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Comprehensive Understanding and Evolutional Therapeutic Schemes for Pseudomyxoma Peritonei

A Literature Review

Suiting Ye, MD and Song Zheng, PhD†‡§*

Abstract: Pseudomyxoma peritonei is an infrequent solid tumor in clinical practice. The low morbidity and deficient understanding of this mucus-secreting malignant disease increase the risks of delayed identification or uncontrollable deterioration. In quite a lot cases, patients go through complete cytoreduction surgery and hyperthermic intraperitoneal chemotherapy could receive a long time survival over 5 years. But the recurrence rate is also hard to overlook. Unlike other types of cancer, the standard treatment for this considerable groups has not been confirmed yet. With the advanced medical progression, studies have been carrying out based on pathogenesis, biological characters, and mutated gene location. All but a few get statistical survival benefits, let alone the breaking progress on research or therapeutic practice in the field. We try to give a comprehensive exposition of pseudomyxoma peritonei around the epidemiology, radiologic features, clinical manifestation, present treatment and promising schemes, hoping to arise much attention and reflection on the feasible solutions, especially for the recrudescent part.

Key Words: pseudomyxoma peritonei, hyperthermic intraperitoneal chemotherapy, cytoreductive surgery, recurrence, treatment, prognosis

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Pseudomyxoma peritonei (PMP) is an infrequent clinical disease with an estimated prevalence of 1 to 3 persons per million annually.[1] PMP, described as "jelly belly," is featured with the intraperitoneal accumulation of mucin produced by malignant mucus-secreting cells in the peritoneum or omentum, which contributes to scattering and progressively aggravating mucinous ascites and gelatinous masses.[2,3] The first clinical case conformed to PMP appeared in 1842, as described by Rokitansky.[4] It was in 1884 that Werth initially put forward the term PMP and explained the origin that concerned with a mucinous carcinoma of the ovary.[5] In 1901, Frankel depicted PMP in correlation with a cyst of the appendix.[6] Recent studies have universally accepted that the appendix is the primary site, nearly 94% of cases arising from mucinous carcinoma of the appendix.[7,8] And ovary is another common origin.[9] Cases of other infrequent origins also have been reported,[7] including pancreas, stomach, gallbladder, colorectum, fallopian tubes, lung, breast, and urachus.[10–17]

From the *Fourth School of Clinical Medicine, Zhejiang Chinese Medical University; †Department of Oncology, Affiliated Hangzhou First People's Hospital; ‡Department of Oncology, Affiliated Hangzhou Cancer Hospital, Zhejiang University School of Medicine; and §Laboratory of Clinical Cancer Pharmacology and Toxicology Research of Zhejiang Province, Hangzhou, China.

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Correspondence: Song Zheng, PhD, Department of Oncology, Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine, No.261, Huansha Road, Hangzhou 310000, China. E-mail: tztree@126.com.

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CLASSIFICATIONS OF PMP

As far as existing documentation recorded, Oscar Polano was the pioneer, who separated PMP into 2 categories: the cystadenoma mucinosum peritonei simplex, and the cystadenoma malignum pseudomucinosum peritonei.[18] The former pointed to superficial implantation on the peritoneum, the latter was prone to be much invasive and presented malignant performance of penetrating abdominal cavity in greater size, spreading to more sites and even perforating the intestines. Until 1995, peritoneal mucinous tumor was officially classified into disseminated peritoneal adenomucinosis (DPAM), peritoneal mucinous carcinomatosis (PMCA), and peritoneal mucinous adenocarcinoma with intermediate features (hybrid tumors).[19] DPAM is comprised of peritoneal lesions, composed of numerous extracellular mucin-containing scant simple to focally proliferative mucinous epithelium with minimal-to-moderate cytologic atypia and inapparent mitotic activity, with or without an associated appendiceal mucinous adenoma. On the contrary, peritoneal lesions that accord with morphologic and cytologic characteristics of carcinoma as more abundant epithelium proliferate in glands, nests, or individual cells, with or without an associated primary mucinous adenocarcinoma, were separated to PMCA.[20] Hybrid tumors share both characteristics and behave as DPMA.[20] In 2010, the American Joint Committee on Cancer (AJCC) and the World Health Organization (WHO) proposed a histologic classification of PMP in terms of histogenesis, molecular genetic distinctions, and clinical behavior of the lesions, which correct previous categories into low-grade and high-grade PMP.[21,22] Low-grade PMP is described as mucin pools with low cellularity (< 10%), bland cytology, nonstratified cuboidal epithelium, and cases that mucin pools with high cellularity, moderate/severe cytologic atypia and cribriform/signet ring morphology with desmoplastic stroma belong to high-grade PMP.[22] The prognosis was related to histologic features closely since patients with DPAM got 5-year and 10-year survival rates of 75% and 68% compared with 14% and 3% for patients with PMCA.[20] In 2016, the Peritoneal Surface Oncology Group International (PSOGI) subdivided classifications into 4 precise descriptions according to immunohistochemical staining, hoping to probe into the pathologic prognostic factors and renovate the management of patients.[23] Generally speaking, it barely differs from the former because it sticks to histologic classifications and does not give specific answer to current confusions. When it comes to gastrointestinal cancers, no matter the viscus is covered by

peritoneum or not, the peritoneal metastasis equals to a signal of terminal event. As to PMP, peritoneum is a target organ in most cases. The PSOGI put forward TNM classification of PMP with 3 selections for voting. The major argument was that whether the metastasis should include both cells and mucin, or evaluate separately.[23] To verify which classification version fitted best with prognosis of PMP, some researchers reclassified patients gone through cytoreduction surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) for an appendiceal mucinous cancer with peritoneal implantation. Survival analysis evaluated the difference of PSOGI and AJCC classification edition on overall survival (OS) and disease free survival (DFS), with the analogous prognostic statistics.[24] The PSOGI version added histopathologic details to distinguish morphologic features and destructive behavior, but that was inappropriate and unconvincing to make the prejudgment by histology simply.

STANDARD REGIMEN OF PMP TREATMENT

The Establishment of Therapeutic Pattern

Over the past decades, constant surgeries of debulking procedures and drainage of mucinous ascites had acted as a major treatment for patients with PMP, though, people needed to accept repeating inventions to fight against recurrence and succumbed to gastrointestinal obstructions or complications of treatment that prohibit subsequent surgeries ultimately.[25] It was in the 1990s that Sugarbaker innovated a brand new and aggressive approach, which connected extensive surgery with regional intraperitoneal chemotherapy during the early postoperative stage.[26] CRS includes peritonectomy procedures as well as excision of all viscera with visible tumor invasion, to create a macroscopic tumor-free condition.[27] After demolition and reconstruction, HIPEC followed. It appeared like a more direct and effective approach to obliterate tumor remnants by regional chemotherapeutics perfusion. CRS combined with HIPEC represented an innovative modality of treatment and distinguished from traditional strategies in 2 features. For one thing, adequate dose-response inhibited the division and differentiation of drug-resistant cells, contributed to boosting the percentage of complete responses. For another thing, chemotherapeutical modality that under visualized surgical guidance probably develop into a special therapy with promising relapse rate and mortality.[28] For now, CRS associated with HIPEC has established its importance as the sole strategy to reach complete remission or long-term disease control.[29]

