European Journal of Surgical Oncology xxx (xxxx) xxx

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Appendiceal tumours and pseudomyxoma peritonei: Literature review with PSOGI/EURACAN clinical practice guidelines for diagnosis and treatment

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ARTICLE INFO

Article history:
Received 10 February 2020
Accepted 12 February 2020
Available online xxx

Keywords:
Appendiceal
Pseudomyxoma peritonei
Cytoreductive surgery
Hyperthermic intraperitoneal chemotherapy
Delphi
GRADE

ABSTRACT

Pseudomyxoma Peritonei (PMP) is a rare peritoneal malignancy, most commonly originating from a perforated epithelial tumour of the appendix. Given its rarity, randomized controlled trials on treatment strategies are lacking, nor likely to be performed in the foreseeable future. However, many questions regarding the management of appendiceal tumours, especially when accompanied by PMP, remain unanswered. This consensus statement was initiated by members of the Peritoneal Surface Oncology Group International (PSOGI) Executive Committee as part of a global advisory role in the management of uncommon peritoneal malignancies. The manuscript concerns an overview and analysis of the literature on mucinous appendiceal tumours with, or without, PMP. Recommendations are provided based on three Delphi voting rounds with GRADE-based questions amongst a panel of 80 worldwide PMP experts.

Introduction

Pseudomyxoma Peritonei (PMP) is a rare peritoneal malignancy, most commonly originating from a perforated epithelial tumour of the appendix. It has an estimated incidence of one to three per million people annually [1]. PMP, also known as "Jelly belly", is characterized by diffuse progressive mucinous ascites. The clinical presentation of PMP is variable, and non-specific. Many patients are asymptomatic and PMP is often found incidentally at cross-sectional imaging, laparoscopy or laparotomy. A proportion of patients present with appendicitis; and the most common symptoms are abdominal bloating, pain an distension [1]. Furthermore, in 0.7–1.7% of appendicectomy specimens removed for suspicion of appendicitis, an epithelial appendiceal tumour is detected unexpectedly at histological assessment [2].

As a consequence of gradual accumulation of intra-abdominal mucinous ascites, patients with PMP usually present at an advanced stage. Since the 1980's, the introduction and widespread use of Cytoreductive Surgery (CRS) and perioperative Hyperthermic Intraperitoneal Chemotherapy (HIPEC) has provided a treatment option improving prognosis, outcome, and quality of life with potential for cure for patients with PMP [3–5]. Given the rarity of PMP, randomized controlled trials on treatment strategies are lacking, nor likely to be performed in the foreseeable future. However, many questions regarding the management of appendiceal tumours, especially when accompanied by PMP, remain unanswered. Therefore, consensus guidelines based on review and analysis of the available literature and expert opinion could help clinical decision making when PMP is encountered.

This consensus statement was initiated by members of the

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https://doi.org/10.1016/j.ejso.2020.02.012
0748-7983/

Peritoneal Surface Oncology Group International (PSOGI) Executive Committee as part of a global advisory role in the management of uncommon peritoneal malignancies. The manuscript concerns an overview and analysis of the literature on mucinous appendiceal tumours with, or without, PMP. Recommendations are provided base on three Delphi voting rounds with GRADE-based questions amongst a panel of 80 worldwide PMP experts [6].

Responsibilities

These recommendations are statements based on review of the evidence and consensus of the authors, regarding their assessment of currently accepted approaches to diagnosis and treatment. They do not include any economic analysis of the strategies. Any clinician applying, or consulting, these recommendations is expected to use independent medical judgment, in the context of individual clinical circumstances, to determine any patient's care or treatment. These recommendations make no representations, nor warranties of any kind, regarding their content, use or application and the authors disclaim any responsibility for their application or use in any way.

Materials and methods

The methodology used in this consensus statement, including the Delphi technique and the GRADE system, has been extensively described elsewhere [6]. In brief, the Delphi technique was used as a framework for this consensus statement.

Questions were set up according to the GRADE system (Grades of Recommendation, Assessment, Development, and Evaluation) using the PICO-model (Patient, Intervention, Control, Outcome). Level of evidence (LoE) was categorized into four answers: 'high', 'moderate', 'low', and 'very low' LoE (Table 1). The strength of recommendation (SoR) was either 'strong' or 'weak', with either a 'positive' or 'negative' answer regarding a certain option, resulting in four possible options (Table 2).

The PMP expert panel consisted of 80 worldwide experts, who participated during three voting rounds to gain consensus on 69 questions.

Results

Terminology and pathological classification

Appendiceal neoplasms are rare but have a range of pathological features, diverse pathological classification systems and variable biological behavior. Generally, the following PSOGI consensus classification has been accepted globally as outlined here [7].

* Mucinous epithelial neoplasms
  - Serrated polyp
  - Low grade mucinous neoplasm - LAMN
  - High grade mucinous neoplasm - HAMN
  - Mucinous adenocarcinoma (with or without signet ring cells)
* Non-mucinous epithelial neoplasms
  - Adenoma (colorectal type)
  - Adenocarcinoma
* Epithelial neoplasms with neuro-endocrine features
  - Neuro-endocrine tumour
  - Goblet Cell Carcinoid -GCC
* Mesenchymal neoplasms

These consensus guidelines mostly relate to mucinous appendiceal neoplasms which can be associated with peritoneal dissemination (pseudomyxoma peritonei (PMP): low grade appendiceal neoplasms (LAMN), high grade appendiceal neoplasms (HAMN), mucinous adenocarcinoma (with or without signet ring cells) and goblet cell carcinoids (GCC). Peritoneal seeding of all other appendiceal lesions should be regarded as peritoneal metastases [8–10]. It is important to appreciate that appendiceal PMP is a clinical entity that incorporates two malignant components -the appendix primary and the secondary peritoneal disease-both having an individual histological subclassification, sometimes with discordance. Appendiceal PMP generally has been classified according to the histology of the peritoneal disease and not specifically on the appendix primary histology. At the PSOGI meeting in Berlin 2012 persistent lack of uniform terminology was recognized and consequently, in 2016, a consensus was adopted on diagnostic terminology for appendiceal mucinous tumours with, or without, peritoneal disease [7]. Tables 3 and 4 provide an overview on categorization of primary appendiceal neoplasms and of concomitant peritoneal disease with agreed PSOGI consensus and comparisons with other commonly used classification systems.

From the first round of voting already 98.2% of the PMP expert panel recommended the PSOGI 2016 consensus terminology for histological classification of appendiceal PMP.

Recommendation 1

Adoption of the PSOGI 2016 consensus terminology for histological classification of appendiceal PMP.

LoE: High

SoR: Strong positive

Consensus: (I)98.2% (II)1.8% (III)0% (IV)0%

Pre-operative evaluation

Serum tumour markers

A histopathological binary classification system does not reliably predict biological behavior of appendiceal PMP [7]. Additionally, the extent of disease does not accurately correlate with outcome, provided complete cytoreduction can be achieved, in either a high or a low grade neoplasm. Numerous articles have been published on the role of tumour markers with respect to biological behavior, the ability to achieve complete cytoreduction and DFS as well as OS after CRS and HIPEC [11–21]. Theoretically, tumour marker elevations could have a role in intra-operative decision making, the use of (neo)adjuvant chemotherapy and the intensity and duration of follow-up. The role of CEA, CA 19-9 and CA 125 in the primary evaluation, as well as follow-up, of patients with colorectal, hepatobiliary, pancreatic and ovarian cancer is well known. However, tumour markers can also be elevated in some benign conditions and can vary with age as well as life-style measures [22].

There have been some publications on tumour markers in appendiceal PMP:

In 2002, Van Ruth et al. from the Netherlands reported that both CEA and CA 19-9 were related to tumour load in 63 PMP patients. However, only patients with a higher initial, or non-normalizing level of CA 19-9, had significantly higher recurrence rates (DFS at 2 years 94% compared with 55%) [21].

The Washington Cancer Institute (Sugarbaker et al.) in 2004 analyzed the role of CEA and CA 19-9 in 532 patients presenting with appendiceal PMP over a period of 12 years. They concluded that normal pre-operative tumour markers correlated with a significantly improved survival. Furthermore, an elevated CEA tumour marker, but not CA 19-9, at the time of recurrence seemed to be associated with a significantly reduced prognosis [13].

The Peritoneal Malignancy Institute Basingstoke (Moran et al.) reported in 2004 that elevated tumour markers (CEA, CA-125 and CA19.9) provided important perioperative information about the behaviour of appendiceal PMP. In their experience the 2 year recurrence free survival of 32 patients was significantly lower for

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Table 1
Level of evidence and implications for recommendations [6].

Level of evidence		
A	High	Further research is unlikely to change our confidence in the estimate of effect
B	Moderate	Further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate
C	Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
D	Very low	Any estimate of the effect is very uncertain

For each statement, PMP experts were asked to assign a letter according to the quality of available literature they believe there exists to support or reject it.

Table 2
Strength of Recommendation and implications for clinical practice [6].

Strength of Recommendation		
I	Strong Positive	Should always be performed
II	Weak positive	Could be considered
III	Weak Negative	Should not be considered
IV	Strong Negative	Has no role and should never be considered

For each statement, PMP experts were asked to assign a digit according necessity to support or reject a statement. To facilitate the ease of interpretation from results of voting by the PMP expert panel, the colours red and green given in Tables 3 and 4 as well as Fig. 2 are assigned to positive respectively negative suggestions.

those with a preoperative elevated CEA [11]. Consequently, in 2014 they published a large series of 752 patients with appendiceal PMP, operated on over an 18 year period. The probability of being able to achieve complete CRS dropped from 97% to 50% when comparing patients with normal tumour markers to patients in whom all three were elevated. Additionally, even after complete CRS and HIPEC, preoperative elevation of tumour markers had a significant negative impact on DFS and OS [20]. Given these findings on the adverse effect of tumour markers on prognosis, even in low-grade tumours, and determining this finding preoperatively may help to identify a subset of patients who might not benefit from (upfront) CRS and HIPEC. Elevation of at least one tumour marker appeared to be the norm in >70% of patients with appendiceal PMP. Of these approximately 60% had a histologically low grade tumour. The most commonly elevated marker was CEA.

In 2007, the peritoneal malignancy group from Milan (Deraco et al.) analyzed CA 19-9, CA 125, CEA and CA 15-3 in 62 patients over a 9 year time period. Baseline CA 125 level was associated with tumor extent and predicted the ability to achieve complete cytoreduction, the latter being the most important prognostic determinant in PMP. CA 19-9 seemed to be an independent predictor of reduced PFS [12]. Subsequently in 2013 they reported on the prognostic significance of preoperative CA 125, CEA and CA19-9 in 150 patients over a 15 year period and proposed that markers were reasonable discriminators for predicting complete cytoreduction. They reported that CA 125 and CA 19.9 in particular were more powerful predictors of outcome compared with traditional prognostic factors such as histology [18].

The Sydney group (D. Morris et al.) have published a number of papers on tumour markers [15–17,23–25]. In 2012 and 2013 they investigated the role of baseline serum levels of CA 19-9, CA 125 and CEA on the outcome of 218 patients treated over 16 years. All tumour markers were identified as factors associated with early recurrence and thus reduced survival, independent of the histological subtype. They identified a subgroup of patients with low grade PMP, but absolute levels of CA 19-9 >1000 U/ml, (in sharp contrast to those where CA 19-9 was <100U/ml) as having comparable 5y OS to high grade lesions. Though it is pertinent to note that PCI was never designed for assessment of PMP, the authors postulated the CA 19-9/PCI ratio was a surrogate for differences in tumour biology within the subgroup of patients with low grade PMP. There seemed to be an additive negative effect of a concurrently elevated CEA/PCI ratio on OS.

A recent study from Finland investigated tissue expression patterns of CEA, CA 19.9 and CA 125 in 91 appendiceal PMP cases by immunohistochemistry. The CEA serum level clearly correlated with PCI but not with histological subtype or prognosis. All PMP tumours showed EpCAM immunopositivity. The authors suggested the possibility of exploiting CEA and EpCAM-targeted therapy against appendiceal PMP [19].

About two-thirds of the PMP expert panel believes there exists moderate evidence to recommend mandatory inclusion of the following tumour markers in the preoperative workup: CEA, CA19.9 and CA 125.

Recommendation 2:

Determination of baseline serum CEA level in the preoperative workup of appendiceal PMP patients is mandatory

LoE: Moderate
SoR: Strong positive
Consensus: (I)69.6% (II)30.4% (III)0% (IV)0%

Recommendation 3:

Determination of baseline serum CA 19.9 level is mandatory in the preoperative workup of appendiceal PMP patients.

LoE: Moderate
SoR: Strong positive
Consensus: (I)67.9% (II)30.4% (III)1.8% (IV)0%

Recommendation 4:

The determination of baseline serum CA 125 level in the preoperative workup of appendiceal PMP patients could be done.

LoE: Moderate
SoR: Weak positive
Consensus: (I)32.1% (II)60.7% (III)7.1% (IV)0%

Cross sectional imaging

* **CT**. Abdomino-pelvic CT has been the most common imaging modality in detection, staging as well as postoperative follow-up of PMP. This may be partly due to accessibility, cost and the ease of interpretation by the relatively non-trained radiological eye. The sensitivity of CT scanning in detecting peritoneal disease depends on the size and location of the tumour nodules but generally underestimates the extent of disease. The reported sensitivity of detecting lesions drops from 59 - 94% in >5 cm nodules to 19–28% for lesions <1 cm and only 11–28% for identifying lesions <0.5 cm. The sensitivity of a CT scan in detecting small bowel involvement and mesenteric involvement is low and ranged between 8 % - 17% in one series [26] and 18%–55% in another [27].

Several attempts have been undertaken to standardize CT

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Table 3
Primary tumours of the appendix [2,6,7,10,59].

