and mortality rates were 27% and 2.7%, respectively (51). Sugarbaker's results identify completeness of cytoreduction ($P<0.0001$), the extent of previous surgical interventions ($P=0.001$), and histopathological character of appendiceal malignancy ($P<0.0001$) to be prognostic markers of survival (42). Lastly, Grotz *et al.* published a study showing the efficacy of CRS + HIPEC in moderately and poorly differentiated appendiceal adenocarcinoma. They examined 116 patients and demonstrated that the 83 patients who underwent CC0 or CC1 cytoreduction had a median DFS of 23 months in comparison to CRS and HIPEC which had a median OS of 48 months (52). At this time, PSOGI recommends that patients undergoing neo-adjuvant or adjuvant systemic chemotherapy (typically a combination of 5-FU, oxaliplatin, or irinotecan with biologic therapy) for high grade PMP ± signet ring cells in addition to CRS and HIPEC (33). When resection is unattainable and maximal tumor debulking (MTD) or "palliative surgery" must be discussed on a case by case basis. Due to lack of level 1 evidence, quality of life (QoL) must be considered when making decisions of MTD. According to PSOGI 2020 guidelines, there is a general consensus of pursuing MTD if it can improve QoL. These procedures include colonic resections, mucin evacuation, pelvic and parietal peritonectomies and even the addition of HIPEC (33).

As with all novel therapies, one must consider the efficacy of the treatment, its potential complications, side-effects, impact on OS, and, perhaps most importantly, the QoL of the patient. High-risk factors for patients with PMP include but aren't limited to the long anesthesia and operation time, extensive resections throughout the surgery, and heavy tumor burden. Perioperative venous thrombosis, bleeding, infection, anastomotic leakage, and postoperative hypermyoglobinemia are among the adverse events that patients may experience. Sugarbaker *et al.* addressed this in a 2006 study utilizing common toxicity grading criteria applied to 8 categories (54). These categories were evaluated on a grade I to V with grade IV indicating an adverse event requiring urgent intervention, and grade V indicating the event led to a patient death. Out of the 356 procedures involving CRS, peritonectomy, and HIPEC, 2% mortality within 30 days post-operation was observed. Additionally, 19% of the procedures involved at least one grade IV adverse event complication, and 11.1% of patients required further operation (55). During CRS, histology can determine DFS and OS, specifically high-grade subtypes, adenocarcinoma, and signet ring cell. Absolute contraindications to CRS + HIPEC that recommended by PSOGI include extensive small bowel serosa involvement and mesenteric retraction. Relative contraindications include liver hilum/porta involvement, extensive infiltration of the pancreatic surface, and ureteric obstruction (33).

HIPEC regimens have remained controversial since their first applications in the 1980s. Oxaliplatin and MMC are among the most popular regimens deployed today and are typically administered in lower doses due to their hemorrhagic complications. Model Oxaliplatin regimens include the "Elias high-dose oxaliplatin regimen" (56), "Glehen medium-dose oxaliplatin regimen" and "Wake Forest University oxaliplatin regimen" (57). Similarly, several model regimens exist for MMC: (I) "Dutch High-Dose Mitomycin C Regimen: 'Triple dosing Regimen'" (55); (II) "Sugarbaker Regimen" (58); (III) the "American Society of Peritoneal Surface Malignancy Low Dose Mitomycin-C regimen: 'Concentration Based Regimen'" (59). The consensus among these various regimens is highly debated due to the lack of significant evidence from properly conducted randomized trials. However, most agree that true efficacy evaluation of these therapeutic drugs and regimens relies on randomized control trials. As of right now, there are multiple studies discussing the efficacy and safety of MMC *vs.* oxaliplatin, with newer studies expressing there is limited difference in safety and efficacy, and an older study showing that MMC is safer than oxaliplatin (60-62). To achieve more accurate multicenter clinical trials and retrospective large sample analyses, standardizing HIPEC methods, temperature, and duration are required. Finally, recurrence in PMP after CRS + HIPEC is incredibly rare 5- and 10-year post operation, which is variable based on histology. If recurrence does occur, further evaluation will

need to be taken in order to determine if the patient should undergo repeat surgery (63).