Surgical New Insights

To attain disease free status or to extend survival time, operation remains the preferred recommendation. Completeness of cytoreduction (CC) scores are calculated depending on the maximum diameter of the residual peritoneal carcinomatosis after the surgery.[30] CC0 represents that there is no visible lesion exists. The score adds one point as CC1 when the remaining nodules are measured below 0.25 cm and pluses two points as CC2 when the diameter goes between 0.25 m to 2.5 cm. CC3 is assessed when it is measured beyond 2.5 cm.[29,31] CC0 and CC1 are labeled as complete cytoreduction surgery (CCRS) and accepted as one of the most crucial indicators that interact with follow-up survival outcomes.[32] Redistribution phenomenon is a feature with PMP, it manifests as enormous quantities of mucinous tumor cells accumulate and proliferate in some specific anatomical location, meantime thimbleful or negligible gelatinous ascites in other position within peritoneal cavity.[33] It indicates that these gelatinous ascites and tumor cells follow the abdominal fluid circulation through lymphoid aggregates.[34] Mucus-secreting cells migrate with peritoneal fluid and keep in dynamic circulation because of the influence of body position, intraperitoneal pressure, and physical peritoneal fluid circulation.[35] Cells merely implant on tissues of relative standstill. This feature triggers the dissemination of malignant mucin-producing cells and broads the extension of colloidal nodules or masses. At the time of absorption, epithelial cells are filtered out and pile up into part of nodules.[36] Hence, operative intervention is impractical, especially when the disease spreads widely, overcomes peristalsis, and implants on the intestine, nonresectability or incomplete CRS is recognized.[37] The peritoneal cancer index (PCI) is calculated in light of the objective quantity of deposits/lesions in 13 abdominopelvic quadrants.[38] PCI score offers a precise message about the real tumor burden and the higher points implicate the poorer prognosis.[39] But it still comes up with a satisfying long-term survival if symptoms are not reckoned.[40]

Some authors questioned the fact that if or not, the debulking procedure was an aggressively feasible solution to resect the majority of deposits and satisfactory enough to obtain better living quality with low mortality when the situation came up with high CC scores and impracticable CCRS.[41] Other voices argued that palliative resection has proved its superiority in safety and effectiveness under that circumstance.[42] Tumor in bulk brings about volume effect related adverse impact and patient's condition deteriorates in fast pace, if not intervene. Postoperative complications, the complexity of surgical procedure and the perplexed scope of the operation all add difficulties to make the treatment decision. In a retrospective study of 39 patients with unresectable PMP, operating maximal tumor debulking brought symptom relief for nearly 2 years of the median time.[43] They proposed the places could be two hemidiaphragms, Glisson's capsule, the whole rectum (if no stricture happened), and the small bowel with nidus <10 mm, where might bear the residual disease.[43] Optimal choices for intractable cases tend to be symptomatic treatment and long-term function preservation.[44] A 2-step surgery for low-grade PMP with high PCI has been put forward, rising the feasibility for resection and reducing the recurrence.[45] The first part needed to achieve CCRS of the inframesocolic compartment and omentum, then the second attempt conducted with adhesiolysis and excision of recurrent lessions. HIPEC followed the second surgery. Therefore, the operating time should not be the occasions when obstruction happens.

HIPEC: Idealized Strategy and Practical Difficulties

HIPEC is expected to eliminate any microscopic malignant implant by an open or closed colosseum technique generating passive afflux to penetrate through nonresectable remains in the peritoneal cavity.[46] Hyperthermia is the essential technique. The predefined temperature of infusion varies in the range of 41 to 42°C and the median time of exposure is around 90 minutes.[47] Under this setting, the selective impact to the tumor of thermoinducible lysosomes is much destructive and it sharply shrinks or even stagnates the blood flow of tumor cells, as a result, accelerating the malignant cells death.[48] In contrast, normal tissues dilate blood vessels and reduce peripheral vascular resistance so that cell oxygenation improves.[49] Every cell seemingly owns exclusive thermal limitation and dies in exponent once the temperature reaches 43°C.[47] The thing is, a specific heating temperature, as well as duration time of exposure has not been established actually. The application of chemotherapy drugs dominates the therapeutic efficacy. It generally has to be of large molecular weight and good water

solubility, could enhance its toxicological effect by hyperthermia and be wiped out of systemic circulation quickly.[47] A function of certain drugs concentration over time was calculated and integrated to measure the pharmaceutical osmosis of diverse chemotherapeutics in the peritoneal cavity and systemic circulation.[48] A higher area under curve ratio of intra-abdominal concentration to peripheral blood concentration time was the identical medical result. Antitumor platinum agents like Cisplatin and Carboplatin are common choices concerning higher area under curve ratio as well as slighter nephrotoxicity characters based on pharmacokinetic studies.[47] Other intracavitary chemotherapeutic drugs like mitomycin C (MMC), 5-fluorouracil, taxanes are also frequently used. In 2020, Chicago Consensus Working Group (CCWG) came to an agreement with the HIPEC regimen with 4 method: (1) Mitomycin, 30 mg at time 0 minutes and 10 mg at time 60 minutes, 90 minutes; (2) Mitomycin at 30 mg/m^2 for 90 to 120 minutes; (3) Mitomycin 15 mg/m^2+doxorubicin 15 mg/m^2, 90 minutes; (4) Oxaliplatin 300 mg/m^2, 30 minutes.[50]

Since the combination of CRS and HIPEC was pioneered, it has been broadly accepted and has become a standard therapeutic scheme for PMP. According to a young peritoneal center, median OS for observed cases was 100 months, a lower recurrence rate of 18.6% after receiving CRS and HIPEC in contrast to other researches that have covered recrudescence rate in 26.4% to 46%, with a 71% 5-year and 42% 10-year survival.[46] The survival results barely differs for the tumor originating from appendix or extra-appendix, it probably has little connection with immunohistologic features that bring about the absence of distinction in malignant behavior.[51]

Confronted Curative Dilemma

The acknowledged strategy for patients diagnosed as PMP is CRS combined with HIPEC.[46,52] The Memorial Sloan Kettering Center reported that 21% of patients with low-grade pathologic subtypes attained 10-year survival, while 90% of them accepted diverse operations because of short-term recrudescence.[44] A 2018 report selected all patients who had experienced CRS+HIPEC for PMP between 1993 and 2015 from a prospective multicenter database (RENAPE working group).[53] The result was that nearly a quarter of patients undergone recurrent disease. High-grade pathology of PMP and preoperative chemotherapy were 2 clues of recurrence within 5 years. There is no denying that CRS+HIPEC brings unparalleled survival benefits, but that does not prevent relapse even attaining tumor-free status. The remaining treatment options are depleted and lack of compelling evidence-based medical data. A second procedure for this condition is feasible, while evidence on prognostic outcomes for repeated intervention is either inadequate.