PSOGI definition	Characteristics	Other classification system	Treatment
Adenoma	Confined to mucosa. Intact muscularis mucosae. Tubular, tubulovillous or villous with low or high grade dysplasia: morphology the same as colorectal lesions. No serrated features.		Follow up **(1B, 96%)**
Serrated polyp	Tumour with serrated features confined to mucosa with low or high grade dysplasia. Commonly resemble sessile serrated adenoma of the colorectum		Follow up **(1B, 96%)**
Low grade appendiceal mucinous neoplasm (LAMN)	Mucinous neoplasm with low grade cytologica atypia (monolayer of cells with small, basally-located nuclei, inconspicuous nucleoli, usually abundant cytoplasmic mucin, rare mitoses) and any of following -loss of lamina propria and muscularis mucosae -fibrosis of submucosa -pushing growth into the wall -dissection acellular mucin in wall -mucin and/or neoplastic cells outside the wall	**8th ed AJCC (TNM) Low grade, well differentiated, G1** *Since usually loss lamina propria, muscularis mucosae and fibrosis submucosa no T1 or T2* *BUT* **pTis (LAMN)** = confined to the muscularis propria including acellular mucin extending into muscularis propria **LAMN pT3 =** invading through muscularis propria into muscularissubserosa or mesoappendix **LAMN pT4a =** Acellular or neoplastic mucinous epithelium penetrates the visceral peritoneal surface **LAMN pT4b** =Acellular or neoplastic mucinous epithelium on adjacent structures **McDonald** **type 1 LAMN=** lesion confined to the appendiceal lumen **Type 2 LAMN=** appendiceal rupture, mucin spillage in the abdominal cavity, mucin and/or neoplastic epithelium in the appendiceal wall	**Perforation** *** NO** RHC **(4B, 89%)** CRS/HIPEC **(4B, 87%)** **→ follow up** *** YES** **a. No PD** **→ pT4M0** **-acellular** RHC **(3C, 60%)** CRS/HIPEC **(2B, 71%)** **-cellular** RHC **(3B, 58%)** CRS/HIPEC **(2B, 79%)** **b. PD** - **PCI <3** **Acellular (M1a)** RHC **(4C, 57%)** CRS/HIPEC **(2B, 61%** **Cellular (M1b)** RHC **(4C, 68%)** CRS/HIPEC **(2B, 61%)** - **PCI >3** RHC **(4B, 70%)** CRS/HIPEC **(1B, 84%)**
High grade appendiceal mucinous neoplasm (HAMN)	(At least focally) high grade cytologic atypia with the architectural features of LAMN but no infiltrative invasion. High grade features include -loss of polarity with full- thickness nuclear stratification -nuclei that are enlarged, markedly hyperchromatic or vesicular -prominent nucleoli -numerous or atypical mitotic figures -cribriform growth		**Perforation** *** NO** RHC **(2C, 67%)** CRS/HIPEC **(2C, 56%)** *** YES** **c. No PD** ReHC/HIPEC **(1B 58,2%)** **(<T4, M0)** ReHC/HIPEC **(1C, 45,5%)** **(M1b, only surface (2C, 40%)** **d. PD** RHC **(2B, 76%)** CRS/HIPEC
Mucinous adenocarcinoma	Mucinous neoplasm with infiltrative invasion (tumour budding, small angulated glands and/or desmoplasia-includes cells within small infiltrative mucin pools) without signet ring cells. Subdivision into well, moderately or poorly differentiated possible	**8th ed AJCC (TNM) G2 or G3 , moderately or poorly differentiated**	**Perforation** *** NO** RHC **(1B, 84%)** CRS/HIPEC **(2C, 58%)** *** YES** **a. No PD** CRS/HIPEC **(1B, 62%)** **b. PD (1C, 76%)**

imaging technique as a preoperative assessment tool in appendiceal PMP. Examples of these are the simplified preoperative assessment for appendix tumor (SPAAT) score, in which a total of less than 3 demonstrated an accuracy of 97.14% in determining complete cytoreduction [28]. Recently a French group published a scoring system, specifically for PMP, based on 5 locations in the perihepatic region predicting resectability, with a sensitivity of 94% and specificity of 81% [29]. Furthermore, the absence of a tumour mass of 5 cm, or greater, in the epigastric region and/or loss of normal architecture of the small bowel causing near-obstruction and/or mesenteric changes on preoperative CT has been shown to predict a 94% probability of complete cytoreductive surgery (CCRS) [30].

Overall 96.4% of the PMP expert panel agreed that a high level of evidence exists for recommending CT-evaluation as the preferred preoperative imaging modality**.**

Recommendation 5:

Preoperative CT evaluation of patients with appendiceal PMP should be the preferred diagnostic imaging modality.

LoE: High

SoR: Strong positive

Consensus: (I)96.4% (II)3.6% (III)0% (IV)0%

* **MRI**. MRI is increasingly being recognized as an alternative imaging modality and, according to some, at least equivalent to CT for diagnosis and surveillance of peritoneal malignancy [31–33]. MRI does not subject the patient to potential risks of exposure to

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Mucinous adenocarcinoma with signet ring cells	Mucinous neoplasm with infiltrative invasion with signet ring cell component accounting for ≤ 50% of the tumour cells	**8th ed AJCC (TNM) G3, poorly differentiated**	
Mucinous signet ring cell carcinoma	Mucinous neoplasm with infiltrative invasion with signet ring cell component accounting for >50% of the tumour cells	**8th ed AJCC (TNM) G3, poorly differentiated**	
Non-mucinous adenocarcinoma	Adenocarcinoma resembling those traditionally seen in colorectal cancer. Can be well, moderately or poorly differentiated		
Neuroendocrine tumour	*Almost all grade 1 or 2 (previously termed "carcinoid"). Thought to arise from subepithelial neuroendocrine cells present in lamina propria and submucosa. Lesions <10mm with no adverse histological features rarely metastasize Of two types: -enterochromaffin cell (EC): common islands of cells, sometimes with acinar structures -L cell: rare trabeculae and small tubules (the very rare "tubular carcinoid" is probably a variant of this type) *Grade 3 is exceptionally rare in the appendix [52]	Carcinoid	
Goblet cell carcinoma (GCC) *We recommend uptake of this suggested alternative terminology for "goblet cell carcinoid"*	A type of adenocarcinoma showing combined mucinous and neuroendocrine differentiation. Metastasis is more likely if there are adverse histological features. Tang classification[179]: - Tang A: typical GCC (cohesive clusters with minimal atypia). - Tang B: adenocarcinoma ex-GCC signet ring type (irregular large clusters, discohesive growth, significant cytological atypia, desmoplasia or destruction of the appendiceal wall). - Tang C: Adenocarcinoma ex-goblet cell carcinoid, poorly differentiated type (a component at least 1mm 2 comprising sheets of signet ring cells or poorly differentiated adenocarcinoma of gland-forming colorectal-type or undifferentiated type).	Mixed GCC-adenocarcinoma Other names: mucinous carcinoid, adenocarcinoid, crypt cell carcinoma, mixed adenoneuroendocrine carcinoma (MANEC – *not recommended in this context*)	**No adverse features:** -Tang A -pT1/T2 <20mm -margin clear -Mesoapp inv. <3mm -No angio- or neuroinvasion -KI-67 <2% **RHC 3C, 66%** **→ follow-up** **Adverse features** **RHC 1B, 78%** **→ Perforation?** **NO** CRS/HIPEC **(3C, 75%)** **YES** CRS/HIPEC **(2C, 76%)**
	Characteristic submucosal concentric growth pattern which makes this disease entity -prone for distant metastasis (mainly peritoneum) even with a low rate of lymph node spread -diffuse thickening whole appendix or at the base but not developing a well circumscribed appendiceal mass, which accounts for the common delay in diagnosis.[180]		
Mesenchymal tumours	GIST, neuroma, lymphoma, Kaposi's sarcoma, granular cell tumour		

This table provides an overview on categorization of primary appendiceal neoplasms according to PSOGI consensus and comparisons with other commonly used classification systems. The figures that are shown between brackets in the treatment column, concern the result of voting by PMP expert panel (according to Delphi and GRADE methodology). Again, in order to facilitate the ease of interpretation, the colours red and green are assigned to positive respectively negative results of voting by the PMP expert panel.

irradiation. In a comparison with surgical PCI, MRI correctly categorized tumor volume in 20 (0.91) of 22 patients in a study by Low et al. [34] However, MRI has been shown to be more difficult to accurately interpret by the less experienced observer [33]. This imaging technique may be particularly useful for evaluation of the hepatic hilar region and for detecting subtle small bowel involvement [32–34].

Recommendation 6:

Cross sectional imaging with MRI could be one of the diagnostic imaging modalities for patients with appendiceal PMP.

LoE: Moderate

SoR: Weak positive

Consensus: (I)8.9% (II)91.1% (III)0% (IV)0%

* **PET CT**. There is limited data on the role of PET-CT in PMP with the known caveat that PET-CT has limitations in mucinous tumour staging. Preoperative ^{18}F-FDG PET may predict pathological grade and completeness of cytoreduction, which are the two main prognostic factors in patients with PMP [35]. Furthermore, FDG-PET

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Table 4
Classification of peritoneal disease [6,7,10].

PSOGI definition	characteristics	Other classification system	Treatment
PSEUDOMYXOMA PERITONEI			
Acellular mucin	Mucin without neoplastic epithelium; can be confined to vicinity of the organ of origin or distant from it	8th ed AJCC (TNM): **M1a**	RHC **(4B, 66%)** CRS/HIPEC(4B, 66%)
Low grade mucinous carcinoma peritonei	Cytologically low grade Few mitoses Mucinous epithelium is scant (<20% tumour volume)	8th ed AJCC (TNM): **M1b**. G1, well differentiated Ronnett: Disseminated peritoneal adenomucinosis (DPAM)	RHC **(3B, 61%)** CRS/HIPEC(3B, 61%)
High grade mucinous carcinoma peritonei	-Presence of one or more of the following, at least focally: * high grade cytology * infiltrative invasion into adjacent tissue * angiolymphatic or perineural invasion * cribriform growth -Abundant neoplastic mucinous epithelium (>20% tumour volume) -Subclassification according to differentiation[181] *Well: °*composed predominantly of single tubular glands* °*tumour cells well polarized* °*remarkable atypia tumour cells* °*invasive component* *Moderately: °*solid sheets of malignant cells admixed with glandular formations* °*minimal or absent polarity* *Poorly: °*highly irregular to no glandular differentiation* °*polarity cells has disappeared*	8th ed AJCC (TNM): M1b. G2 or G3, moderately or poorly differentiated Ronnett: Peritoneal mucinous carcinomatosis which can be well (PMCA-I), moderately or poorly differentiated (both PMCA)	RHC **(2B, 59%)** CRS/HIPEC**(2B, 59%)**
High grade mucinous carcinoma peritonei with signet ring cells	Neoplasm with signet ring cell component (we recommend a minimum of 10% signet ring cells for this classification)	8th ed AJCC (TNM): M1b. G3, poorly differentiated Peritoneal mucinous carcinomatosis with signet ring cells (PMCA-S)	RHC **(1B, 71%)** CRS/HIPEC(1B, 71%)
PERITONEAL CARCINOMATOSIS	Peritoneal dissemination from a non-mucinous appendiceal adenocarcinoma	Intestinal type peritoneal metastasis	

This table provides an overview on categorization of peritoneal disease in appendiceal PMP according to PSOGI consensus and comparisons with other commonly used classification systems. The figures that are shown between brackets in the treatment column, concern the result of voting by PMP expert panel (according to Delphi and GRADE methodology). Again, in order to facilitate the ease of interpretation, the colours red and green are assigned to positive respectively negative results of voting by the PMP expert panel.

CT can be used as a predictive factor for PFS as well as for exclusion of extra-abdominal or systemic metastases [36].

Recommendation 7:

PETCT could be one of the diagnostic imaging modalities in the preoperative evaluation of appendiceal PMP

LoE: Low

SoR: Weak positive

Consensus: (I)3.6% (II)48.2% (III)35.7% (IV)12.5%

Colonoscopy

Embryologically the appendix is derived from the colon and thus has a similar histological structure. In patients with colorectal cancer, pre- and postoperative colonoscopic assessment is recommended given the known risk of 3–5% synchronous and 2–3% metachronous colorectal neoplasia [37,38]. There have been reports of an increased incidence of appendiceal neoplasia in patients presenting with a colorectal cancer [39,40]. The opposite (an increased risk of colorectal neoplasia in a patient with an appendix tumour) has also been reported [41–44].

In total 76.8% of the PMP expert panel voted that moderate level of evidence exists for strongly advising colonoscopy in the preoperative work-up of patients with appendiceal PMP.

Recommendation 8:

In appendiceal PMP patients eligible for CRS and HIPEC a preoperative colonoscopy to exclude second primaries should be performed.

LoE: Moderate

SoR: Strong positive

Consensus: (I)76.8% (II)21.4% (III)1.8% (IV)0%

Role of laparoscopy in diagnosis and staging of appendiceal PMP

The extent of disease and, more importantly, the ability to achieve complete cytoreduction, determines the appropriateness and effectiveness of CRS and HIPEC. The limiting factor often is low volume or miliary small bowel involvement, which is currently undetectable by cross-sectional imaging.

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The best method for assessing peritoneal malignancy is undoubtedly laparotomy. However, exploratory laparotomy to determine resectability involves substantial morbidity, a risk of tumor seeding in the wound and might delay adjuvant treatment. For these reasons diagnostic laparoscopy has some advantages. Laparoscopy can be a minimal access means to predict resectability, gain pathological proof and avoid futile laparotomy [45–47]. If laparoscopic evaluation is performed, some authors advocate midline positioning of the trocars, if at all feasible, in order to decrease morbidity of subsequent resection of these potential seeding pathways during CRS/HIPEC [48]. Some authors suggest that, in general, diaphragmatic biopsies at laparoscopy should be avoided because of the risk of diaphragmatic perforation and subsequent pleural seeding [45].