Systemic chemotherapy

Due to the rarity of the disease, there are limited studies assessing the efficacy of systemic chemotherapy in patients with appendiceal neoplasms. However, similar to other GI malignancies, multimodal therapy with and without systemic chemotherapy for patients with appendiceal neoplasms should be carefully considered in a multidisciplinary tumor board setting. In patients with diagnosis of LAMN, systemic chemotherapy remains ineffective due to the biologic, indolent nature of the disease (64-66). In comparison, systemic therapy is utilized in patients with MACA or GCC diagnosis, similar to colorectal cancer (67). The regimen utilized is extrapolated from the colorectal cancer studies which include 5-FU based regimens such as FOLFOX, FOLFIRI, or FOLFOXIRI with and without biologic therapy. The sequencing and timing of the chemotherapy remains controversial with studies suggesting for both pre-operative, post-operative, or both (68). Finally, there are considerations for clinical trials involving KRAS, p53, GNAS, SMAD4, APC, ATM, PIK3CA, FBXW7, and BRAF (69).

Novel therapies

In later stages of PMP, patients accumulate mucin in their intra-abdominal cavity which promotes an inflammatory/fibrotic reaction causing bowel obstruction, malnutrition and even mortality. Additionally, deregulated expression of mucin contributes to tumorigenesis and metastasis. Principles of mucolytic therapy for PMP include dissolving the mucin, which decreases abdominal compression and improves CRS + HIPEC success. Some agents that have been studied include celecoxib, dexamethasone, N-acetylcysteine (NAC) and bromelain. Celecoxib and dexamethasone have been shown to inhibit extracellular mucin production by targeting the inflammatory cascade, which downregulates mucin production (70). NAC, on the other hand, decreases mucin viscosity by reducing disulfide bonds and possesses antioxidant and anti-inflammatory properties. Finally, bromelain is a mixture of proteolytic and non-proteolytic enzymes extracted from pineapple which has immunomodulatory, anti-inflammatory and anti-neoplastic effects. Bromelain and NAC may be used in conjunction or separately to potentially improve symptoms and QoL in patients with PMP (71).

Conclusions

With updated guidelines from AJCC, PSOGI, and WHO, there is a greater consensus on nomenclature of appendiceal neoplasms. As covered in this review, the mechanism of the PMP is considerably different per individual benign or malignant neoplasms. Although the current available classification provides a framework for PMP diagnosis and treatment, there still lacks a comprehensive system that includes both the primary tumor and PMP. As such, the goal of this review was to provide further clarification on different histologic findings, genetics, diagnostic workup, and treatment for appendiceal neoplasm. While there have been excellent retrospective reviews, there still exists lack of level 1 evidence for PMP management stemming from the disease rarity. Data sharing among institutions has been the pillar for retrospective reviews in order to provide insight into treatment options. Currently, multiple expert consensus guidelines state that multimodal therapy including CRS + HIPEC should be considered whenever possible. Additionally, the use of systemic chemotherapy is recommended to be reserved for higher grade tumors including GCC and MACA (67). Novel therapies such as anti-mucin therapy have been promising in improving patient's symptoms and QoL. Despite some advances in the field, there is still need for better understanding of this rare disease with a goal of improving patient outcomes through innovative therapies.