RADIOGRAPHIC DETECTION

Discerning obscure features of PMP at an early stage is of great significance, which determines survival time and quality. Mucinous neoplasm is perceived when high attenuation peritoneal thickening or masses breaking natural anatomy is shown on computed tomography (CT) images.[37] Typically, visceral scalloping, especially liver scalloping suggests mucinous ascites caused by PMP when a subphrenic implant is excluded.[54] Some came up with hypotheses that the imaging of liver scalloping was relevant to the accumulation of mucin deposition and predicted a high risk of recurrence after CRS.[55] When radiologists detect peritoneal nodules, visceral compression and mucinous low density ascites in compartment (Fig. 1), PMP should be taken into account. Although regular CT has been chosen as the preferred technique in the follow-up, omitting recurrence could happen when both peritoneum and omentum resections have been done and tumor infiltration comes along the small bowel.[56] It is appropriate for low-grade PMP patients to get annual CT scan of abdomen and pelvis in the first 6 years, chest examination and the frequency should be added if meets high-grade lesion.[57] Magnetic resonance imaging owns particular advantages in high sensitivity of the assessment of PMP, as gelatinous implants that consist of plenty of water molecules show high signal intensity on T2-weighted images.[58] It is deemed a normal phenomenon if peritoneal enhancement is equivalent to muscle enhancement.[59] Magnetic resonance imaging provides tough evidence of metastasis in the liver and perihepatic region for its favorable soft tissue contrast which is related to poor prognosis.[56]

ATTEMPTS FOR PROGRESSIVE STAGE

Systematic Chemotherapy

Unlike other types of solid tumor, PMP is not sensitive to systematic chemotherapy that works in inhibiting DNA replication and transcription. Preoperative systematic chemotherapy, theoretically, should help minish the tumor burden, ease the complexity of surgical procedure and decrease the risks of recurrence. Ideal neoadjuvant chemotherapy should be comprised of an alkylating associated with a fluoropyrimidine for around 6 months.[50] But practical experience turns out that neoadjuvant chemotherapy fails to achieve the assumed effect regardless of low-grade or high-grade histology, and additionally put off the time for standard remedy.[60] For conditions that are unresectable or relapse, the chief target for palliative chemotherapy is to delay disease progression and manage symptoms. As mentioned before, PMP is characterized by massive mucinous agglomerate. This kind of special tumor microenvironment is differentiated from traditional tumor microenvironment, that is constituted with oncocytes and inflammatory cells. Gelatinous masses may play a role in barrier and reduce chemosensitivity. Authorized system chemotherapy pattern has not been formulated yet. Tables 1 and 2 summarizes several reported chemotherapeutic approaches and their clinical effect in PMP patients.

Pressurized Intraperitoneal Aerosolized Chemotherapy (PIPAC)

Another method that has been reported to help surmount pharmacokinetic defects is PIPAC, since gas molecule of drugs under certain pressure dramatically boost the antineoplastic agents' absorptivity.[66] PIPAC as an innovative laparoscopic approach launched in 2011 utilizes peritoneal-plasma barrier pharmacokinetics to improve the drug concentration with better penetration and homogenous distribution.[67] Fewer adverse events occur and concrete statistic incidence of ileus, bleeding and bellyache is 12% to 15%.[68] Compared with systemic chemotherapy, PIPAC prevails over drugs absorption and physical condition improvement. Recent studies dig out broader benefit of PIPAC for it gave patients in unresectable conditions the second chance to undergo CRS and HIPEC.[69] There have been several reports that affirm the feasibility of PIPAC in neoadjuvant set up, regimens of cisplatin and doxorubicin or oxaliplatin alone show promising survival benefit in colorectal peritoneal metastases, peritoneal metastases of gastric cancer, ovarian cancer and peritoneal carcinomatosis.[70–72]

Antiangiogenic Treatment

Owing to the unsatisfactory curative result with system chemotherapy, angiogenesis inhibitors have been treated as an emerging therapeutic alternative. Fundamental mechanisms of antiangiogenic agents include inducing the normalization of tumor vasculature, inhibiting renascent vessels and degenerating