Advantages of laparoscopy [47,49].

- Assessing overt small bowel serosal and mesenteric involvement
- Estimating PCI and specific organ involvement in order to have accurate knowledge to predict likelihood of completeness of cytoreduction
- Allowing a biopsy if required
- Facilitating restaging after neo-adjuvant treatment
- assessing low grade disease with only minimal involvement, or acellular mucin, where a watch and wait protocol might be appropriate, especially in young women of childbearing age
- staging high grade disease with extensive small bowel involvement who might benefit from systemic chemotherapy rather than from extensive surgery. This may be appropriate for appendiceal lesions with more aggressive biological behavior, and thus more likely to involve the small bowel, such as Goblet Cell Carcinomas (GCC), or high grade appendiceal mucinous neoplasms with signet ring cells.

Limitations of laparoscopy include [47,49].

- The inability to correctly assess involvement of retro-peritoneal structures such as ureters and pancreas
- Difficulty in assessing the depth of involvement of the hepatic pedicle
- Difficulty in assessing depth of involvement of diaphragmatic lesions
- Inaccessibility to the lesser sac and coeliac axis
- Limitations due to extensive masses, thick mucin and/or a large omental cake

A further reason for the ongoing debate on the role of laparoscopy, in advanced PMP, concerns the fact that even in cases in which complete CRS may not be achievable, major tumour debulking might improve quality and quantity of life [8,50].

Recommendation 9:

Laparoscopic evaluation in the preoperative work-up of patients expected to have appendiceal PMP, in order to obtain tissue diagnosis and estimate resectability, could be done

LoE: Moderate
SoR: Weak positive
Consensus: (I)7.1% (II)83.9% (III)8.9% (IV)0%

Recommendation 10:

If indicated, the preoperative laparoscopic evaluation of appendiceal PMP patients should necessarily be done by a surgeon with expertise in PSM.

LoE: Low
SoR: Strong positive
Consensus: (I)73.2% (II)23.2% (III)3.6% (IV)0%

Recommendation 11:

In patients with appendiceal PMP who undergo preoperative laparoscopic evaluation, midline placement of trocars, if feasible, to allow port excision during subsequent surgery is mandatory.

LoE: Low
SoR: Strong positive
Consensus: (I)71.4% (II)26.8% (III)1.8% (IV)0%

Histological confirmation appendix primary necessary? In specialized center?

The widespread availability and increased use of cross-sectional imaging has resulted in an increased detection of appendiceal lesions and/or PMP. Since radiological findings may strongly predict appendiceal PMP, it is debatable as to whether histological confirmation is necessary prior to definitive treatment and if so, the best mechanism to obtain representative tissue. Image guided cytology usually is associated with difficulty in aspirating the mucinous content. Additionally, cytological examination frequently only results in acellular mucin.

Recommendation 12:

In case of a clear diagnosis of appendiceal PMP, based on clinical presentation, imaging and laboratory findings, histological diagnostic confirmation prior to therapeutic decision making, could be done.

LoE: Low
SoR: Weak positive
Consensus: (I)19.6% (II)71.4% (III)7.1% (IV)1.8%

Recommendation 13:

In case there is a need for pathological diagnosis of appendiceal PMP, the analysis of adequate tissue specimens obtained from core needle biopsy or explorative laparoscopy could be done, as an option to cytologic examination of material collected by fine needle biopsy

LoE: Moderate
SoR: Weak positive
Consensus: (I)23.2% (II)75% (III)1.8% (IV)0%

Recommendation 14:

A histological review of the diagnosis of an appendiceal neoplasm or PMP by a pathologist with expertise in PSM should always be done

LoE: High
SoR: Strong positive
Consensus: (I)92.9% (II)7.1% (III)0% (IV)0%

Unexpected appendiceal tumour

Incidental appendiceal malignancy in appendectomy specimen

* **Mucinous cystadenoma, serrated adenomas and hyperplastic polyps**. Lee et al. analyzed the occurrence of 14 mucinous cystadenomas in 3744 appendectomies. There was no tumour recurrence observed during a median follow up of 31.9 months when a clear tumour resection margin was achieved [51]. Murphy et al. performed a systematic review on unexpected appendiceal neoplasms and concluded that serrated adenomas and hyperplastic polyps have no cellular atypia and thus only require an appendicectomy [2].

Recommendation 15:

In case a serrated adenoma or hyperplastic polyp is found after appendicectomy, with clear margins, follow-up is indicated.

LoE: Moderate
SoR: Strong positive
Consensus: (I) 96.4%, (II) 3.6%, (III) 0.0%, (IV) 0.0%

* **Carcinoid tumours**. A consensus statement on the treatment of neuroendocrine tumours (NET) of the appendix (excluding goblet cell carcinomas) was performed by Pape et al., in 2016 [52]. They concluded that an appendectomy was sufficient in tumours smaller than 1 cm with clear resection margins. A right sided

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hemicolectomy could be performed in any tumour of 1–2 cm, or with positive or unclear margins, or with mesoappendiceal invasion >3 mm, or with vascular invasion, or with a G2 proliferation rate (Ki67 3–20%). A right sided hemicolectomy was recommended for a carcinoid tumour larger than 2 cm or with a G3 proliferation rate (Ki67 > 20%).

A systematic review by Murphy et al. and a retrospective analysis from Lee et al. were in agreement with these recommendations [2,51].

Goblet cell carcinomas (GCC) of the appendix are considered more aggressive than (other) NETs, and could behave more like appendiceal adenocarcinomas in terms of lymph node involvement, chance of peritoneal spread, and prognosis [53–56].Thus, they should not be considered merely a variant of neuro-endocrine tumours, as this would suggest a low-grade behaviour. Staging, treatment and follow-up of a Goblet cell carcinoma in presence of negative prognostic factors, probably requires a more aggressive approach similar to that of adenocarcinomas [55,56].

Clift et al. reported on 21 patients with a goblet cell carcinoma of the appendix [57]. Tang A, B, and C lesions were present in 10, 8, and 3 patients, respectively. They concluded that patients with a Tang A or B lesion had superior OS in comparison with patients with a Tang C lesion (73.1–83.7 vs. 28.5 months). Smaller tumour size (pT1/T2) and/or tumours with Ki67 < 2% also correlated with an increased OS.

McConnell et al. compared 45 patients with a goblet cell carcinoma treated with CRS and HIPEC with 708 patients with other appendiceal neoplasms treated with CRS and HIPEC [58]. A particularly striking observation was the high rate of lymph node involvement in patients with a goblet cell adenocarcinoma (52%) compared to patients with low (6.4%) or high (20%) grade appendiceal malignancies. The rate of complete cytoreduction was comparable in the three groups. The 3-year DFS and OS were 72.6% and 91.6%, respectively, for patients with low grade appendiceal malignancies compared with 44.2% and 61.5%, respectively, for patients with high grade appendiceal malignancies, and 47.7% and 68.1%, respectively, in patients with goblet cell adenocarcinomas.

In conclusion, there is general consensus on the treatment of neuro-endocrine tumours (excluding goblet cell carcinoid tumours). Goblet cell carcinomas, in presence of negative prognostic factors, express such an aggressive behaviour that probably an approach similar to that of a (mucinous) adenocarcinoma of the appendix is required. For this reason, the latter appendiceal malignancy is displayed faded in Fig. 2.

Recommendation 16

In case of a neuro-endocrine tumour smaller than* 10 mm, *with clear margins, mesoappendiceal invasion* <3 mm, *absence of angio- or neuro-invasion, and Ki67* < *2%, without evidence of PMP, there is no role for a right-sided hemicolectomy and this should never be considered.

LoE: Moderate

SoR: Strong negative

Consensus: (I) 0.0%, (II) 1.8%, (III) 9.1%, (IV) 89.1%

Recommendation 17

In case of a neuro-endocrine tumour that deviates from one or more of the following features (*<10 mm, *clear margins, mesoappendiceal invasion* <3 mm, *no angio- or neuro-invasion, and Ki67* < *2%), without evidence of PMP, a right-sided hemicolectomy could be considered.

LoE: Moderate

SoR: Weak positive

Consensus: (I) 7.3%, (II) 87.3%, (III) 5.5%, (IV) 0.0%

Recommendation 18

In a patient with an appendiceal goblet cell carcinoma which has been classified as a Tang A lesion, with a pT1/T2 tumour* <20 mm, *clear margins, mesoappendiceal invasion* <3 mm, *no angio- or neuro-invasion, and Ki67* < *2%, a right-sided hemicolectomy should not be considered.

LoE: Low

SoR: Weak negative

Consensus: (I) 0.0%, (II) 14.5%, (III) 65.5%, (IV) 20.0%

Recommendation 19

In a patient with a goblet cell carcinoma that deviates from one or more of the following features (Tang A lesion, pT1/T2 tumour* <20 mm, *clear margins, mesoappendiceal invasion* <3 mm, *no angio- or neuro-invasion, and Ki67* < *2%), a right sided hemicolectomy should always be performed.

LoE: Moderate

SoR: Strong positive

Consensus: (I) 78.2%, (II) 18.2%, (III) 3.6%, (IV) 0.0%

Recommendation 20

In a patient diagnosed with a non-perforated goblet cell carcinoma and without evidence of peritoneal spread after preoperative staging, adjuvant CRS and HIPEC should not be considered.

LoE: Low

SoR: Weak negative

Consensus: (I) 1.8%, (II) 9.1%, (III) 74.5%, (IV) 14.5%

Recommendation 21

In a patient diagnosed with a perforated goblet cell carcinoma and without evidence of peritoneal spread after preoperative staging, adjuvant CRS and HIPEC could be considered.

LoE: Very lowSoR: Weak positive

Consensus: (I) 9.1%, (II) 76.4%, (III) 14.5%, (IV) 0.0%

Recommendation 22

In a patient diagnosed with a goblet cell carcinoma and with evidence of peritoneal spread deemed resectable (CCR 0–1) after preoperative staging, adjuvant CRS and HIPEC should always be performed.

LoE: Moderate

SoR: Strong positive

Consensus: (I) 81.8%, (II) 18.2%, (III) 0.0%, (IV) 0.0%

* **Low grade appendiceal mucinous neoplasms**. Two studies, from McDonald et al. and Guaglio et al. described low recurrence rates in 84 patients with a LAMN [59,60]. In the study by Guaglio et al., patients with a PCI up to 3, confined to the right lower quadrant or pelvis, were included in the follow up regime [59,60]. Initial surgery consisted of an appendicectomy in 68 (81%) patients and a right sided hemicolectomy in 16 (19%) patients. The appendix had ruptured in 26 (31%) patients, and mucin was found outside the appendiceal wall in 36 (42.9%) patients. In Guaglio's study, allowing a PCI up to 3, peritoneal implants and/or mucinous ascites were removed at the initial surgery in 9/41 patients. McDonald et al. performed CRS and HIPEC in 17/43 patients, without finding microscopic disseminated disease in any of their patients. In these two studies, at a median follow-up of 40 [13–79] and 58 [9–162] months, none and two patients, respectively, were diagnosed with recurrent disease. With these low recurrence rates, it was proposed that an expectant approach could be considered in LAMN with, or without, low volume PMP.

However, higher recurrence rates were observed by two other cohorts [61,62]. Foster et al. described that 5 (23%) out of 22 patients treated with an appendicectomy for LAMN were found to have recurrent disease during the first year of follow-up [61,62]. In this study, 18 out of 22 (81.2%) appendices had perforated before appendicectomy.

Honore et al. reported on 25 patients with an appendiceal neoplasm, of which 18 were LAMNs. Overall, 19 (76%) appendices had ruptured with free mucin next to the appendix in 9 (36%) patients and disseminated free acellular intraperitoneal mucin without PMP in 10 (25%) patients [62].