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References

1. Shaib WL, Goodman M, Chen Z, et al. Incidence and Survival of Appendiceal Mucinous Neoplasms: A SEER Analysis. Am J Clin Oncol 2017;40:569-73.
2. Singhi AD, Davison JM, Choudry HA, et al. GNAS is frequently mutated in both low-grade and high-grade disseminated appendiceal mucinous neoplasms but does not affect survival. Hum Pathol 2014;45:1737-43.
3. Singh H, Koomson AS, Decker KM, et al. Continued increasing incidence of malignant appendiceal tumors in Canada and the United States: A population-based study. Cancer 2020;126:2206-16.
4. Smeenk RM, van Velthuysen ML, Verwaal VJ, et al. Appendiceal neoplasms and pseudomyxoma peritonei: a population based study. Eur J Surg Oncol 2008;34:196-201.
5. Pai RK, Longacre TA. Appendiceal mucinous tumors and pseudomyxoma peritonei: histologic features, diagnostic problems, and proposed classification. Adv Anat Pathol 2005;12:291-311.
6. Young RH. Pseudomyxoma peritonei and selected other aspects of the spread of appendiceal neoplasms. Semin Diagn Pathol 2004;21:134-50.
7. Carr NJ, Finch J, Ilesley IC, et al. Pathology and prognosis in pseudomyxoma peritonei: a review of 274 cases. J Clin Pathol 2012;65:919-23.
8. Ronnett BM, Zahn CM, Kurman RJ, et al. Disseminated peritoneal adenomucinosis and peritoneal mucinous carcinomatosis. A clinicopathologic analysis of 109 cases with emphasis on distinguishing pathologic features, site of origin, prognosis, and relationship to "pseudomyxoma peritonei". Am J Surg Pathol 1995;19:1390-408.
9. Järvinen P, Lepistö A. Clinical presentation of pseudomyxoma peritonei. Scand J Surg 2010;99:213-6.
10. Carr NJ, Sobin LH. Unusual tumors of the appendix and pseudomyxoma peritonei. Semin Diagn Pathol 1996;13:314-25.
11. Rosenberger LH, Stein LH, Witkiewicz AK, et al. Intraductal papillary mucinous neoplasm (IPMN) with extra-pancreatic mucin: a case series and review of the literature. J Gastrointest Surg 2012;16:762-70.
12. Agrawal AK, Bobiński P, Grzebieniak Z, et al. Pseudomyxoma peritonei originating from urachus-case report and review of the literature. Curr Oncol 2014;21:e155-65.
13. Sugarbaker PH. Pseudomyxoma peritonei. A cancer whose biology is characterized by a redistribution phenomenon. Ann Surg 1994;219:109-11.
14. Bradley RF, Stewart JH 4th, Russell GB, et al. Pseudomyxoma peritonei of appendiceal origin: a clinicopathologic analysis of 101 patients uniformly treated at a single institution, with literature review. Am J Surg Pathol 2006;30:551-9.
15. Carr N, Arends M, Deans G, et al. Adenocarcinoma of the appendix. In: World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of the Digestive System. IARC Press, 2000:93-8.
16. Carr NJ, Cecil TD, Mohamed F, et al. A Consensus for Classification and Pathologic Reporting of Pseudomyxoma Peritonei and Associated Appendiceal Neoplasia: The Results of the Peritoneal Surface Oncology Group International (PSOGI) Modified Delphi Process. Am J Surg Pathol 2016;40:14-26.
17. Overman MJ, Asare EA, Compton CC. American Joint Committe on Cancer (AJCC) cancer staging manual, 8th Edition. Appendix-Carcinoma. American Joint Committee on Cancer 2017:237-50.
18. Hoehn RS, Rieser CJ, Choudry MH, et al. Current Management of Appendiceal Neoplasms. Am Soc Clin Oncol Educ Book 2021;41:1-15.
19. Misdraji J, Carr N, Pai R. Appendiceal serrated lesions