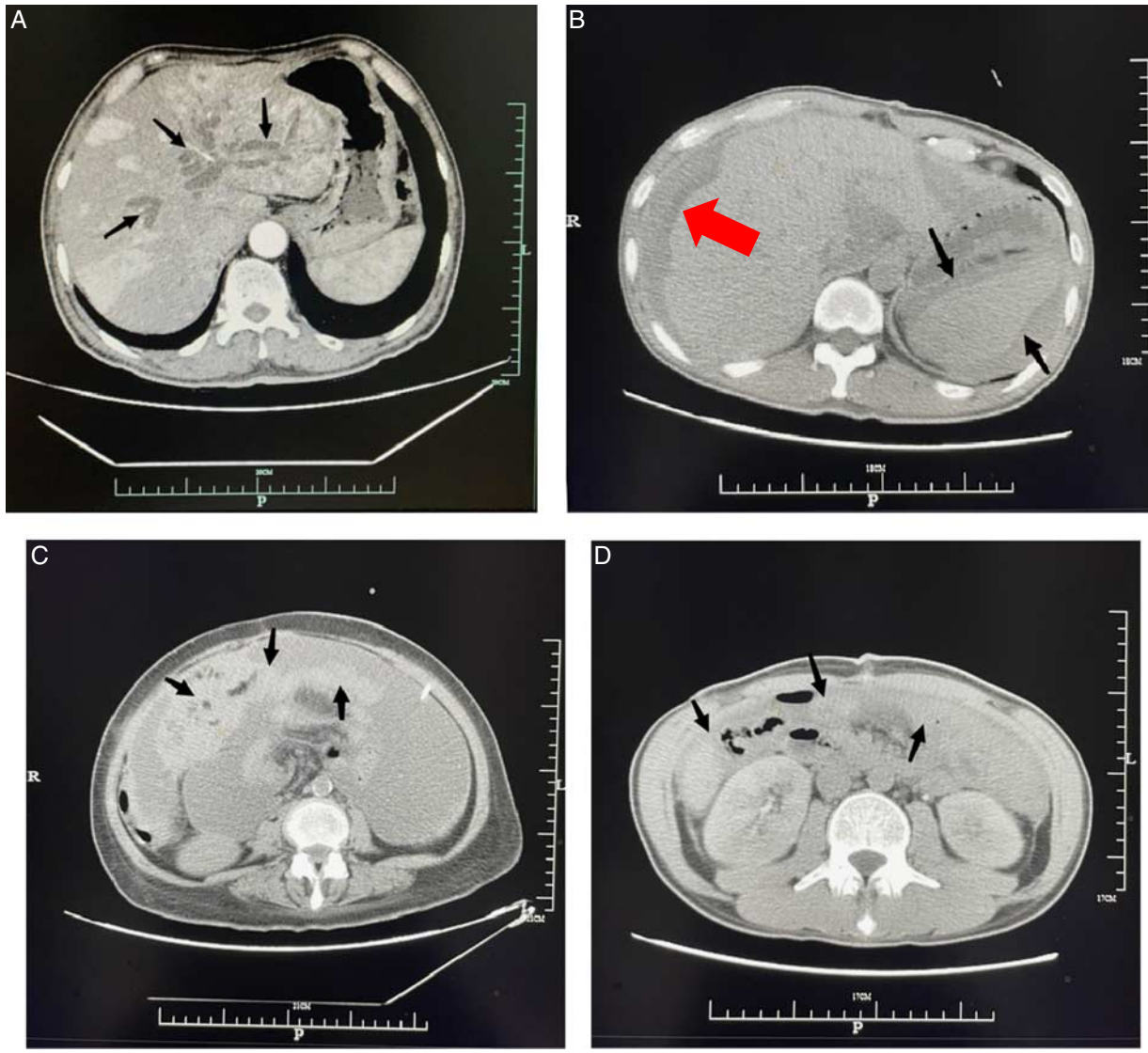

FIGURE 1. A, Scattered accumulations on liver (arrows in A). B, Sign of liver scalloping (red arrow in B) and deformation of spleen (arrows in B). C, Omental cake: floccus soft tissue density masses diffused inside the greater omentum and shaped it like biscuits (arrows in C). D, Massive mucus implanted in the abdominal cavity (arrows in D). full color online

immature parts.[73] PMP lacks in epithelial tumor cells and riches in mucin, that character does not influence the degree of vascularization and bears slight difference with other solid neoplasms.[74] Compared with healthy population, higher expression of angiogenic signaling pathway protein were detected in PMP serum specimens, like VEGFA, PIGF, FGF2, and sflt1.[74] The synergistic action could promote the vascularization. Cases of apatinib treatment, trifluridine/tipiracil (TAS-102) plus bevacizumab and other protocols all have reported with prolonged PFS and improved life quality.[75,76] The combination of chemotherapy together with a neoangiogenesis inhibitor could be an effective measure to strive for longer survival. The main purpose is to stabilize the tumor and to relieve symptoms after considering this therapeutic schedule, instead of remission of disease.

Epithelial Cell Adhesion Molecule (EpCAM, CD326)

Epithelial cell adhesion molecule (EpCAM, CD326) is a type-1 transmembrane glycoprotein and the most widely studied tumor-associated antibodies.[77] The upregulation of EpCAM is tested in various tumors and considered an immunogenic molecule that associates with prognosis and clinical intervention.[77] The MOC31PE immunotoxin links to tumor cells expressing the EpCAM, then it exert cytotoxic effects in the way of interrupting protein synthesis, triggering apoptosis and finally leading cell death.[78] The efficacy of intraperitoneal injection with MOC31PE and MMC has been proved in animal models of human mucinous peritoneal surface malignancies.[79] Frøysnes IS and coworkers carried out a phase I trial, giving the intraperitoneal administration of MOC31PE to patients with colorectal cancer, after undergoing CRS and HIPEC with MMC, which assured its good security and tolerance.[80] Though, every participant developed neutralizing antibodies. Then, the research group took further investigations, giving a positive outcome of 21 months mDFS, estimated 3-year OS of 78% (mOS was not reached) and estimated 5-year OS of 53% according to updated follow-up data (not published yet).[81,82] In

TABLE 1. Different Histologic Classifications of PMP

	Classification	Description
Oscar Polano 1921[18]	The cystadenoma mucinosum peritonei simplex	Superficial implantation on the peritoneum
	The cystadenoma malignum pseudomucinosum peritonei	Aggressive and destructive features with malignant performance of penetrating abdominal cavity in greater size, spreading to more sites and even perforating the intestines
Ronnett et al[19]	Disseminated peritoneal adenomucinosis (DPAM)	DPAM comprised peritoneal lesions composed of numerous extracellular mucin-containing scant simple to focally proliferative mucinous epithelium with minimal-to-moderate cytologic atypia and inapparent mitotic activity, with or without an associated appendiceal mucinous adenoma
	Peritoneal mucinous carcinomatosis (PMCA)	Peritoneal lesions that accord with morphologic and cytologic characteristics of carcinoma as more abundant epithelium proliferate in glands, nests, or individual cells, with or without an associated primary mucinous adenocarcinoma
	Hybrid tumors	Peritoneal mucinous adenocarcinoma with intermediate features
Bradley et al[61]	Low-grade mucinous carcinoma peritonei (MCP-L)	Cases have a significant adenoma-like or well-differentiated component and should lack a poorly differentiated component including Signet ring cells
	High-grade mucinous carcinoma peritonei (MCP-H)	Cases with moderately or any poorly differentiated component, that includes all cases with a well-developed signet-ring cell component
AJCC and WHO 2010[21]	Low-grade PMP	Mucin pools with low cellularity (< 10%), bland cytology and nonstratified cuboidal epithelium
	High-grade PMP	Mucin pools with high cellularity, moderate/severe cytologic atypia and cribriform/signet ring morphology with desmoplastic stroma
PSOGI 2016[23]	Acellular mucin (AC)	Mucin without epithelial cells
	Low-grade mucinous carcinoma peritonei/disseminated peritoneal adenomucinosis (DPAM)	PMP with low-grade histologic features
	High-grade mucinous carcinoma peritonei/peritoneal mucinous carcinomatosis (PMCA)	PMP with high-grade histologic features
	High-grade mucinous carcinoma peritonei with signet ring cells/Peritoneal mucinous carcinomatosis with signet ring cells (PMCA-S)	PMP with signet ring cells

addition, the immunotoxin contributes to immune activation, as an enhanced local inflammatory response could be checked.[82] With the increased concentration of interleukin (IL)-6, IL-8, IL-1β, IP-10, tumor necrosis factor, interferon-γ and other innate proinflammatory cytokines, the MOC31PE-trigered immunogenic cell death made remnant cancer cells harder to survive after CRS and HIPEC.[83] The antitumor effect have been supported with the successful application of MOC31PE combined with cytotoxic drugs in vitro and in mouse models for peritoneal metastasis of epithelial ovarian cancer.[78] Preclinical and clinical studies prove the EpCAM a promising candidate for targeted therapy.

PROGNOSTIC SIGNIFICANCE OF BIOMARKERS

Serum Tumor Markers in PMP

The prediction of tumor behavior of PMP, for instance, recrudesce does not thoroughly rely on histopathology. Nummela et al[84] found that 56% of their cases were tested out abnormal CEA levels and closely related to PCI scores ($P < 0.001$).

TABLE 2. Chemotherapy Protocols With Treatment Reaction

Chemotherapy Protocols	References	No. of Enrolled Patients	Histologic Grade	Median Follow-up (mo)	mPFS (mo)	mOS (mo)	Major Adverse Event
Capecitabine+ mitomycin C	Farquharson et al[62]	40	DPAM 27 PMCA-I/D 10 PMCA 3	17.0	Not described	Year OS 84% Year OS 61%	Hand and foot Syndrome
Capecitabine+ cyclophosphamide	Raimondi et al[63]	23	Low-grade 22 High-grade 1	22.4	9.5	1-year OS 73.7%	Anemia
FOLFOX-4	Pietrantonio et al[64]	20	Low-grade 12 High-grade 8	18	8.0	26.2	Neutropenia
FOLFOX6	Hiraide et al[65]	8	Low-grade 1 High-grade 7	27.2	13.0	27.9	Leukocytopenia

mPFS indicates median progression-free survival; PMCA-I/D, PMCA with intermediate or discordant features.