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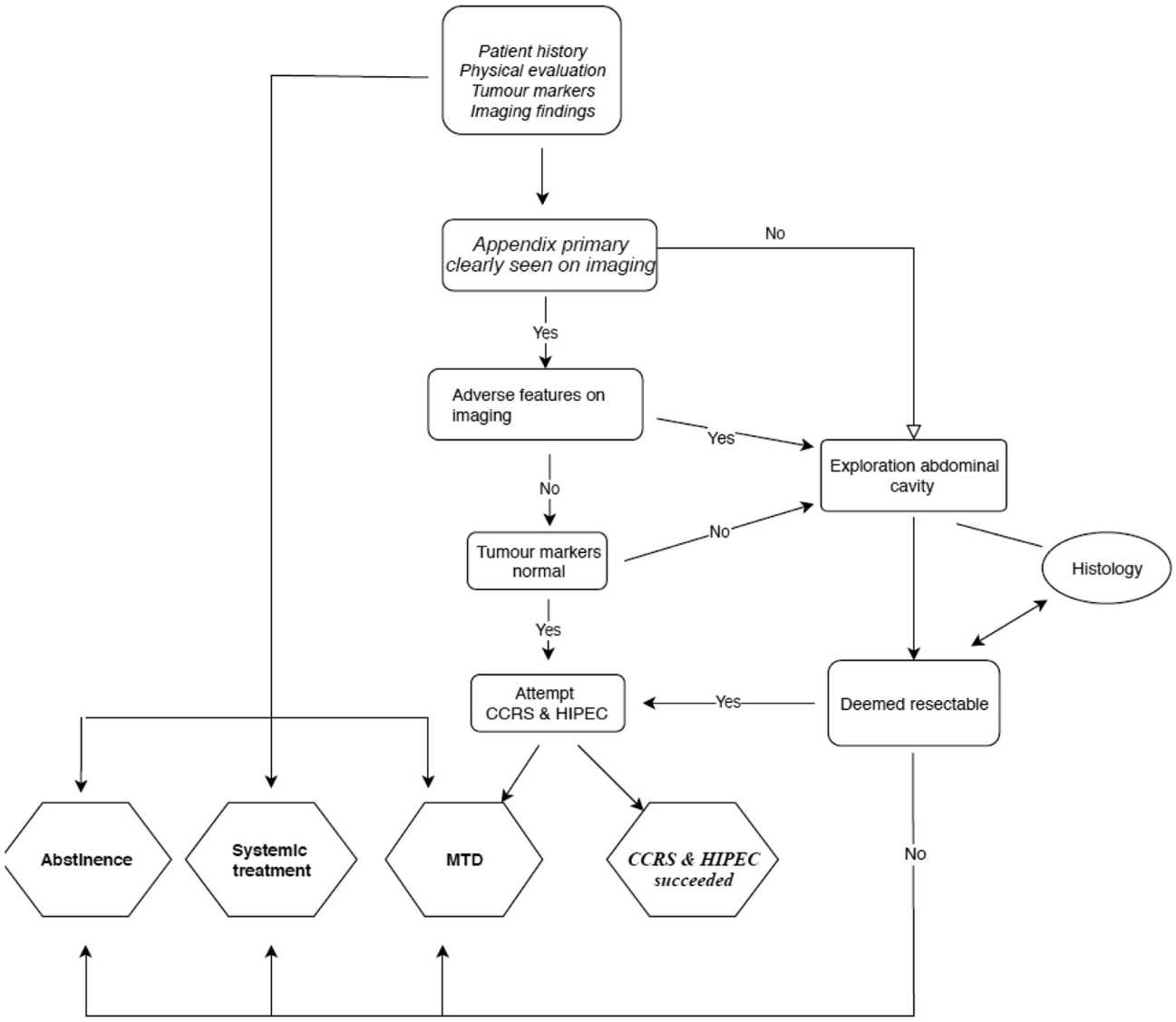

Fig. 1. pre-operative work-up.
Proposal for suggestion for pre-operative evaluation.

In total, 12 (48%) patients developed recurrent disease at a median follow up of 61 [13–121] months. A perforated appendix was associated with a higher recurrence rate (65%) as compared to non-perforated appendices (17%) though the difference was not statistically significant ($p = 0.068$, HR 8.29, 95% CI 0.69–470.4).

This higher recurrence rate in perforated appendices was also reported by Murphy et al. who recommend the consideration of CRS and HIPEC in perforated LAMNs [2].

A retrospective analysis by Fournier et al. searched for prognostic factors predicting the development of PMP in 98 patients with a LAMN of unknown malignant potential (UMP) [63]. Primary surgery was either an appendicectomy in 63 (64.3%) patients or a right sided hemicolectomy in 35 (35.7%) patients. Appendiceal rupture was confirmed at histological analysis in 51 (52%) appendices. Mucin was found on the appendiceal serosa or adjacent peritoneum in 64 (65.3%) patients, and confined to the appendiceal wall in 14 (14.3%) patients. Overall, 19 patients were treated with CRS and HIPEC, although the indication for this approach was not documented. At a median follow-up of 2.6 years (range 0.1–15.3 years), 25 (26%) patients had developed recurrent disease and 10 (10.2%) had died.

In univariate analysis, positive margins, elevated CEA (>3), elevated CA 19.9 (>35), and elevated CA 125 (>35) were significantly associated with a decreased DFS, although only elevated CA 19.9 persisted as a negative prognostic factor in multivariate analysis. OS was not significantly influenced by these factors, though a trend was observed for an elevated CEA and CA 125 correlating with OS in univariate analysis ($p = 0.06$ and $p = 0.08$, respectively). This evidence suggests that normal levels of CEA, CA 125 and CA 19.9 could be used to select patients for expectant treatment.

* **High grade appendiceal mucinous malignancies and adenocarcinomas**. Mehta et al. investigated the incidence of peritoneal spread in 62 patients with a high grade appendiceal malignancy after appendicectomy, of which had 39 appendiceal adenocarcinomas, 21 goblet cell carcinoma and 2 had high grade appendiceal mucinous malignancies (HAMN)at primary surgery [64]. Overall, 35/62 (56.5%) patients had histologically proven peritoneal disease at primary surgery. There was no detectable disease at pre-operative CT imaging and all tumour markers were normal. All 62 patients underwent CRS and HIPEC at 4 (range 1–10)

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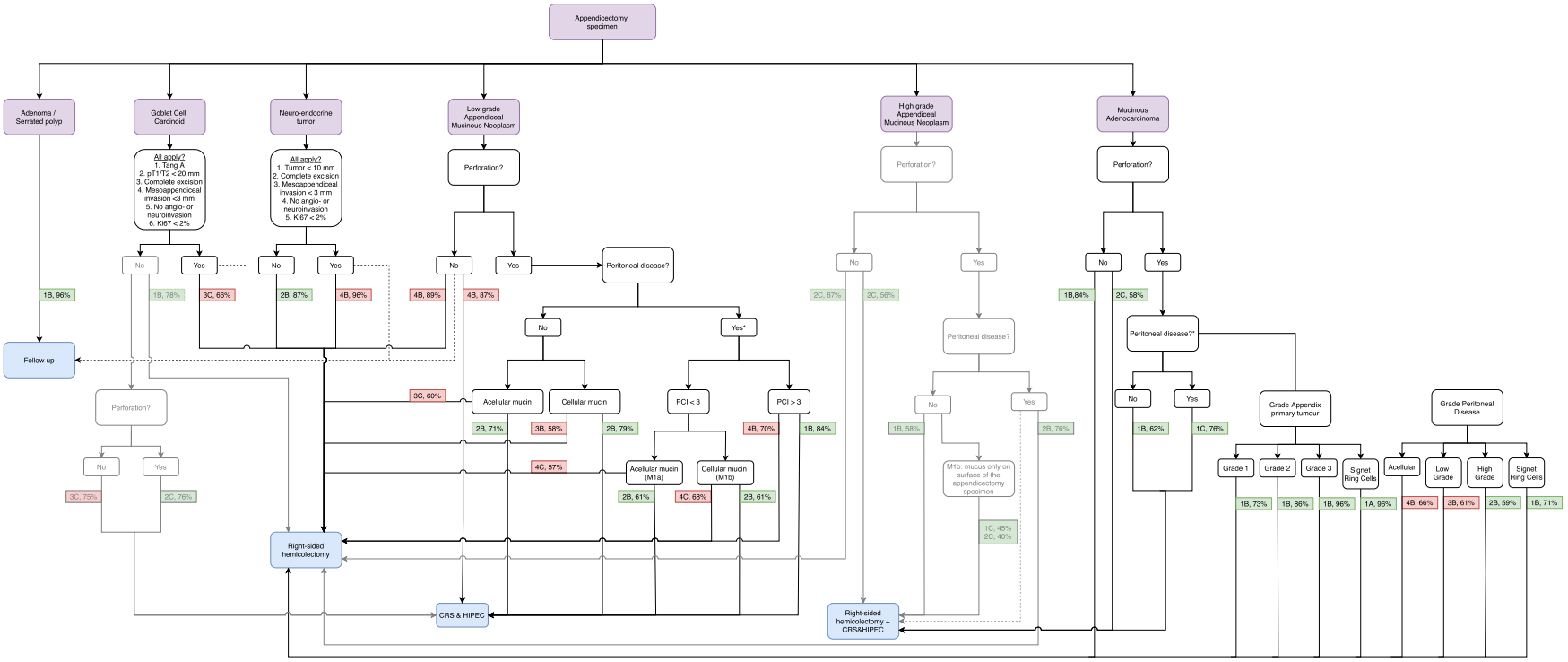

Fig. 2. Treatment algorithm appendiceal neoplasms with or without PMP.
All arrows represent recommendations that were asked to the PMP expert panel. Each arrow is accompanied by a red or green label, containing a digit [1–4], a letter (A-D), and a percentage.The numbers represent the grade of recommendation (Table 2)The letters the quality of evidence (Table 1)The percentage represents the percentage of votes for the recommendation.The red or green flag represents the general direction of the recommendation; red = negative recommendation, green = positive recommendation.Dotted arrows represent recommendations that were not voted for, but can logically be extracted from previous voting.HAMN and GCC are displayed faded because they should prapably be approached like mucinous adenocarcinoma [55–57].

months after appendicectomy, during which macroscopic peritoneal disease was found in 24/62 (39.3%) patients. In 16/24 (67%) patients, peritoneal disease was evident outside the confines of a standard right sided hemicolectomy.

Non-GCC tumours had a significantly higher risk of peritoneal spread as compared to GCC tumours (66% vs. 38%, $p = 0.037$). Remarkably, appendiceal perforation was not associated with a higher risk of peritoneal spread (56.4% vs. 56.5%, $p > 0.05$).

During a median follow-up of 16 [1–128] months, 7 (11.3%) patients developed recurrent disease, of which 3 were able to undergo a second CRS and HIPEC.

Finally, Lee et al. described a small cohort of 5 patients with either a mucinous cystadenocarcinoma ($n = 3$) or an adenocarcinoma ($n = 2$) [51]. Only two patients remained disease-free and were alive at a median follow-up of 31.9 [6–110] months.

Murphy et al. concluded in their systematic review that appendiceal adenocarcinomas are rare, but have a greater tendency for appendiceal rupture and peritoneal spread, leading to PMP [2]. In non-perforated appendices, a right sided hemicolectomy provides a longer OS than an appendicectomy alone. In perforated appendices, or clinical signs of PMP, the authors only advise a right sided hemicolectomy if it's part of a complete CRS and HIPEC.

This evidence suggests that appendiceal (mucinous) adenocarcinomas require a more aggressive treatment approach, such as a right sided hemicolectomy and/or CRS and HIPEC, due to their higher tendency of peritoneal spread, even from non-ruptured appendices. Unfortunately, only a few cases of HAMN have been described, which complicates the formation of a reliable recommendation. Therefore, we would rather suggest that HAMN should be graded, treated, and followed as an appendiceal (mucinous) adenocarcinoma.

Incidental finding of PMP

The common presentations of PMP include acute appendicitis, ovarian mass in females, increasing abdominal distention with, or without, an acute abdomen and a new-onset hernia. If PMP secondary to an appendix primary is detected unexpectedly at surgery, Murphy et al. proposed an appendicectomy with sampling of intraperitoneal mucin. This approach was proposed to confirm histological classification which helps in determination of the next treatment steps [2]. Performing an appendectomy with, or without, caecectomy will provide tissue diagnosis for adequate staging and frequently may achieve definite treatment. According to Gonzalez-Moreno and Sugarbaker, a so called “radical appendectomy” will provide information on the resection margin at the appendix stump or caecum level, surrounding soft tissue and right paracolic sulcus near the appendix, the peritoneum beneath the appendix on the small bowel mesentery, ligament of Treves- and the meso-appendiceal lymph nodes. A radical appendicectomy can be performed at open surgery or laparoscopically [65]. The available literature suggests that a right hemicolectomy (RHC) at this stage, in the absence of HIPEC, is best avoided in order to reduce the risk of tumour implantation in the retro-peritoneal space as well as tumour cell entrapment at the anastomosis complicating any further surgery at a later date. The detrimental effects of violating tissue planes, enabling deep invasion, may compromise definitive treatment and worsen survival outcomes [66,67].

Ovarian metastases from appendiceal neoplasms, commonly known as Krukenberg tumours, may grow rapidly, become increasingly symptomatic and can mimic ovarian cancer. A Taiwanese publication investigated the effect of the extent of surgery during the index operation on the prognosis of patients with an unexpected ovarian metastasis compared with patients with primary ovarian pathology [68]. To minimize misdiagnosis a greater awareness of a differential diagnosis of gastrointestinal, or appendiceal primary tumor metastasis, is strongly recommended. Preoperative determination of serum tumour marker profiles may help. The ratio of cancer antigen 125 (CA-125) to carcinoembryonic antigen (CEA) greater than 25 has been shown to be useful, although not absolute, in distinguishing ovarian cancer from primary gastrointestinal tumours that have metastasized to the peritoneum, the ovaries, or both [68–72]. Sørensen et al. even proposed to increase the CA-125/CEA ratio cut-off value from 25 to 100 since in their retrospective study of patients referred with an undiagnosed tumour in the pelvis they identified an increased specificity to around 85% when applying this [70]. In any case, by using CA-125/CEA ratio rather than one of these tumour markers alone, it seems to be possible to identify a larger proportion of patients with non-ovarian cancers.

The discovery of mucin in a hernia sac should prompt histological assessment of the resected sac and subsequent abdominal imaging [48]. Sugarbaker analyzed his patients who had an inguinal hernia prior to, or at the time of, CRS and HIPEC for appendiceal PMP. At the time of CRS, care was taken in all patients to remove the peritoneal lining of the inguinal canal but no repair of the open inguinal canal was attempted. Patients who had the inguinal hernia repaired prior to definitive treatment with CRS and HIPEC had all tissue and mesh associated with prior herniorrhaphy resected. Since no recurrent inguinal hernias were recorded, Sugarbaker concluded inguinal hernias caused by mucinous ascites and tumor can be definitively treated by CRS plus HIPEC, probably because extraction of tumor and peritoneum from the inguinal canal facilitates fibrous closure of the abdominal wall defect [73].

Recommendation 23

In a patient in whom a non perforated LAMN* is found after appendicectomy, pTis/pT3, pNx, cM0, R0** and no postoperative radiological/biochemical signs of residual disease, there is no role for an additional right sided hemicolectomy and this should never be considered.