and polyps. Appendiceal mucinous neoplasm. WHO Classifcation of Tumours of Digestive System 2019:141-6.
20. Carr NJ, Bibeau F, Bradley RF, et al. The histopathological classification, diagnosis and differential diagnosis of mucinous appendiceal neoplasms, appendiceal adenocarcinomas and pseudomyxoma peritonei. Histopathology 2017;71:847-58.
21. Carr NJ, McCarthy WF, Sobin LH. Epithelial noncarcinoid tumors and tumor-like lesions of the appendix. A clinicopathologic study of 184 patients with a multivariate analysis of prognostic factors. Cancer 1995;75:757-68.
22. Nishikawa G, Sekine S, Ogawa R, et al. Frequent GNAS mutations in low-grade appendiceal mucinous neoplasms. Br J Cancer 2013;108:951-8.
23. Liu X, Mody K, de Abreu FB, et al. Molecular profiling of appendiceal epithelial tumors using massively parallel sequencing to identify somatic mutations. Clin Chem 2014;60:1004-11.
24. LaFramboise WA, Pai RK, Petrosko P, et al. Discrimination of low- and high-grade appendiceal mucinous neoplasms by targeted sequencing of cancer-related variants. Mod Pathol 2019;32:1197-209.
25. Ang CS, Shen JP, Hardy-Abeloos CJ, et al. Genomic Landscape of Appendiceal Neoplasms. JCO Precis Oncol 2018;2:PO.17.00302.
26. Choudry HA, Pai RK, Parimi A, et al. Discordant Diagnostic Terminology and Pathologic Grading of Primary Appendiceal Mucinous Neoplasms Reviewed at a High-Volume Center. Ann Surg Oncol 2019;26:2607-14.
27. Liao X, Vavinskaya V, Sun K, et al. Mutation profile of high-grade appendiceal mucinous neoplasm. Histopathology 2020;76:461-9.
28. Davison JM, Hartman DA, Singhi AD, et al. Loss of SMAD4 protein expression is associated with high tumor grade and poor prognosis in disseminated appendiceal mucinous neoplasms. Am J Surg Pathol 2014;38:583-92.
29. Mikaeel RR, Young JP, Tapia Rico G, et al. Immunohistochemistry features and molecular pathology of appendiceal neoplasms. Crit Rev Clin Lab Sci 2021;58:369-84.
30. Holt N, Grønbæk H. Goblet cell carcinoids of the appendix. ScientificWorldJournal 2013;2013:543696.
31. Sigley K, Franklin M, Welch S. Appendiceal Goblet Cell Adenocarcinoma Case Report and Review of the Literature. Cureus 2021;13:e13511.
32. Tang LH, Shia J, Soslow RA, et al. Pathologic classification and clinical behavior of the spectrum of goblet cell carcinoid tumors of the appendix. Am J Surg Pathol 2008;32:1429-43.
33. Govaerts K, Lurvink RJ, De Hingh IHJT, et al. Appendiceal tumours and pseudomyxoma peritonei: Literature review with PSOGI/EURACAN clinical practice guidelines for diagnosis and treatment. Eur J Surg Oncol 2021;47:11-35.
34. Menassel B, Duclos A, Passot G, et al. Preoperative CT and MRI prediction of non-resectability in patients treated for pseudomyxoma peritonei from mucinous appendiceal neoplasms. Eur J Surg Oncol 2016;42:558-66.
35. Low RN, Barone RM, Lucero J. Comparison of MRI and CT for predicting the Peritoneal Cancer Index (PCI) preoperatively in patients being considered for cytoreductive surgical procedures. Ann Surg Oncol 2015;22:1708-15.
36. Low RN, Barone RM, Gurney JM, et al. Mucinous appendiceal neoplasms: preoperative MR staging and classification compared with surgical and histopathologic findings. AJR Am J Roentgenol 2008;190:656-65.
37. Carmignani CP, Hampton R, Sugarbaker CE, et al. Utility of CEA and CA 19-9 tumor markers in diagnosis and prognostic assessment of mucinous epithelial cancers of the appendix. J Surg Oncol 2004;87:162-6.
38. Sadeghi B, Arvieux C, Glehen O, et al. Peritoneal carcinomatosis from non-gynecologic malignancies: results of the EVOCAPE 1 multicentric prospective study. Cancer 2000;88:358-63.
39. Glehen O, Mithieux F, Osinsky D, et al. Surgery combined with peritonectomy procedures and intraperitoneal chemohyperthermia in abdominal cancers with peritoneal carcinomatosis: a phase II study. J Clin Oncol 2003;21:799-806.
40. Jacquet P, Sugarbaker PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. Cancer Treat Res 1996;82:359-74.
41. Harmon RL, Sugarbaker PH. Prognostic indicators in peritoneal carcinomatosis from gastrointestinal cancer. Int Semin Surg Oncol 2005;2:3.
42. Sugarbaker PH. Management of peritoneal-surface malignancy: the surgeon's role. Langenbecks Arch Surg 1999;384:576-87.
43. Yantiss RK, Shia J, Klimstra DS, et al. Prognostic significance of localized extra-appendiceal mucin deposition in appendiceal mucinous neoplasms. Am J Surg Pathol 2009;33:248-55.
44. Lo NS, Sarr MG. Mucinous cystadenocarcinoma of the appendix. The controversy persists: a review.