Yan et al[85] reported that CEA expressed immunopositivity in a majority of cases and had no relevant accordance with OS. CA19-9 showed strong staining in the multitude of PMP cases. The secretory vesicles of tumor cells and secreted mucus pools staining displayed intensive positive demonstrated that plentiful secretion of CA19-9 was excreted to mucus.[84] Baratti et al[86] and van Ruth et al[87] manifested the relationship of CA 19-9 positive with elevated threats of recurrence but made no obvious effect on survival. Otherwise, some authors recognized CA19-9 as a strong prognostic indicator peculiarly in the DPAM/PMCA-I/D subgroup and considered that testing results were conducted to sift out patients who probably obtain benefits from adjuvant chemotherapy.[88] CA125, encoded by the homonymous MUC16, is the repeating peptide epitope of tandem repeat domains.[89] Evidence for MUC16 direct contributions to peritoneal metastasis has been supported by its high affinity to bind to mesothelin and selectins.[90,91] MUC16 was known to refrain natural killer cells from exerting their effect of antitumor cytotoxic responses and induce immune escape.[92,93] The lifted serum CA125 levels was rare and mainly resulted from adjacent noncancerous mesothelium stimulated by advancing PMP.[84] Therefore, it partly indicates the extension of tumor spread. Preoperative tumor marker levels are an independent prognostic predictor, which is potentially a represent of tumor biological phenomena.[94] It is appropriate to stratify patients on account of serum tumor marker levels and to identify those who are much possible to benefit from postoperative systemic chemotherapy, scheduled reoperation and supervision of reaction. The chance of reaching a complete tumor resection could be elevated when CEA, CA19-9, and CA125 are all range within limits and could be halved if all increase out of normal upper limits.[94] An observational study using a prospectively designed database observed poorer survival when CEA and CA19-9 levels trebled.[95]

Molecular Predictors

MUC1, MUC2, MUC5AC, and MUC6 are the main mucin genes commonly seen in positive expression, particularly MUC2 and MUC5AC that have tissue expression of sialomucins and sulfated mucins act as prominent components of PMP mucin, could be observed in nearly every patient.[96,97] The ideal assumption of preventing the secretion or sclerosis of MUC2 and MUC5AC, if realizes, will ameliorate symptoms of mucin accumulation significantly. It needs sufficient researches to verify the feasibility from preclinical trials to clinical stage.

Ki-67 labeling index and p53 status have been brought to the forefront as attractive indicators in malignant tumor growth, differentiation, and metastasis.[98] The presence of Ki-67 in the G1, S (synthesis), G2, and M (mitosis) phases of the cell cycle except for the G0 phase was frequently regarded as a tumor proliferative marker.[99] According to PSOGI viewpoint, Ki-67 is an independent indicator for survival and 15% is the settled limitation.[100] P53 regulates apoptosis and DNA repair, thereby, closely monitors cell proliferation.[101] The mutation of p53 could directly incur abnormal proliferation, the occurrence of neoplasm, and progression. Current data suggest that p53 wild type (Wtp53) normally suppresses tumor cell growth by controlling the expression and activity of functional enzymes to impend metabolic transformation from oxidative phosphorylation to glycolysis.[102] P53 mutant type (Mtp53) fails to touch off activation of signaling cascades to initiate DNA repair or programmed cell death.[103] A retrospective study analyzed the levels of Ki-67 and p53 of 141 patients with PMP of appendiceal origin, and it hypothesized that high Ki-67 labeling index combined with aberrant p53 may provide the basis for a bad outcome.[85]

The Mutational Landscape and Treatment Prospects

To learn somatic mutations and to evaluate the loss of heterozygosity events do good to exploit novel therapeutic strategies based on tumor targets. Studies have found that PMP originated from appendix carried the mutations of KRAS and GNAS in a noticeable proportion.[104] KRAS and GNAS signal transductions are likely to share crosstalk and synergy.[105] In a small sample size analysis of PMP, the variant rate was 72% in KRAS, 52% in GNAS.[106] Both GNAS and KRAS mutations highly suggested poorer PFS, and the multivariable analysis proved KRAS mutation affected prognostic survival as an independent factor.[106] In another 2 relapsing panels of PMP patients that respectively accepted with capecitabine and bevacizumab, FOLFOX4 regimen both presented shorter median PFS if GNAS mutation was detected (5.1 vs. 13 mo).[107] GNAS mutation activates downstream protein factors in protein kinase A pathway and produces abnormal amounts of mucin.[108] Existing researches have proven the powerful immunogen with guanine nucleotidebinding protein α subunti (Gsα) peptide which provokes de novo immunity targeting the tumor driver signaling molecule.[108] That established a sound foundation to antitumor vaccination and open a novel affiliated therapy strategy. The activation of the RAS-MAPK signaling pathway induces adverse molecular biological effects in whether KRAS or GNAS mutation, the medicine blocking this pathway could be another effective targeting treatment opportunity.[109]

CONCLUSION

Depending on symptoms, auxiliary inspections, response to treatment and clinical experience, the comprehensive strategy turns out to be practical and helps patients realize an over 10-year survival with satisfied life quality. One of the reasons is the indolence feature of this kind of tumor, but if treated inappropriately, the malignant nature would emerge with the rapid progression. We made a detailed description of this infrequent malignant syndrome from background, symptoms, treatment, and prognostic factors. There is still a long way to run for the establishment of accurate therapy, especially for unresectable and recurrent groups. To some degree, it is a plausible schema to link up tumor biomarkers or mutations with classification. A more precise and targeted therapeutic armamentarium could earn longer survival time from recent advances in developing medical oncology. Efforts in further foundational studies and clinical analysis would be required to make up for the blank, that may derive significant benefits to a larger group.

REFERENCES

1. Rizvi SA, Syed W, Shergill R. Approach to pseudomyxoma peritonei. *World J Gastrointest Surg*. 2018;10:49–56.
2. García KM, Flores KM, Ruiz A, et al. Pseudomyxoma peritonei: case report and literature review. *J Gastrointest Cancer*. 2019;50:1037–1042.
3. Govaerts K, Lurvink RJ, De Hingh IHJT, et al. PSOGI. 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.
4. Weaver CH. Mucocele of appendix with pseudomucinous degeneration. *Am J Surg*. 1937;36:523–526.
5. Werth R. Klinische und Anatomische Untersuchungen zur Lehre von den Bauchgeschwullsten und der Laparotomie. *Arch Gynecol Obstet*. 1884;24:100–118.
6. Frankel E. Uber das sogenannte pseudomyxoma peritonei. *Med Wochenschr*. 1901;48:965–970.