LoE: Moderate
SoR: Strong negative
Consensus: (I) 0.0%, (II) 1.8%, (III) 9.1%, (IV) 89.1%

Recommendation 24

In a patient in whom a perforated LAMN* is found after appendicectomy, pT4a-b, pNx, cM0, R0**, with acellular mucin in the visceral peritoneum, and no postoperative radiological/biochemical signs of residual disease, an additional right sided hemicolectomy should not be considered.

LoE: Low
SoR: Weak negative
Consensus: (I) 0.0%, (II) 14.5%, (III) 60.0%, (IV) 25.5%

Recommendation 25

In a patient in whom a perforated LAMN* is found after appendicectomy, pT4a-b, pNx, cM0 R0** with cellular in the visceral peritoneum, and no postoperative radiological/biochemical signs of residual disease, an additional right sided hemicolectomy should not be considered.

LoE: Moderate
SoR: Weak negative
Consensus: (I) 3.6%, (II) 20.0%, (III) 58.2%, (IV) 18.2%

Recommendation 26

In a patient in whom a LAMN* is found after appendicectomy, any pT, pNx, pM1a (acellular mucin, PCI$\leq$3), R0** and no postoperative radiological/biochemical signs of residual disease, there is no role for an additional right sided hemicolectomy and this should never be considered.

LoE: Low
SoR: Strong negative
Consensus: (I) 0.0%, (II) 3.6%, (III) 39.3%, (IV) 57.1%

Recommendation 27

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In a patient in whom a LAMN* is found after appendicectomy, any pT, pNx, pM1b (cellular mucin, PCI≤3), R0** and no postoperative radiological/biochemical signs of residual disease, there is no role for an additional right sided hemicolectomy and this should never be considered.

LoE: Low

SoR: Strong negative

Consensus: (I) 0.0%, (II) 14.3%, (III) 17.9%, (IV) 67.9%

Recommendation 28

In a patient in whom a non perforated LAMN* is found after appendicectomy, pTis-3, pNx, cM0, R0** and no postoperative radiological/biochemical signs of residual disease, there is no role for an adjuvant CRS and HIPEC and this should never be considered.

LoE: Moderate

SoR: Strong negative

Consensus: (I) 0.0%, (II) 3.6%, (III) 9.1%, (IV) 87.3%

Recommendation 29

In a patient in whom a perforated LAMN* is found after appendicectomy, pT4a-b, pNx, cM0, R0** with acellular mucin in the periappendiceal visceral peritoneum, and no postoperative radiological/biochemical signs of residual disease, an adjuvant CRS and HIPEC could be considered.

LoE: Moderate

SoR: Weak positive

Consensus: (I) 3.6%, (II) 71.4%, (III) 17.9%, (IV) 7.1%

Recommendation 30

In a patient in whom a perforated LAMN* is found after appendicectomy, pT4a-b, pNx, cM0, R0** with cellular mucin in the periappendiceal visceral peritoneum, and no postoperative radiological/biochemical signs of residual disease, an adjuvant CRS and HIPEC could be considered.

LoE: Moderate

SoR: Weak positive

Consensus: (I) 10.7%, (II) 78.6%, (III) 10.7%, (IV) 0.0%

Recommendation 31

In a patient in whom a LAMN* is found after appendicectomy, any pT, pNx, pM1a (acellular mucin, PCI ≤3), R0** and no postoperative radiological/biochemical signs of residual disease, an adjuvant CRS and HIPEC could be considered.

LoE: Moderate

SoR: Weak positive

Consensus: (I) 7.1%, (II) 60.7%, (III) 28.6%, (IV) 3.6%

Recommendation 32

In a patient in whom a LAMN* is found after appendicectomy, any pT, pNx, pM1b (cellular mucin, PCI ≤3), R0** and no postoperative radiological/biochemical signs of residual disease, an adjuvant CRS and HIPEC could be considered.

LoE: Moderate

SoR: Weak positive

Consensus: (I) 25.0%, (II) 60.7%, (III) 14.3%, (IV) 0.0%

Recommendation 33

In a patient in whom a non perforated HAMN* is found after appendicectomy, pT < 4, pNx, cM0, R0** and no postoperative radiological/biochemical signs of residual disease, an adjuvant right sided hemicolectomy could be considered.

LoE: Low

SoR: Weak positive

Consensus: (I) 12.7%, (II) 67.3%, (III) 18.2%, (IV) 1.8%

Recommendation 34

In a patient in whom a non perforated HAMN* is found after appendicectomy, pT < 4, pNx, cM0, R0** and no postoperative radiological/biochemical signs of residual disease, an adjuvant right sided hemicolectomy and CRS and HIPEC could be considered.

LoE: Low

SoR: Weak positive

Consensus: (I) 0.0%, (II) 56.4%, (III) 36.4%, (IV) 7.3%

Recommendation 35

In a patient in whom a perforated HAMN* is found after appendicectomy, pT < 4, pNx, cM0, R0** and no postoperative radiological/biochemical signs of residual disease, an adjuvant right sided hemicolectomy and CRS and HIPEC should always be performed.

LoE: Moderate

SoR: Strong positive

Consensus: (I) 58.2%, (II) 29.1%, (III) 12.7%, (IV) 0.0%

Recommendation 36

In a patient in whom a HAMN is found after appendicectomy, any pT, pNx, pM1b, R0** and no postoperative radiological/biochemical signs of residual disease, a CRS and HIPEC with a right sided hemicolectomy should or could be performed.

LoE: Low

SoR: Strong positive

Consensus: (I) 45.5%, (II) 40.0%, (III) 14.5%, (IV) 0.0%

Recommendation 37

In a patient in whom a non perforated mucinous adenocarcinoma* is found after appendicectomy, pT < 4, pNx, cM0, R0** and no postoperative radiological/biochemical signs of residual disease, an adjuvant right sided hemicolectomy should always be performed.

LoE: Moderate

SoR: Strong positive

Consensus: (I) 83.6%, (II) 9.1%, (III) 3.6%, (IV) 3.6%

Recommendation 38

In a patient in whom a non perforated mucinous adenocarcinoma* is found after appendicectomy, pT < 4, pNx, cM0, R0** and no postoperative radiological/biochemical signs of peritoneal disease, the addition of CRS and HIPEC following right sided hemicolectomy could be considered.

****PSOGI 2016 Classification for appendiceal tumours***

*****8***th ***edition AJCC TNM staging system***

LoE: Low

SoR: Weak positive

Consensus: (I) 1.8%, (II) 58.2%, (III) 34.5%, (IV) 5.5%

Recommendation 39

In a patient in whom a perforated mucinous adenocarcinoma* is found after appendicectomy, pT4a-b, pNx, cM0, R0** and no postoperative radiological/biochemical signs of peritoneal disease, the addition of CRS and HIPEC following right sided hemicolectomy should always be performed.

LoE: Moderate

SoR: Strong positive

Consensus: (I) 61.8%, (II) 27.3%, (III) 10.9%, (IV) 0.0%

Recommendation 40

In a patient in whom a mucinous adenocarcinoma* is found after appendicectomy, any pT, pNx, pM1b, R0**, performing a right sided hemicolectomy during CRS and HIPEC should always be performed.

LoE: Moderate

SoR: Strong positive

Consensus: (I) 76.4%, (II) 21.8%, (III) 1.8%, (IV) 0.0%

Recommendation 41

Determination of serum baseline CEA as part of the diagnostic work-up of female patients with a pelvic mass suspicious for ovarian cancer, without a history of previous appendectomy is mandatory to evaluate CA125/CEA ratio and help rule out metastasis from gastro-intestinal origin

LoE: Moderate

SoR: Strong positive

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Consensus: (I)76.8% (II)23.2% (III)0% (IV)0%

Recommendation 42

At a gynaecological procedure, perioperative identification of a krükenberg secondary to a ruptured appendiceal PMP should be treated by oophorectomy and appendectomy without hysterectomy

LoE: Moderate

SoR: Strong positive

Consensus: (I)82.1% (II)17.9% (III)0% (IV)0%

Recommendation 43

In case of an unexpected finding of PMP during the course of elective abdominal surgery for non-oncological reasons (like cholecystectomy, hernia repair,…) the surgeon should abort the programmed procedure and limited surgical maneuvers to biopsies that will allow histological diagnosis of peritoneal disease and/or primary appendiceal tumour; decisionfor right hemicolectomy should await definite histological result

LoE: Moderate

SoR: Strong positive

Consensus: (I)96.4% (II)3.6% (III)0% (IV)0%

***PSOGI 2016 Classification for appendiceal tumours**

****8*th *edition AJCC TNM staging system***

Based on voting by the PMP expert panel, Fig. 2 provides a flowchart concerning a treatment algorithm for appendiceal malignancy with or without PMP.

Cytoreductive surgery (CRS)

The main determinants of outcome are histological type and completeness of cytoreduction. For appendiceal PMP complete cytoreduction (CCRS) encompasses CC0 (no visible disease) as well as CC1 (remaining nodules < 2.5 mm). Several high volume centers have published good DFS and OS rates after achieving CCRS with the combination of HIPEC [74]. The previous consensus statement reported on comparative survival rates from historical reports on debulking, comprising so called repeated mucinous ascites evacuation [8]. The 5- and 10-year published survival rates for serial debulking ranged from 15.3 - 20% and 0–8.3% at 5 and 10 years respectively [75]. In 1952, the Mayo Clinic reported a 14%, 5-year OS. In an update on PMP from the Mayo Clinic in 1994, Gough et al. reported a 50% recurrence rate by 30 months postoperatively despite a strategy combining surgery with radiotherapy and systemic chemotherapy [76]. Järvinen et al., who retrospectively compared CRS and HIPEC (n = 87) to serial debulking (n = 33), were not able to show significant differences between both treatment strategies in terms of 5 years overall survival (69% vs 67%). However, the study is hampered by its retrospective nature, small sample size and lack of any matching method to ensure homogeneity in distribution of prognostic factors between the two groups. No multivariable analysis was performed to control confounders. The low 5 year OS in the CRS and HIPEC group for example could be explained by skewed histological distribution with a high proportion of high grade PMP [77].

The PMI Basingstoke group reported their experience in treating 1000 perforated epithelial appendiceal tumours. Complete CRS was achieved in 73.8%, with a post-op mortality of 0.8% and a major morbidity rate of 15.2%. This resulted in OS rates at 3-, 5- and 10-years of 94.1%, 87.4% and 70.3% respectively [78]. In another multicentric cohort study on 2298 appendiceal PMP patients treated by a strategy of CRS and HIPEC, the treatment related mortality was 2% and major operative complications occurred in 24% of patients. The median survival rate was 196 months (16.3years) and median PFS rate was 98 months (8.2 years) with 10- and 15-year survival rates of 63% and 59% respectively [74].

High grade histology adversely affects outcome. Patients with histological subtypes high grade and adenocarcinoma have significantly reduced DFS and OS. However, in the PMI Basingstoke experience the 5-year DFS in this group was nevertheless greater than 52% if CCRS could be achieved [78]. Furthermore, in contrast to what has been observed for colorectal peritoneal metastases, even signet ring cell histology does not render complete CRS and HIPEC futile [79–82]. However, signet ring cell histology is associated with decreased OS and DFS rates (25% 5y survival) [83].

In summary, the 5- and 10-year published survival rates for (serial) debulking with, or without, other adjuvant therapies vary between 15 - 67% at 5 years and 0–32% at 10 years. The postoperative mortality rates range between 0 and 2.7% with major morbidity rates between 2.7 and 33% [75–77,84,74]. For patients submitted to CRS and HIPEC, OS rates at 5- and 10-years ranging from 74% to 87.4% and 63%–70.3%, respectively are described [78].

In case of overt appendiceal PMP, according to 83.9% of the PMP specialists CRS and HIPEC should be performed whenever possible. However, one should keep in mind the contra-indications listed in Table 6.

Recommendation 44

Balance of benefits and harms of CRS and HIPEC for appendicel PMP patients as an option to serial debulking, provided that the patient has a sufficient clinical condition for a major surgery, has resectable disease and the treatment is performed in a specialized PSM centre.

LoE: Moderate

SoR: Strong positive

Consensus: (I)83.9% (II)16.1% (III)0% (IV)0%

Balance of benefits (OS) and harms (severe morbidity and mortality).

Favorable 89.3%

Uncertain favorable 10.7%

Intraoperative criteria for non resectability

Several studies have reported on factors precluding complete CRS (CCRS) and the following have been published:

- *Extensive small bowel serosa involvement,* where it is not possible to leave at least 1.5–2 m of small bowel has been reported consistently. This may also be compounded by coexistent concomitant gastric and/or colon resection. Gross involvement of the small bowel is a well-known indicator of non resectability, particularly with involvement of the distal jejunum [34,85,86].
- *Mesenteric retraction.* [85].
- *Liver hilum/porta.* [87,88] Massive involvement of the hepatic pedicle is repeatedly being reported as a contra-indication for performing CRS and HIPEC. MRI may be more accurate in assessing this pre-operatively. The adherence and depth of infiltration in this region tends to be less in low grade compared with high grade disease.
- *Extensive Infiltration of the pancreatic surface.* A number of studies have shown that the morbidity of CRS and HIPEC is significantly increased by performing a concomitant pancreatectomy, or indeed in patients who require a splenectomy where damage to the tail of the pancreas is an associated risk. The development of a post-operative pancreatic fistula has been reported to have a negative effect on DFS after treatment of (colorectal) peritoneal metastasis [89]. However, particularly in cases with low grade appendiceal PMP, most can have the

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Table 5
HIIPEC regimens in PMP.[182].