Hepatogastroenterology 2003;50:432-7.
45. Barrios P, Losa F, Gonzalez-Moreno S, et al. Recommendations in the management of epithelial appendiceal neoplasms and peritoneal dissemination from mucinous tumours (pseudomyxoma peritonei). Clin Transl Oncol 2016;18:437-48.
46. Shaib WL, Assi R, Shamseddine A, et al. Appendiceal Mucinous Neoplasms: Diagnosis and Management. Oncologist 2017;22:1107-16.
47. Turaga KK, Pappas S, Gamblin TC. Right hemicolectomy for mucinous adenocarcinoma of the appendix: just right or too much? Ann Surg Oncol 2013;20:1063-7.
48. Nash GM, Smith JD, Tang L, et al. Lymph Node Metastasis Predicts Disease Recurrence in a Single-Center Experience of 70 Stages 1-3 Appendix Cancers: A Retrospective Review. Ann Surg Oncol 2015;22:3613-7.
49. Rossi RE, Luong TV, Caplin ME, et al. Goblet cell appendiceal tumors--management dilemmas and long-term outcomes. Surg Oncol 2015;24:47-53.
50. Madsen AH, Ladekarl M, Villadsen GE, et al. Effects of Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in the Treatment of Goblet Cell Carcinoma: A Prospective Cohort Study. Ann Surg Oncol 2018;25:422-30.
51. Sugarbaker PH, Chang D. Results of treatment of 385 patients with peritoneal surface spread of appendiceal malignancy. Ann Surg Oncol 1999;6:727-31.
52. Grotz TE, Overman MJ, Eng C, et al. Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Moderately and Poorly Differentiated Appendiceal Adenocarcinoma: Survival Outcomes and Patient Selection. Ann Surg Oncol 2017;24:2646-54.
53. Vaira M, Cioppa T, DE Marco G, et al. Management of pseudomyxoma peritonei by cytoreduction+HIPEC (hyperthermic intraperitoneal chemotherapy): results analysis of a twelve-year experience. In Vivo 2009;23:639-44.
54. Sugarbaker PH, Alderman R, Edwards G, et al. Prospective morbidity and mortality assessment of cytoreductive surgery plus perioperative intraperitoneal chemotherapy to treat peritoneal dissemination of appendiceal mucinous malignancy. Ann Surg Oncol 2006;13:635-44.
55. Witkamp A. Dose finding study of hyperthermic intraperitoneal chemotherapy with mitomycin C in patients with carcinosis of colorectal origin. Eur J Surg Oncol 1998;(136):699-708.
56. Elias D, Bonnay M, Puizillou JM, et al. Heated intra-operative intraperitoneal oxaliplatin after complete resection of peritoneal carcinomatosis: pharmacokinetics and tissue distribution. Ann Oncol 2002;13:267-72.
57. Stewart JH 4th, Shen P, Russell G, et al. A phase I trial of oxaliplatin for intraperitoneal hyperthermic chemoperfusion for the treatment of peritoneal surface dissemination from colorectal and appendiceal cancers. Ann Surg Oncol 2008;15:2137-45.
58. Van der Speeten K, Stuart OA, Chang D, et al. Changes induced by surgical and clinical factors in the pharmacology of intraperitoneal mitomycin C in 145 patients with peritoneal carcinomatosis. Cancer Chemother Pharmacol 2011;68:147-56.
59. Turaga K, Levine E, Barone R, et al. Consensus guidelines from The American Society of Peritoneal Surface Malignancies on standardizing the delivery of hyperthermic intraperitoneal chemotherapy (HIPEC) in colorectal cancer patients in the United States. Ann Surg Oncol 2014;21:1501-5.
60. Prada-Villaverde A, Esquivel J, Lowy AM, et al. The American Society of Peritoneal Surface Malignancies evaluation of HIPEC with Mitomycin C versus Oxaliplatin in 539 patients with colon cancer undergoing a complete cytoreductive surgery. J Surg Oncol 2014;110:779-85.
61. Benzaquen E, Wang Y, Wiseman S, et al. Morbidity associated with the use of oxaliplatin versus mitomycin C in hyperthermic intraperitoneal chemotherapy (HIPEC) for peritoneal carcinomatosis of colorectal or appendiceal origin: a multi-institutional comparative study. Can J Surg 2021;64:E111-8.
62. Forsythe SD, Sasikumar S, Moaven O, et al. Personalized Identification of Optimal HIPEC Perfusion Protocol in Patient-Derived Tumor Organoid Platform. Ann Surg Oncol 2020;27:4950-60.
63. Mercier F, Dagbert F, Pocard M, et al. Recurrence of pseudomyxoma peritonei after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. BJS Open 2019;3:195-202.
64. Asare EA, Compton CC, Hanna NN, et al. The impact of stage, grade, and mucinous histology on the efficacy of systemic chemotherapy in adenocarcinomas of the appendix: Analysis of the National Cancer Data Base. Cancer 2016;122:213-21.
65. Blackham AU, Swett K, Eng C, et al. Perioperative systemic chemotherapy for appendiceal mucinous carcinoma peritonei treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. J Surg Oncol 2014;109:740-5.
66. Delhorme JB, Villeneuve L, Bouché O, et al. Appendiceal