7. Darr U, Renno A, Alkully T, et al. Diagnosis of Pseudomyxoma peritonei via endoscopic ultrasound guided fine needle aspiration: a case report and review of literature. *Scand J Gastroenterol*. 2017;52:609–612.
8. Spyropoulos C, Rentis A, Alexaki E, et al. Appendiceal mucocele and pseudomyxoma peritonei: the clinical boundaries of a subtle disease. *Am J case rep*. 2014;15:355–360.
9. Laila TR, Das S, Ahmed SS, et al. Pseudomyxoma peritonei—a case report. *Mymensingh Med J*. 2012;21:759–762.
10. Kataoka A, Ito K, Takemura N, et al. Immunohistochemical staining as supportive diagnostic tool for pseudomyxoma peritonei arising from intraductal papillary mucinous neoplasm: a report of two cases and literature review. *Pancreatology*. 2020;20:1226–1233.
11. Wang W, Meng L, Crespo E, et al. Gelatinous abdomen: a rare case of pseudomyxoma peritonei arising from metastatic gastric adenocarcinoma. *Cureus*. 2019;11:e4666.
12. Giang TH, Ngoc TT, Hassell LA. Carcinoma involving the gallbladder: a retrospective review of 23 cases—pitfalls in diagnosis of gallbladder carcinoma. *Diagn Pathol*. 2012;7:10.
13. Jackson SL, Fleming RA, Loggie BW, et al. Gelatinous ascites: a cytohistologic study of pseudomyxoma peritonei in 67 patients. *Mod Pathol*. 2001;14:664–671.
14. Minguillon C, Friedmann W, Vogel M, et al. Muzinöse Metaplasie der Tubenschleimhaut als Ursache eines Pseudomyxoma peritonei [German] [Mucinous metaplasia of fallopian tube mucous membrane as a cause of pseudomyxoma peritonei]. *Zentralbl Pathol*. 1992;138:363–365.
15. Kurita M, Komatsu H, Hata Y, et al. Pseudomyxoma peritonei due to adenocarcinoma of the lung: case report. *J Gastroenterol*. 1994;29:344–348.
16. Hawes D, Robinson R, Wira R. Pseudomyxoma peritonei from metastatic colloid carcinoma of the breast. *Gastrointest Radiol*. 1991;16:80–82.
17. 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–e165.
18. Krivsky LA. On the pseudomyxoma peritonei. *BJOG Int J Obstet Gynaecol*. 1921;28:204–227.
19. 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;19:1390–1408.
20. Misdraji J. Mucinous epithelial neoplasms of the appendix and pseudomyxoma peritonei. *Mod Pathol*. 2015;28(suppl 1):S67–S79.
21. Panarelli N, Yantiss R. Mucinous neoplasms of the appendix and peritoneum. *Arch Path Lab Med*. 2011;135:1261–1268.
22. Carr NJ, Sobin LH. Adenocarcinoma of the appendix. In: Bosman FT, Carneiro F, Hruban RH, eds. *WHO Classification of Tumors of the Digestive System*. Lyon: IARC; 2010:122–125.
23. Carr NJ, Cecil TD, Mohamed F, et al. Peritoneal Surface Oncology Group International. 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.
24. Martín-Román L, Lozano P, Gómez Y, et al. Which classification system defines best prognosis of mucinous neoplasms of the appendix with peritoneal dissemination: TNM vs PSOGI? *J Clin Pathol*. 2021. [Epub ahead of print].
25. Smeenk RM, Verwaal VJ, Zoetmulder FA. Pseudomyxoma peritonei. *Cancer Treat Rev*. 2007;33:138–145.
26. Sugarbaker PH, Zhu BW, Sese GB, et al. Peritoneal carcinomatosis from appendiceal cancer: results in 69 patients treated by cytoreductive surgery and intraperitoneal chemotherapy. *Dis Colon Rectum*. 1993;36:323–329.
27. Sugarbaker PH. Peritonectomy procedures. *Surg Oncol Clin N Am*. 2003;12:703–727.
28. Sugarbaker PH. Patient selection and treatment of peritoneal carcinomatosis from colorectal and appendiceal cancer. *World J Surg*. 1995;19:235–240.
29. Chua TC, Moran BJ, Sugarbaker PH, et al. Early- and long-term outcome data of patients with pseudomyxoma peritonei from appendiceal origin treated by a strategy of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *J Clin Oncol*. 2012;30:2449–2456.
30. Jacquet P, Sugarbaker PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. *Cancer Treat Res*. 1996;82:359–374.
31. Glehen O, Kwiatkowski F, Sugarbaker PH, et al. Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer: a multi-institutional study. *J Clin Oncol*. 2004; 22:3284–3292.
32. Mittal R, Chandramohan A, Moran B. Pseudomyxoma peritonei: natural history and treatment. *Int J Hyperthermia*. 2017;33:511–519.
33. Sugarbaker PH, Ronnett BM, Archer A, et al. Pseudomyxoma peritonei syndrome. *Adv Surg*. 1996;30:233–280.
34. Fonseca C, Carvalho S, Cunha TM, et al. The many faces of pseudomyxoma peritonei: a radiological review based on 30 cases. *Radiol Bras*. 2019;52:372–377.
35. Meyers MA. Distribution of intra-abdominal malignant seeding: dependency on dynamics of flow of ascitic fluid. *Am J Roentgenol Radium Ther Nucl Med*. 1973;119:198–206.
36. 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;71:847–858.
37. 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;42:558–566.
38. Bhatt A, Yonemura Y, Mehta S, et al. The pathologic peritoneal cancer index (PCI) strongly differs from the surgical PCI in peritoneal metastases arising from various primary tumors. *Ann Surg Oncol*. 2020;27:2985–2996.
39. Llueca A, Escrig J, MUAPOS working group (Multidisciplinary Unit of Abdominal Pelvic Oncology Surgery). Prognostic value of peritoneal cancer index in primary advanced ovarian cancer. *Eur J Surg Oncol*. 2018;44:163–169.
40. Morris DL. Peritonectomy HIPEC-contemporary results, indications. *Chin J Cancer Res*. 2013;25:373–374.
41. Iavazzo C, Spiliotis J. Clinical findings of patients with pseudomyxoma peritonei of appendiceal origin undergoing cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). *Updates Surg*. 2020;72:923–924.
42. Zhou S, Zhao H, He X. The prognostic impact of pathology on patients with pseudomyxoma peritonei undergoing debulking surgery: a systematic review and meta-analysis of retrospective studies. *Front Surg*. 2020;7:554910.
43. Delhorme JB, Elias D, Varatharajah S, et al. Can a benefit be expected from surgical debulking of unresectable pseudomyxoma peritonei? *Ann Surg Oncol*. 2016;23:1618–1624.
44. Miner TJ, Shia J, Jaques DP, et al. Long-term survival following treatment of pseudomyxoma peritonei: an analysis of surgical therapy. *Ann Surg*. 2005;241:300–308.
45. Trilling B, Brind'Amour A, Hamad R, et al. Two-step cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for pseudomyxoma peritonei with high peritoneal carcinomatosis index. *World J Surg Oncol*. 2021;19:60.
46. Narasimhan V, Wilson K, Britto M, et al. Outcomes following cytoreduction and HIPEC for pseudomyxoma peritonei: 10-year experience. *J Gastrointest Surg*. 2020;24:899–906.
47. Crestani A, Benoit L, Touboul C, et al. Hyperthermic intraperitoneal chemotherapy (HIPEC): should we look closer at the microenvironment? *Gynecol Oncol*. 2020;159:285–294.
48. González-Moreno S, González-Bayón LA, Ortega-Pérez G. Hyperthermic intraperitoneal chemotherapy: rationale and technique. *World J Gastrointest Oncol*. 2010;2:68–75.
49. Seegenschmiedt MH, Fessenden P, Vernon CC. *Thermoradiotherapy and Thermochemotherapy*. In: Song CW, Choi IB, Nah BS, Sahu SK, Osborn JL, eds. Microvasculature and perfusion in normal tissues and tumors. 1995:139–156.