Oxaliplatin-based regimens
Elias High Dose Oxaliplatin Regimen
1. Dose of oxaliplatin is 460 mg/m2 2. Add oxaliplatin to 2 L/m2 5% dextrose solution 3. 30-minute HIPEC treatment *Intravenous Component*4. Add 5-fluorouracil 400 mg/m^2 and leucovorin 20 mg/m^2 to separate bags of 250 mL normal saline. Begin rapid intravenous infusion of both drugs 1 h before intraperitoneal chemotherapy
Glehen Medium Dose Oxaliplatin Regimen
1. Dose of oxaliplatin is 360 mg/m^2 2. Add oxaliplatin to 2 L/m^2 5% dextrose solution 3. 30-minute HIPEC treatment *Intravenous Component*4. Add 5-fluorouracil 400 mg/m^2 and leucovorin 20 mg/m^2 to separate bags of 250 mL normal saline. Begin rapid intravenous infusion of both drugs 1 h before intraperitoneal chemotherapy
Wake Forest University Oxaliplatin Regimen
1. Dose of oxaliplatin is 200 mg/m^2 2. Add oxaliplatin to 3 L 5% dextrose solution 3. Two hour HIPEC treatment
Mitomycin C-based regimens
Sugarbaker Regimen
1. Dose of mitomycin C and doxorubicin is 15 mg/m^2 for each chemotherapy agent 2. Add mitomycin C to 2 L 1.5% dextrose peritoneal dialysis solution 3. Add doxorubicin to the same 2 L 1.5% peritoneal dialysis solution 4. Add 5-fluorouracil (400 mg/m^2) and leucovorin (20 mg/m^2) to separate bags of 250 mL normal saline. Begin rapid intravenous infusion of both drugs simultaneous with intraperitoneal chemotherapy
Dutch High Dose Mitomycin C Regimen: 'Triple Dosing Regimen'
1. Total dose of mitomycin C 35 mg/m^2 for 90-min HIPEC treatment 2. Add mitomycin C to 3 L 1.5% dextrose peritoneal dialysis solution 3. Add mitomycin C to the 1.5% peritoneal dialysis solution at a dose of 17.5 mg/m^2 followed by 8.8 mg/m^2 at 30 min and 8.8 mg/m^2 at 60 min
American Society of Peritoneal Surface Malignancy Low Dose Mitomycin C Regimen: 'Concentration-Based Regimen'
1. Dose of mitomycin C 40 mg/3 L for 90-min HIPEC treatment 2. Add mitomycin C to 3 L 1.5% dextrose peritoneal dialysis solution 3. Add mitomycin C to the 1.5% peritoneal dialysis solution at a dose of 30 mg/3 L followed by 10 mg at 60 min
PMI Basingstoke IP chemotherapy regimen: 'Body Surface Area-based'
Mitomycin 10 mg/m^2 in 1000 ml of sodium chloride 0.9% during 60 min 42 °CConsider dose reduction by 33% in case of following risk factors: a Obese (BMI>40) b Severe abdominal distension c Prior heavy chemotherapy (last 3 months)

Table 6
Based on expert voting absolute and relative contra-indications for CCRS/HIPEC.

Absolute	Relative
Extensive small bowel serosal involvement (58.9%) Mesenteric involvement causing retraction (64.3%)	Age > 75 years (85.7%) Aggressive histology with PCI > 20 (87.5%) Involvement of the liver hilum (87.5%) Infiltration of the anterior pancreatic surface (82.1%) Ureteric obstruction (64.3%) Need for complete gastric resection (80.4%)

disease removed without pancreatic resection and a distal pancreatectomy should not be omitted because of the associated increased risk of morbidity [90].

- *Ureteric obstruction.* In colorectal peritoneal metastasis (CPM) hydronephrosis secondary to ureteric obstruction has been reported as a relative contra-indication for CRS and HIPEC [88]. Ureteral obstruction is seen as an indicator of the presence of more biologically aggressive and infiltrative disease. However, urinary tract involvement, especially after previous surgery is not uncommon. A retrospective review on the effect of concomitant urinary tract surgery during CRS and HIPEC for appendiceal, colon, ovarian and mesothelioma peritoneal malignancy reported no differences in major morbidity, mortality or survival [91]. Honore et al. observed the need for urologic surgery in 8% of their patients with little impact on major morbidity [92].
- *Need for (partial) gastric resection.* The PMI Basingstoke group specifically reported on the effect of performing a partial or total gastrectomy as part of CRS and HIPEC in appendiceal PMP. This was required in 12% of their total patient cohort in order to achieve complete cytoreduction; the majority undergoing a partial gastrectomy with gastroduodenostomy [93]. Even though they observed a significant difference in grade III/IV complications in the gastrectomy group, this did not translate

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into significant differences in the 30 day mortality, nor on the 3- and 5-year DFS and OS rates.

- *Liver metastases.* Most available literature on this topic of liver metastases and peritoneal malignancy addresses peritoneal metastasis of colorectal origin [94–97]. One study reported decreased, though still meaningful survival figures, after limited hepatic resection combined with CRS and HIPEC for peritoneal metastases from colorectal cancer or appendiceal malignancy [98].

Recommendation 45

Which factors do you consider contra-indications for CRS and HIPEC in patients with appendiceal PMP? Note that the list comprises factors related to the patient, the biology of the tumour and surgical resectability.

1. ***Age >75 years***
   LoE: Moderate
   Qualification: Absolute (1.8%) Relative (85.7%) No contra-indication (1.7%)
2. ***Positivity of all baseline serum tumour markers (CEA, CA125, CA 19.9)***
   LoE: Moderate
   Quali fication: Absolute (0%) Relative (21.4%) No contra-indication (78.6%)
3. ***Aggressive histologies (like high grade PMP with SRC, mucinous adenocarcinoma with SRC, GCC) and PCI > 20***
   LoE: Moderate
   Qualification: Absolute (5.4%) Relative (87.5%) No contra-indication (7.1%)
4. ***Extensive small bowel serosal involvement***
   LoE: High
   Qualification: Absolute (58.9%) Relative (41.1%) No contra-indication (0%)
5. ***Mesenteric involvement causing retraction***
   LoE: High
   Qualification: Absolute (64.3%) Relative (35.7%) No contra-indication (0%)
6. ***Involvement of the liver hilum***
   LoE: Moderate
   Qualification: Absolute (5.4%) Relative (87.5%) No contra-indication (7.1%)
7. ***Infiltration of the anterior pancreatic surface (lesser sac)***
   LoE: Moderate
   Qualification: Absolute (0%) Relative (82.1%) No contra-indication (17.9%)
8. ***Ureteric obstruction***
   LoE: Moderate
   Qualification: Absolute (1.8%) Relative (64.3%) No contra-indication (33.9%)
9. ***Need for complete gastric resection***
   LoE: Moderate
   Qualification: Absolute (3.6%) Relative (80.4%) No contra-indication (16.1%)
10. ***Need for partial gastric resection***
    LoE: Moderate
    Qualification: Absolute (1.8%) Relative (23.2%) No contra-indication (75%)

Recommendation 46

In case small bowel excision is required:

1. ***Which length of remaining small bowel is needed?***
   - *It does not matter: 0%*
   - *>1 m: 3.6%*
   - ***>1.5 m:** 78.6%*
   - *>2 m: 14.3%*
   - *Other: 3.6%*
2. ***Is this influenced by the necessity of concomitant resections?***
   - *No: 1.8%*
   - *Gastric resection: 14.3%*
   - ***Colon resection:** 69.6%*
   - *Other: 16.1%*

When is right hemicolectomy indicated?

Gonzalez-Moreno and Sugarbaker were the first to question the necessity of performing a right hemicolectomy in all patients with peritoneal disseminated epithelial appendiceal tumours [66,99,100]. Consequently, they published the suggestion of performing a "radical appendectomy" for suspected appendiceal neoplasms [65]. Another recent publication questions the necessity of performing a completion right hemicolectomy in patients with peritoneal dissemination from a high grade appendix tumour. They reported that only a subgroup of these patients, namely those with poorly differentiated high grade peritoneal disease, would benefit from a right hemicolectomy during their CRS and HIPEC [101]. As mentioned before, the PMI Basingstoke group retrospectively analyzed 62 patients with a high grade lesion in the appendectomy specimen (64% perforated) and reported that the likelihood of peritoneal involvement (57%) was greater than nodal involvement (15%) during subsequent surgery [64]. Currently, offering a completion right hemicolectomy seems to be common practice in a patient with high grade histology found at histological assessment, with or without PMP. In either scenario, CRS principles and HIPEC is recommended [64,65,99,102].

Recommendation 47

Is right hemicolectomy indicated in case of the following histological characteristics of the appendix primary tumour respectively concomitant peritoneal disease?

PRIMARY APPENDIX TUMOUR

1. ***LAMN***
   LoE: Moderate
   SoR: Strong negative
   Consensus: (I)0% (II)6.1% (III)6.1% (IV)87.9%
2. ***HAMN***
   LoE: Moderate
   SoR: Weak positive
   Consensus: (I)10.7% (II)76.8% (III)12.5% (IV)0%
3. ***Mucinous adenocarcinoma, G1***
   LoE: Moderate
   SoR: Strong positive
   Consensus: (I)73.2% (II)25% (III)1.8% (IV)0%
4. ***Mucinous adenocarcinoma, G2***
   LoE: Moderate
   SoR: Strong positive
   Consensus: (I)85.7% (II)12.5% (III)1.8% (IV)0%
5. ***Mucinous adenocarcinoma, G3***
   LoE: Moderate
   SoR: Strong positive
   Consensus: (I)96.4% (II)1.8% (III)1.8% (IV)0%
6. ***Mucinous adenocarcinoma with SRC component***
   LoE: High
   SoR: Strong positive
   Consensus: (I)96.4% (II)1.8% (III)1.8% (IV)0%
7. ***GCC***
   LoE: Moderate
   SoR: Strong positive
   Consensus: (I)82.1% (II)14.3% (III)3.6% (IV)0%

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PERITONEAL DISEASE

8. ***Acellular mucin***
   LoE: Moderate
   SoR: Strong negative
   Consensus: (I)1.8% (II)8.9% (III)23.2% (IV)66.1%
9. ***Low grade PMP***
   LoE: Moderate
   SoR: Weak negative
   Consensus: (I)1.8% (II)16.1% (III)60.7% (IV)21.4%
10. ***High grade PMP***
   LoE: Moderate
   SoR: Weak positive
   Consensus: (I)35.7% (II)58.9% (III)5.4% (IV)0%
11. ***High grade PMP with SRC***
   LoE: Moderate
   SoR: Strong positive
   Consensus: (I)71.4% (II)26.8% (III)1.8% (IV)0%

Ovarian involvement

The incidence of ovarian metastases in patients with a colorectal primary cancer varies between 3% and 8% [103–105]. The risk of ovarian involvement increases in patients with advanced disease, especially in patients with peritoneal metastases from a colorectal primary [106,107]. Ovarian metastases are commonly metachronous. It is a known negative prognostic factor for cancer relapse but has not been shown to significantly impact on survival [104–106,108,109]. The published literature on ovarian involvement secondary to advanced colorectal primary cancer can be extrapolated to peritoneal metastases from mucinous appendiceal malignancies [106,108,110]. In this context the PMI Basingstoke Group investigated the rate of macroscopic, as well as occult, ovarian involvement in patients with advanced colorectal and appendiceal tumours [111]. In the appendiceal tumour group, ovarian metastasis were reported in 58.1% of their patients. Interestingly involvement was occult in 18.2%, if both ovaries had a normal appearance. A macroscopically involved ovary was associated with a risk of 48.6% microscopic ovarian involvement in a contralateral macroscopically normal ovary [111]. Furthermore, a report by the Institut Gustave Roussy in France revealed retroperitoneal lymph node recurrence in 30% of the women previously treated for ovarian metastases (compared to 2% in those without ovarian involvement, or historically, 1% in patients with metastatic colorectal cancer) [107].

Krukenberg tumours are known to be relatively chemo-resistant and may rapidly progress, leading to significant morbidity due to discomfort, abdominal distension and obstructive symptoms [109,112,113].

Clearly these findings have major implications for all women, but particularly pre-menopausal women where bilateral oophorectomy impacts on fertility and can have significant psychological, emotional and physical sequelae. Balancing the indolent behavior of some variants of appendiceal PMP with the risk of undetected ovarian involvement in macroscopically normal ovaries is an important aspect in treatment of PMP, particularly in pre-menopausal patients (whether or not actively pursuing pregnancy). Preoperative counseling on possible options for assisted reproductive techniques including cryopreservation, IVF, surrogacy, etc. is indicated. It is also relevant to be aware that ovarian cancer is the 7th most common female cancer with a woman's lifetime risk between 1 and 2% and approximately 1 in 100 women actually dying from ovarian cancer [114,115].

Recommendation 48

In premenopausal women, affected by appendiceal PMP, and deemed candidates for CRS and HIPEC, fertility specialist counseling and consideration of cryopreservation of oocytes or alternative fertility prese rving is strongly advised.

LoE: Moderate
SoR: Strong positive
Consensus: (I)82.1% (II)17.9% (III)0% (IV)0%

Recommendation 49

In postmenopausal women undergoing CRS and HIPEC for appendiceal PMP, the performance of bilateral (salpingo-)oophorectomy, regardless of the macroscopic appearance of their ovaries o reduce recurrence and avoid second primaries should be done routinely.

LoE: Moderate
SoR: Strong positive
Consensus: (I)80.4% (II)12.5% (III)7.1% (IV)0%

Recommendation 50

In premenopausal women undergoing CRS and HIPEC for appendiceal PMP, the performance of prophylactic bilateral (salpingo-)oophorectomy regardless of the macroscopic appearance of their ovaries to reduce recurrence and avoid second primaries could be done.

LoE: Moderate
SoR: Weak positive
Consensus: (I)7.1% (II)87.5% (III)5.4% (IV)0%

Recommendation 51

In women of reproductive age, with limited low grade PMP, without other adverse prognostic factors, deemed candidates for CRS and HIPEC, with a desire for childbearing, the preservation of uterus and ovaries provided that careful counseling about risks and prognostic implications was performed could be offered.