tumors and pseudomyxoma peritonei: French Intergroup Clinical Practice Guidelines for diagnosis, treatments and follow-up (RENAPE, RENAPATH, SNFGE, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO, ACHBT, SFR). Dig Liver Dis 2022;54:30-9.
67. Lieu CH, Lambert LA, Wolff RA, et al. Systemic chemotherapy and surgical cytoreduction for poorly differentiated and signet ring cell adenocarcinomas of the appendix. Ann Oncol 2012;23:652-8.
68. The Chicago Consensus on Peritoneal Surface Malignancies: Management of Appendiceal Neoplasms. Ann Surg Oncol 2020;27:1753-60.
69. Borazanci E, Millis SZ, Kimbrough J, et al. Potential actionable targets in appendiceal cancer detected by immunohistochemistry, fluorescent in situ hybridization, and mutational analysis. J Gastrointest Oncol 2017;8:164-72.
70. Choudry HA, Mavanur A, O'Malley ME, et al. Chronic anti-inflammatory drug therapy inhibits gel-forming mucin production in a murine xenograft model of human pseudomyxoma peritonei. Ann Surg Oncol 2012;19:1402-9.
71. Sommariva A, Tonello M, Rigotto G, et al. Novel Perspectives in Pseudomyxoma Peritonei Treatment. Cancers (Basel) 2021;13:5965.

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