50. Lin YL, Xu DZ, Li XB, et al. Consensuses and controversies on pseudomyxoma peritonei: a review of the published consensus statements and guidelines. *Orphanet J Rare Dis*. 2021;16:85.
51. Delhorme JB, Severac F, Averous G, et al. French National Network of Peritoneal Surface Malignancies (RENAPE). Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for pseudomyxoma peritonei of appendicular and extra-appendicular origin. *Br J Surg*. 2018;105:668–676.
52. Bartlett DJ, Thacker PG Jr, Grotz TE, et al. Mucinous appendiceal neoplasms: classification, imaging, and HIPEC. *Abdom Radiol (NY)*. 2019;44:1686–1702.
53. Mercier F, Dagbert F, Pocard M, et al. RENAPE Network. Recurrence of pseudomyxoma peritonei after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *BJS Open*. 2018;3:195–202.
54. Fonseca EKUN, Martins AN, Tridente CF, et al. Liver scalloping in pseudomyxoma peritonei. *Abdom Radiol (NY)*. 2017;42:2003–2004.
55. Hotta M, Minamimoto R, Gohda Y, et al. Pseudomyxoma peritonei: visceral scalloping on CT is a predictor of recurrence after complete cytoreductive surgery. *Eur Radiol*. 2020;30:4193–4200.
56. Klumpp B, Aschoff P, Schwenzer N, et al. Correlation of preoperative magnetic resonance imaging of peritoneal carcinomatosis and clinical outcome after peritonectomy and HIPEC after 3 years of follow-up: preliminary results. *Cancer Imaging*. 2013;13:540–547.
57. Govaerts K, Chandrakumaran K, Carr NJ, et al. Single centre guidelines for radiological follow-up based on 775 patients treated by cytoreductive surgery and HIPEC for appendiceal pseudomyxoma peritonei. *Eur J Surg Oncol*. 2018;44:1371–1377.
58. Bouquot M, Dohan A, Gayat E, et al. Prediction of resectability in pseudomyxoma peritonei with a new CT score. *Ann Surg Oncol*. 2018;25:694–701.
59. 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;22:1708–1715.
60. Sommariva A, Tonello M, Rigotto G, et al. Novel perspectives in pseudomyxoma peritonei treatment. *Cancers (Basel)*. 2021;13:5965.
61. Bradley RF, Stewart JH IVth, 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;30:551–559.
62. Farquharson AL, Pranesh N, Witham G, et al. A phase II study evaluating the use of concurrent mitomycin C and capecitabine in patients with advanced unresectable pseudomyxoma peritonei. *Br J Cancer*. 2008;99:591–596.
63. Raimondi A, Corallo S, Niger M, et al. Metronomic capecitabine with cyclophosphamide regimen in unresectable or relapsed pseudomyxoma peritonei. *Clin Colorectal Cancer*. 2019;18:e179–e190.
64. Pietrantonio F, Maggi C, Fanetti G, et al. FOLFOX-4 chemotherapy for patients with unresectable or relapsed peritoneal pseudomyxoma. *Oncologist*. 2014;19:845–850.
65. Hiraide S, Komine K, Sato Y, et al. Efficacy of modified FOLFOX6 chemotherapy for patients with unresectable pseudomyxoma peritonei. *Int J Clin Oncol*. 2020;25:774–781.
66. Tempfer CB, Solass W, Buerkle B, et al. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) with cisplatin and doxorubicin in a woman with pseudomyxoma peritonei: a case report. *Gynecol Oncol Rep*. 2014;10:32–35.
67. Davigo A, Passot G, Vassal O, et al. PIPAC versus HIPEC: cisplatin spatial distribution and diffusion in a swine model. *Int J Hyperthermia*. 2020;37:144–150.
68. Alyami M, Hübner M, Grass F, et al. Pressurised intraperitoneal aerosol chemotherapy: rationale, evidence, and potential indications. *Lancet Oncol*. 2019;20:e368–e377.
69. Alyami M, Mercier F, Siebert M, et al. Unresectable peritoneal metastasis treated by pressurized intraperitoneal aerosol chemotherapy (PIPAC) leading to cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Eur J Surg Oncol*. 2021;47:128–133.
70. Lurvink RJ, Rovers KP, Nienhuijs SW, et al. Pressurized intraperitoneal aerosol chemotherapy with oxaliplatin (PIPAC-OX) in patients with colorectal peritoneal metastases-a systematic review. *J Gastrointest Oncol*. 2021;12(suppl 1):S242–S258.
71. Badgwell B. Is PIPAC a new summit for peritoneal disease treatment or are we lost in the snowstorm? *Ann Surg Oncol*. 2022;29:13–14.
72. Tempfer CB, Giger-Pabst U, Seebacher V, et al. A phase I, single-arm, open-label, dose escalation study of intraperitoneal cisplatin and doxorubicin in patients with recurrent ovarian cancer and peritoneal carcinomatosis. *Gynecol Oncol*. 2018;150:23–30.
73. Sun WL, Hutarew G, Gradl J, et al. Successful antiangiogenic combination therapy for pseudomyxoma peritonei with bevacizumab and capecitabine. *Cancer Biol Ther*. 2009;8:1459–1462.
74. Andersson Y, Fleten KG, Abrahamsen TW, et al. Anti-angiogenic treatment in pseudomyxoma peritonei-still a strong preclinical rationale. *Cancers (Basel)*. 2021;13:2819.
75. Huang R, Shi XL, Wang YF, et al. Apatinib for treatment of a pseudomyxoma peritonei patient after surgical treatment and hyperthermic intraperitoneal chemotherapy: a case report. *World J Clin Cases*. 2019;7:3881–3886.
76. Hirano S, Gohda Y, Miyazaki H, et al. A case of pseudomyxoma peritonei successfully treated with trifluridine/tipiracil (TAS-102) and bevacizumab after palliative debulking surgery. *Chin Clin Oncol*. 2021;10:29.
77. Mohtar MA, Syafruddin SE, Nasir SN, et al. Revisiting the roles of pro-metastatic EpCAM in cancer. *Biomolecules*. 2020;10:255.
78. Andersson Y, Haavardtun SI, Davidson B, et al. MOC31PE immunotoxin—targeting peritoneal metastasis from epithelial ovarian cancer. *Oncotarget*. 2017;8:61800–61809.
79. Flatmark K, Guldvik IJ, Svensson H, et al. Immunotoxin targeting EpCAM effectively inhibits peritoneal tumor growth in experimental models of mucinous peritoneal surface malignancies. *Int J Cancer*. 2013;133:1497–1506.
80. Frøysnes IS, Andersson Y, Larsen SG, et al. Novel treatment with intraperitoneal MOC31PE immunotoxin in colorectal peritoneal metastasis: results from the ImmunoPeCa Phase 1 Trial. *Ann Surg Oncol*. 2017;24:1916–1922.
81. Frøysnes IS, Andersson Y, Larsen SG, et al. ImmunoPeCa trial: long-term outcome following intraperitoneal MOC31PE immunotoxin treatment in colorectal peritoneal metastasis. *Eur J Surg Oncol*. 2021;47:134–138.
82. Thorgersen EB, Asvall J, Frøysnes IS, et al. Increased local inflammatory response to MOC31PE immunotoxin after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Ann Surg Oncol*. 2021;28:5252–5262.
83. Ceelen W. Intraperitoneal EpCAM-targeted immunotoxin: a first step towards engineering the immune environment in colorectal peritoneal metastases? *Ann Surg Oncol*. 2021;28:4772–4774.
84. Nummela P, Leinonen H, Järvinen P, et al. Expression of CEA, CA19-9, CA125, and EpCAM in pseudomyxoma peritonei. *Hum Pathol*. 2016;54:47–54.
85. Yan F, Shi F, Li X, et al. Prognostic significance of CEA, Ki67 and p53 in pseudomyxoma peritonei of appendiceal origin. *J Int Med Res*. 2021;49:3000605211022297.
86. Baratti D, Kusamura S, Martinetti A, et al. Prognostic value of circulating tumor markers in patients with pseudomyxoma peritonei treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Ann Surg Oncol*. 2007;14:2300–2308.
87. van Ruth S, Hart AA, Bonfrer JM, et al. Prognostic value of baseline and serial carcinoembryonic antigen and carbohydrate antigen 19-9 measurements in patients with pseudomyxoma peritonei treated with cytoreduction and hyperthermic intraperitoneal chemotherapy. *Ann Surg Oncol*. 2002;9:961–967.
88. Koh JL, Liauw W, Chua T, et al. Carbohydrate antigen 19-9 (CA 19-9) is an independent prognostic indicator in pseudomyxoma peritonei post cytoreductive surgery and perioperative intraperitoneal chemotherapy. *J Gastrointest Oncol*. 2013;4:173–181.
89. Li X, Pasche B, Zhang W, et al. Association of MUC16 mutation with tumor mutation load and outcomes in patients with gastric cancer. *JAMA Oncol*. 2018;4:1691–1698.
90. Rump A, Morikawa Y, Tanaka M, et al. Binding of ovarian cancer antigen CA125/MUC16 to mesothelin mediates cell adhesion. *J Biol Chem*. 2004;279:9190–9198.