LoE: Moderate
SoR: Weak positive
Consensus: (I)48.2% (II)51.8% (III)0% (IV)0%

Management of diaphragmatic disease and thoracic extension of PMP

Hyperthermic intrathoracic chemotherapy (HITHOC)

The involvement of the pleural cavity by appendiceal PMP is not an infrequent event in the natural course of the disease (5% of cases) and is associated with adverse prognosis [116–118]. The thoracic extension of appendiceal PMP is thought to be related to either a pleuro-peritoneal fistula, lymphatic shunts or tumor seeding at surgical treatments, rather than a systemic metastatic phenomenon [117,119,120].

Massive involvement of the diaphragmatic peritoneum in appendiceal PMP can require aggressive surgical treatment by subdiaphragmatic cytoreduction, often complicated by tumor invasiveness or fibrotic scarring due to previous surgical manipulation. During peritonectomy the diaphragmatic muscle or tendon can inadvertently be opened, thereby entering the pleural cavity. Subsequent intra operative decisions vary between immediate closure of the diaphragmatic defect or leaving access to the pleural cavity for the performance of hyperthermic intra thoracic chemotherapy (HITHOC) at the same time as HIPEC, in an attempt to minimize the chances of pleural recurrence [121]. Data on hyperthermic intrathoracic chemotherapy is limited (small case series or expert opinion) but the few available papers do not report an increase in perioperative systemic or general complications [122].

Recommendation 52

In case where there is a diaphragmatic opening into the pleural cavity, as a consequence of aggressive subdiaphragmatic cytoreduction, due to high tumor burd en in this region, intrathoracic hyperthermic perfusion together with HIPEC could be offered.

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LoE: Low
SoR: Weak positive
Consensus: (I)26.8% (II)62.5% (III)10.7% (IV)0%

Routine chest drain insertion after diaphragmatic peritonectomy

In some series diaphragmatic peritonectomy is associated with an increased risk of pulmonary complications including pleural effusions, especially in obese patients [123]. In a retrospective analysis on 76 patients, Mahteme reported that 6/76 required thoracocentesis and 6 required chest tube insertion [124]. In contrast, Sugarbaker et al. reported no statistically increased pulmonary complications associated with chest drains in patients who had right or left hemi-diaphragmatic stripping in 147 consecutive patients [125].

Recommendation 53

If diaphragmatic peritonectomy (stripping) is required during CRS and HIPEC for appendiceal PMP, the placement of a chest drain with prophylactic intent to reduce respiratory complications

LoE: Low
SoR: Weak positive
Consensus: (I)45.5% (II)54.5% (III)0% (IV)0%

Maximal tumour debulking (MTD)

Even though incomplete cytoreduction is known to be associated with significantly decreased OS rates compared with complete CRS (CCRS), debulking surgery (with or without HIPEC) may still benefit a patient with appendiceal PMP. This is not only due to relief of symptoms such as acute obstruction, post-renal failure, intestinal fistulation, sepsis but may also result in prolongation of so called "obstruction-free survival". The concept of what has been termed a "maximum tumour debulking" (MTD) has been proposed as an alternative to a CCRS/HIPEC in patients where complete removal of the tumor is not possible or for patients who are not fit enough to withstand an extended surgical procedure [126]. Recent publications suggest that a MTD is achievable with an acceptable morbidity and mortality, reaching an overall survival of half of the patients at 3 years post-operatively (which is better than has been published with repeat mucin evacuation).

Examples of available literature on this topic include:

- In an update on PMP from the Mayo Clinic in 1994, Gough et al. reported a 50% recurrence rate by 30 months postoperatively despite a strategy combining surgery with radiotherapy and systemic chemotherapy [76].
- The previous consensus statement reported expectations from so called repeated mucinous ascites evacuation with 5- and 10-year survival rates for serial debulking varying between 15.3 to 20% and 0–8.3% respectively [8]. Postoperative mortality ranged between 0 and 2.7% and major morbidity rates between 2.7 and 33% [75].
- The PMI Basingstoke group reported their experience in treating 1000 perforated epithelial appendiceal tumours. In 24.2% who underwent MTD, the post-operative mortality was 1.7% and major morbidity 14.5%. The OS rates at 3-, 5- and 10-years in this group were 66.5%, 39.2% and 8.1% [78].
- A multicenter retrospective study of 2298 patients reported a 5-year OS rate of 74% in patients who had CCRS compared with 24% after MTD [74].
- Sugarbaker and colleagues reported that incomplete cytoreduction in the Washington cancer institute resulted in 1-, 3- and 5-year OS rates of 71%, 34% and 15% respectively with 0% post-operative mortality and 33% morbidity. In this study, signet ring histology and lymph node involvement were identified as particularly negative prognostic factors [75].
- Investigators from Paris recently reported a morbidity rate of 23% and post-operative mortality rate of 2.5% after MTD. They reported that 50% of the patients remained asymptomatic after a median follow-up of 24.5 months with five year OS and PFS rates of 46% and 11%, respectively [127].

MTD usually involves a greater omentectomy, lower abdominal peritonectomies and an extended right hemicolectomy. Alternatively, to decrease morbidity associated with anastomotic leakage and perhaps increase "obstruction free survival" a total colectomy with end ileostomy can be considered [126]. In women a bilateral oophorectomy is advised and in most cases surgery is followed by HIPEC to reduce post-operative ascites accumulation [50,128,129]. However, many critics of CRS and HIPEC have suggested that patients with slowly progressive low grade disease would do equally well without palliative surgery. Debate concerning risk/benefit of this type of "palliative surgery" becomes even more pronounced for patients with advanced disease and patients with clinical, histological and/or radiological negative prognostic factors [130]. Due to the lack of randomized trials in this scenario, other metrics such as quality of life (QOL) require to be evaluated in these cases. The PMI Basingstoke group reported on a prospective sequential evaluation of QOL in 46 patients treated with CRS and HIPEC for PMP, 20 of whom underwent MTD and 26 CCRS. They reported clinically significant improvement in emotional well-being, appetite and global health related QOL at one year after both CCRS and MTD [3]. Interestingly patients undergoing MTD seemed to have significantly more problems with diarrhea, which might be related to more extensive small bowel involvement, the main reason for an inability to achieve complete CRS. The concept of MTD has become more popular in recent years for the management of inoperable appendiceal PMP. This concept challenges the goal of complete cytoreduction at all cost, in an attempt to obtain a more rational balance between prognostic gain, postoperative morbidity and mortality and QOL. Although routinely practiced in centers like PMI Basingstoke, more data on outcomes and the definition of more clear-cut selection criteria for MTD is needed. Another interesting aspect concerns MTD as a first step to improve the patients' general condition prior to CCRS and HIPEC [131]. In this context Chua et al., in 2011 concluded that upfront CRS and HIPEC is associated with a lower morbidity, and recurrence, compared with delayed treatment [132]. Unsurprisingly, previous surgery causes disruption of surgical planes with formation of adhesions resulting in technical difficulty in disease clearance in that region with tumour cell entrapment within scar tissue. Such cases are less amenable to CCRS surgery and perhaps adverse penetration of intraperitoneal chemotherapy. Furthermore, it is also debatable as to whether extensive "once off MTD" is better than repeated debulking procedures [50]. Repeated debulking is known to become more difficult, less effective and more dangerous, with respect to the risk of iatrogenic gastro-intestinal injury leading to entero-cutaneous fistulation, sepsis and prolonged morbidity and mortality on occasions. In one report, Sugarbaker et al. from the Washington Cancer institute reported a median survival of 36.8 months in patients treated with more than 1 procedure in contrast to 18.1 months in those undergoing only 1 debulking procedure [75]. However, much of the difference is likely to be related to disease biology with less aggressive disease allowing repeat intervention.

Recommendation 54

In patients with appendiceal PMP who are not fit for a major procedure and/or have unresectable disease, maximal tumour debulking (MTD), provided that the treatment is offered in a specialized centre could be considered.

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LoE: Moderate
SoR: Weak positive
Consensus: (I)12.5% (II)85.7% (III)1.8% (IV)0%

Recommendation 55

In case a patient is excluded from CRS and HIPEC and he/she needs palliative surgery (Maximal tumour debulking or other), what kind of operation would you propose?

a. ***As limited as possible to ameliorate symptoms (so called mucin evacuation) and omentectomy***
   Yes (87.5%)
   No (12.5%)
b. ***Resection of digestive organs***
   1. ***Gastrectomy***
      Total (0%)
      Partial (21.4%)
      No, never (78.6%)
   2. ***Colonic resection***
      Yes, total colectomy is an essential part of MTD (1.8%)
      Yes, whenever required (92.9%)
      No, never (5.4%)
c. ***Diaphragmatic peritonectomy***
   Yes, always (1.8%)
   Yes, only when indicated (41.1%)
   No, never because this is unlikely to increase the QOL (57.1%)
d. ***Pelvic and parietal peritonectomies***
   Yes, always (1.8%)
   Yes, when indicated *(89.3%)*
   No, never (10.7%)
e. ***Addition of HIPEC***
   Yes, always at the same dose and duration as would be for HIPEC *(55.4%)*
   Yes, but different drug and/or dose and/or duration (5.3%)
   No, never (39.3%)

Recommendation 56

In an operable patient with resectable appendiceal PMP and negative prognostic factors (high grade, signet ring cell histology), rather than pursuing complete CRS and HIPEC at all cost, MTD/HIPEC, which is associated with acceptable morbidity, mortality and post-op QOL could be considered.

LoE: Low
SoR: Weak positive
Consensus: (I)3.6% (II)64.3% (III)21.4% (IV)10.7%

Recommendation 57

In high risk patients with appendiceal PMP, with borderline operability, a so called "two-stage" or "delayed" CRS and HIPEC, instead of a one single upfront CRS/HIPEC could be considered.

LoE: Low
SoR: Weak positive
Consensus: (I)5.4% (II)69.6% (III)19.6% (IV)5.4%

HIPEC regimens

Since Spratt et al. reported for the first time (in 1980) the use of heated triethylenethiophophoramide (thiotepa) in a patient with pseudomyxoma peritonei [133], HIPEC has been an integral part of the treatment strategy for PMP. A clear pharmacologic and clinical rationale for this treatment strategy has been demonstrated. Whereas the cytoreductive surgery has generally been highly standardized, reproducible and predictable, there are numerous permutations in the intraperitoneal chemotherapy regimens and techniques. The majority of regimens have been based on extrapolation of systemic chemotherapy data. Standardization of the intraperitoneal chemotherapy modalities is needed.

Table 5 summarizes the most frequently used intra-peritoneal chemotherapy regimens in colorectal and appendiceal peritoneal malignancy. Drugs that form the backbone of these regimens are oxaliplatin and mitomycin C.

Oxaliplatin

Oxaliplatin (oxalato-1,2-diaminocyclohexane-platinum (II)) is a third generation platinum complex with proven cytotoxicity in colon and appendiceal neoplasms [134]. In a dose escalation and pharmacokinetic study, Elias et al. demonstrated that 460 mg/m^2 of oxaliplatin in 2L/m^2 of chemotherapy solution over 30 min was well tolerated [135,136]. The low AUC ratio is compensated by the rapid absorption of the drug into the tissue, allowing for a short application time. However since the introduction of oxaliplatin into intra-peritoneal chemotherapy regimens at the beginning of the 2000's, there has been a trend towards lower dose oxaliplatin based regimens. This is a consequence of increasing concern about unacceptable bleeding complications with the initial 460mg/m^2-based regimens. In a phase I trial, Elias et al. evaluated the pharmacokinetics of heated IP oxaliplatin administered in increasingly hypotonic solutions of 5% dextrose [137]. They reported that oxaliplatin clearance from the IP cavity was similar regardless of the osmolarity, but that very hypotonic solutions induced a high incidence of IP haemorrhage and thrombocytopenia. As a consequence of a high incidence of haemorrhagic complications in another prospective multicentre trial reported by Pomel et al. the dose of oxaliplatin was reduced to 350 mg/m2. However, the incidence of the haemorrhagic complications (29%) did not decrease and the trial was closed prematurely [138]. Chalret du Rieu et al. performed a population pharmacokinetics study and reported grade 3/4 thrombocytopenia in 14% of patients undergoing oxaliplatin-based HIPEC [139]. Moreover, they concluded that the higher the absorbed dose from the peritoneal cavity, highly dependent on the initial oxaliplatin concentration, the lower the resultant thrombocytopenia. In an analysis of 701 patients treated with CRS and HIPEC with oxaliplatin or other chemotherapeutic agents, Charrier et al. reported that oxaliplatin-based HIPEC increased the risk of haemorrhagic complications compared with other drugs [140]. Furthermore, in early reports from the PRODIGE 7 trial, the increased 60 day morbidity observed in the CRS-HIPEC (oxaliplatin 460 mg/m^2) group was partly attributable to increased bleeding. Currently different oxaliplatin-based HIPEC regimens are used in clinical practice including the 'Elias High Dose Oxaliplatin Regimen' [135], 'Glehen Medium Dose Oxaliplatin Regimen' and the 'Wake Forest University Oxaliplatin Regimen' [134].

Mitomycin C

Mitomycin C is an alkylating tumour antibiotic extracted from Streptomyces species with the most important mechanism of action being through DNA cross-linking. Jacquet et al. reported a clear pharmacokinetic advantage after IP administration with an AUC IP/IV ratio of 23.5 [141]. Mitomycin is mainly used for peritoneal malignancy from colorectal cancer, appendiceal tumours, ovarian cancer, gastric cancer and, for diffuse malignant peritoneal mesothelioma, both as HIPEC and EPIC [142]. Barlogie et al. reported in vitro thermal enhancement of mitomycin C [143]. Van der Speeten and colleagues have reported pharmacokinetic data in 145 patients undergoing CRS and HIPEC and found that the largest proportion (62%) of the total drug administered remained in the body at 90 min [144]. Controversies still exist regarding the dose level, concentration and dosimetry of the mitomycin chemotherapy solution [145,146]. A triple dosing regimen may result in more stable peritoneal levels of the drug throughout the time of IP chemotherapy. Current applied HIPEC dosing regimens include the 'Sugarbaker Regimen' [144], The 'Dutch High Dose Triple dosing

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Mitomcyin C Regimen [147,148] and the 'American Society of Peritoneal Surface Malignancy Low Dose Mitomycin C concentration based regimen [149].