91. Chen SH, Dallas MR, Balzer EM, et al. Mucin 16 is a functional selectin ligand on pancreatic cancer cells. *FASEB J*. 2012;26:1349–1359.
92. Kusamura S, Hutanu I, Baratti D, et al. Circulating tumor markers: predictors of incomplete cytoreduction and powerful determinants of outcome in pseudomyxoma peritonei. *J Surg Oncol*. 2013;108:1–8.
93. Aithal A, Rauth S, Kshirsagar P, et al. MUC16 as a novel target for cancer therapy. *Expert Opin Ther Targets*. 2018;22:675–686.
94. Taflampas P, Dayal S, Chandrakumaran K, et al. Pre-operative tumour marker status predicts recurrence and survival after complete cytoreduction and hyperthermic intraperitoneal chemotherapy for appendiceal Pseudomyxoma Peritonei: analysis of 519 patients. *Eur J Surg Oncol*. 2014;40:515–520.
95. van Eden WJ, Kok NFM, Snaebjornsson P, et al. Factors influencing long-term survival after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for pseudomyxoma peritonei originating from appendiceal neoplasms. *BJS Open*. 2019;3:376–386.
96. Yan F, Lin Y, Zhou Q, et al. Pathological prognostic factors of pseudomyxoma peritonei: comprehensive clinicopathological analysis of 155 cases. *Hum Pathol*. 2020;97:9–18.
97. Mall AS, Chirwa N, Govender D, et al. MUC2, MUC5AC and MUC5B in the mucus of a patient with pseudomyxoma peritonei: biochemical and immunohistochemical study. *Pathol Int*. 2007;57:537–547.
98. Wang L, Liu Z, Fisher KW, et al. Prognostic value of programmed death ligand 1, p53, and Ki-67 in patients with advanced-stage colorectal cancer. *Hum Pathol*. 2018;71:20–29.
99. Prueter J, Norvell D, Backous D. Ki-67 index as a predictor of vestibular schwannoma regrowth or recurrence. *J Laryngol Otol*. 2019;133:205–207.
100. Arjona-Sánchez Á, Martínez-López A, Valenzuela-Molina F, et al. A proposal for modification of the PSOGI classification according to the Ki-67 proliferation index in pseudomyxoma peritonei. *Ann Surg Oncol*. 2022;29:126–136.
101. Kanapathipillai M. Treating p53 mutant aggregation-associated cancer. *Cancers (Basel)*. 2018;10:154.
102. Kim J, Yu L, Chen W, et al. Wild-type p53 promotes cancer metabolic switch by inducing PUMA-dependent suppression of oxidative phosphorylation. *Cancer Cell*. 2019;35:191–203.e8.
103. Shi M, Shtraizent N, Polotskaia A, et al. Impedimetric detection of mutant p53 biomarker-driven metastatic breast cancers under hyposmotic pressure. *PLoS One*. 2014;9:e99351.
104. Pengelly RJ, Rowaiye B, Pickard K, et al. Analysis of mutation and loss of heterozygosity by whole-exome sequencing yields insights into pseudomyxoma peritonei. *J Mol Diagn*. 2018;20:635–642.
105. Haluska F, Pemberton T, Ibrahim N, et al. The RTK/RAS/BRAF/PI3K pathways in melanoma: biology, small molecule inhibitors, and potential applications. *Semin Oncol*. 2007;34:546–554.
106. Pietrantonio F, Perrone F, Mennitto A, et al. Toward the molecular dissection of peritoneal pseudomyxoma. *Ann Oncol*. 2016;27:2097–2103.
107. Pietrantonio F, Berenato R, Maggi C, et al. GNAS mutations as prognostic biomarker in patients with relapsed peritoneal pseudomyxoma receiving metronomic capecitabine and bevacizumab: a clinical and translational study. *J Transl Med*. 2016;14:125.
108. Flatmark K, Torgunrud A, Fleten KG, et al. Peptide vaccine targeting mutated GNAS: a potential novel treatment for pseudomyxoma peritonei. *J Immunother Cancer*. 2021;9:e003109.
109. Noguchi R, Yano H, Gohda Y, et al. Molecular profiles of high-grade and low-grade pseudomyxoma peritonei. *Cancer Med*. 2015;4:1809–1816.