Recently, Levine et al. published the first (multi-centre) randomized controlled trial evaluating the haematologic toxicity, quality of life, and 3 year DFS and OS of closed HIPEC with Oxaliplatin (200 mg/m^2) compared to Mitomycin (40 mg), both administered for 120 min, in patients with appendiceal PMP [150]. They observed similar OS and DFS rates in both regimens. Regarding the toxicity profile, in the mitomycin group the white blood cell count decreased significantly more between postoperative days 5–10 whereas the platelet count was significantly lower in the oxaliplatin group on postoperative days 5–6. However, when considering only grade 3–4 toxicity, according to CTCAE criteria, the differences between groups were not significant ($p = 0.67$) both for leucopenia and thrombocytopenia. Short term outcomes of quality of life scores according to the general version of the Functional Assessment of Cancer Therapy (FACT-G) were similar between groups overall. However scores were better in the oxaliplatin group for physical well-being (24.2 vs 22.4, $p = 0.015$) and emotional well-being (19.4 vs 18.0, $p = 0.048$) up to 1 year after surgery.

Recommendation 58

Based on the current pharmacologic and clinical data on quality of life for patients with appendiceal PMP, oxaliplatin for HIPEC could be used instead of mitomycin C.

LoE: Moderate

SoR: Weak positive

Consensus: (I)3.6% (II)66.1% (III)30.4% (IV)0%

Based on the current pharmacologic and clinical data available on appendiceal PMP, which of the following HIPEC regimens listed in Table 3 should be adopted in future clinical trials:

- Elias High Dose Oxaliplatin Regimen (8.9%)
- Glehen Medium Dose Oxaliplatin Regimen (28.6%)
- Wake Forest University Oxaliplatin Regimen (1.8%)
- Sugarbaker Mitomycin C based Regimen (1.8%)
- Dutch High Dose Mitomycin C Regimen: 'Triple Dosing Regimen' (42.9%)
- American Society of Peritoneal Surface Malignancy Low Dose Mitomycin C Regimen (14.3%)
- PMI Basingstoke low dose mitomycin C based regimen (10.7%)
- Other (3.6%)

Early postoperative intraperitoneal chemotherapy (EPIC)

EPIC has some conceptual advantages. It is administered shortly after CRS at the time of minimal residual tumour burden. In addition, IP treatments initiated before wound healing occurs can minimize non-uniform drug distribution and reduce, or eliminate, residual cancer cell entrapment in postoperative fibrin deposits. The disadvantages associated with EPIC are the increased risks of infection and postoperative complications. EPIC does not involve hyperthermia and is administered postoperatively (typically from day 1 post-operative to day 4/5) through an inflow catheter, and outflow drains, inserted at the time of CRS and, can be used in addition to, or without, HIPEC. Proper selection of chemotherapy agents based on pharmacologic principles suggests the use of cell-cycle specific drugs such as 5-fluorouracil and the taxanes. This implies administrating multiple cycles, each with a dwell time of around 23 h before renewal. This ensures that all the residual tumour cells are susceptible to the cell cycle specific drug.

The application of EPIC in adjunction to CRS and HIPEC in appendiceal PMP has been reported in several retrospective series.

Chua et al. have evaluated whether different regimens of peri-operative intraperitoneal chemotherapy (HIPEC or EPIC vs. HIPEC + EPIC) could be related to different prognostic results in patients affected by low-grade pseudomyxoma peritonei (n = 108), appendiceal peritoneal carcinomatosis (n = 56) and colorectal cancer (n = 98). For pseudomyxoma peritonei, recurrence-free survival (RFS) was not significantly different with different peri-operative intraperitoneal chemotherapy regimens. Overall, 5-year survival was 86% in the HIPEC + EPIC group and 64% in the HIPEC or EPIC group (P = 0.070). For appendiceal peritoneal carcinomatosis, RFS and OS did not vary with the peri-operative regimen [14]. The same group of investigators subsequently repeated a similar evaluation on larger cohorts of patients affected by low [151] and high [152] grade PMP. Multivariate analysis suggested that a combination of HIPEC with EPIC was an independent prognostic factor for better survival outcomes (OS and DFS), adjusted for other prognostic factors, both in low and high grade PMP. The authors claimed that EPIC could be performed after CRS and HIPEC in PMP patients, with potential benefit in terms of survival. Regarding the safety of CRS with both HIPEC and EPIC as compared with CRS and HIPEC, the literature data is contradictory. Some groups have reported higher rates of morbidity when EPIC is added to the CRS and HIPEC [153,154] while the St Georges, Sydney group have reported no difference [151,152].

Rather than as an additional therapy following CRS and HIPEC, investigators from Paris have investigated EPIC, as a substitute for HIPEC after complete CRS (CRS + EPIC) for colorectal peritoneal metastases (CPM) [155] They found a significantly lower morbidity rate in favour of HIPEC. Literature data are scanty on this issue and investigators form Memorial Sloan Kettering have instigated a multicentre, prospective, randomized study comparing CRS and HIPEC with CRS and EPIC for the treatment of CPM or appendiceal neoplasms [156].

Recommendation 59

In patients with low or high grade appendiceal PMP who have undergone complete CRS and HIPEC, adjuvant EPIC in the immediate postoperative period:

LoE: Low

SoR: Weak positive

Consensus: (I)0% (II)60.7% (III)37.5% (IV)1.8%

Systemic therapy

Neoadjuvant systemic chemotherapy

Three studies were identified reporting the use of neoadjuvant systemic chemotherapy in PMP from a low grade appendiceal malignancy [74,157,158]. Blackham et al. described no significant improvement in progression free survival (PFS) or overall survival (OS) (n = 13), whereas Chua et al. (n = 168) and Baratti et al. (n = 22) reported that neoadjuvant treatment was a significant adverse prognostic factor for both PFS and OS.

Comparable results were observed in studies investigating the use of neoadjuvant systemic chemotherapy in PMP from a high grade appendiceal malignancy: seven studies, resulting in a total group of 265 patients, found no improvement in either PFS or OS when neoadjuvant systemic chemotherapy was administered [157,159–164]. Inferior PFS and OS was also reported in three other studies [74,165,166].

In 20 patients with high grade histology with signet ring cell differentiation, peri-operative systemic chemotherapy combined with complete cytoreductive surgery was reported to enhance PFS and OS [167]. Similarly, Milovanov et al. [160] found an improvement of OS in 30 patients treated with neoadjuvant chemotherapy. In contrast, Blackham et al. reported no benefit in 37 patients treated with neo-adjuvant chemotherapy [157].

In conclusion, there is no published evidence suggesting significant benefits from neoadjuvant systemic chemotherapy in PMP

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from either low grade, or high grade, appendiceal tumours. In patients with signet ring cell histology, there may be an increased OS with the use of neoadjuvant therapy, although high quality evidence from randomized controlled trials is lacking.

Recommendation 60

In patients with low grade PMP, suitable for complete CRS and HIPEC on pre-operative staging, there is no role for neoadjuvant chemotherapy and this should never be considered.

LoE: Low
SoR: Strong negative
Consensus: (I) 0.0%, (II) 0.0%, (III) 7.3%, (IV) 92.7%

Recommendation 61

In patients with high grade PMP or high grade PMP with signet ring cells, suitable for complete CRS and HIPEC on pre-operative staging, neoadjuvant chemotherapy could be considered.

LoE: Low
SoR: Weak positive
Consensus: (I) 1.8%, (II) 76.4%, (III) 18.2%, (IV) 3.6%

Recommendation 62

In case neo-adjuvant systemic chemotherapy is offered in patients with high grade PMP or high grade PMP with signet ring cells, suitable for complete CRS and HIPEC on pre-operative staging, the chemotherapy regimen should ideally consist of a combination of a fluoropyrimidin and an alkylating agent (e.g. oxaliplatin).

Consensus:

- ***Combination of a fluoropyrimidin and an alkylating agent (e.g. oxaliplatin)*** *(87.3%)*
- *Combination chemotherapy together with a neo-angiogenesis inhibitor (e.g. bevacizumab) (5.5%)*
- *Combination of a fluoropyrimidine and a neo-angiogenesis inhibitor (0.0%)*
- *Neo-angiogenesis inhibitor alone (0.0%)*
- *Fluoropyrimidin monotherapy (e.g. 5-FU) (0.0%)*
- *No neo-adjuvant systemic chemotherapy (7.3%)*

Adjuvant systemic chemotherapy

Asare et al. described a large cohort of 5971 patients in which 1919 (32.1%) patients with well differentiated stage IV mucinous appendiceal tumours did not benefit from adjuvant chemotherapy in contrast to 1414 (23.7%) patients with moderately and 658 (11.0%) patients with poorly differentiated tumours where OS was significantly increased [168].

Three other studies reported contrasting results [157,166,169]: Blackham et al. reported that adjuvant chemotherapy in patients with high-grade mucinous carcinoma peritonei ($n = 22$) led to an increased PFS (13.6 vs. 7.0 months, $p = 0.03$), but not to a significantly increased OS (36.4 vs. 19.4 months, $p = 0.14$). Schomas et al. observed a decreased OS in 22 patients with peritoneal mucinous carcinomatosis (PMCA) when treated with adjuvant systemic chemotherapy, although the difference was no longer significant on multivariate analysis. Finally, Cummins et al. reported that adjuvant chemotherapy in 44 patients, after CRS and HIPEC, led to a decreased OS (4.8 vs. 34.8 months, $p < 0.0001$).

In conclusion, no study showed a benefit from adjuvant chemotherapy in well differentiated mucinous appendiceal tumours. In high grade appendiceal tumours, one large study showed a beneficial effect of adjuvant chemotherapy, but this finding was not supported in three other small studies.

Recommendation 63

In patients with low grade PMP, in whom complete CRS (CCR 0–1) and HIPEC was performed, there is no role for adjuvant chemotherapy and this should never be considered.

LoE: Low
SoR: Strong negative
Consensus: (I) 0.0%, (II) 9.1%, (III) 16.4%, (IV) 74.5%

Recommendation 64

In patients with high grade PMP or high grade PMP with signet ring cells, in whom complete CRS (CCR 0–1) and HIPEC was performed, adjuvant chemotherapy could be considered.

LoE: Low
SoR: Weak positive
Consensus: (I) 3.6%, (II) 85.5%, (III) 7.3%, (IV) 3.6%

Recommendation 65

In case adjuvant systemic chemotherapy is offered in patients with high grade PMP or high grade PMP with signet ring cells, in whom complete CRS (CCR 0–1) and HIPEC was performed, the chemotherapy regimen should ideally consist of a combination of a fluoropyrimidin and an alkylating agent (e.g. oxaliplatin).

Consensus:

- ***Combination of a fluoropyrimidin and an alkylating agent (e.g. oxaliplatin)*** *(87.3%)*
- *Combination chemotherapy together with a neo-angiogenesis inhibitor (e.g. bevacizumab) (9.1%)*
- *Combination of a fluoropyrimidine and a neo-angiogenesis inhibitor (0.0%)*
- *Neo-angiogenesis inhibitor alone (0.0%)*
- *Fluoropyrimidin monotherapy (e.g. 5-FU) (0.0%)*
- No neo-adjuvant systemic chemotherapy (3.6%)

Palliative systemic chemotherapy

The effect of palliative systemic chemotherapy was investigated by four groups, comprising in total 168 patients with recurrent, or unresectable, PMP treated with palliative systemic chemotherapy [170–174]. One third of patients had histologically low grade disease and one third had high grade disease, and tumour differentiation was not mentioned in the remainder. PFS ranged from 6 to 8 months, and OS ranged from 26 to 61 months. Adverse events were observed in 53–70% of patients. Grade 3 or 4 adverse events were mentioned in 6–13% of chemotherapy cycles, mainly consisting of hand-foot syndrome.

Choe et al. noted the additional value of bevacizumab in 65 patients treated with palliative chemotherapy. Both PFS (9 vs. 4 months, $p = 0.047$) and OS (76 vs. 42 months, $p = 0.03$) were significantly higher compared with 65 patients who received standard palliative chemotherapy [175].

This suggests a possible role for bevacizumab when palliative chemotherapy is administered.

Recommendation 66

In patients with low grade PMP, considered inoperable and/or unresectable but who are fit enough for medical treatment, palliative systemic treatment could be considered.

LoE: Low
SoR: Weak positive
Consensus: (I) 1.8%, (II) 89.1%, (III) 9.1%, (IV) 0.0%

Recommendation 67

In patients with high grade PMP or high grade PMP with signet ring cells, considered inoperable and/or unresectable but who are fit enough for medical treatment, palliative systemic treatment could be considered.

LoE: Moderate
SoR: Weak positive
Consensus: (I) 32.7%, (II) 67.3%, (III) 0.0%, (IV) 0.0%

Recommendation 68

In case palliative systemic chemotherapy is offered in patients

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with low grade PMP, high grade PMP, or high grade PMP with signet ring cells, considered inoperable and/or unresectable but who are fit enough for medical treatment, the chemotherapy regimen should ideally consist of combination chemotherapy together with a neo-angiogenesis inhibitor (e.g. bevacizumab).

Consensus:

- ***Combination chemotherapy together with a neo-angiogenesis inhibitor (e.g. bevacizumab)*** *(78.2%)*
- *Combination of a fluoropyrimidin and an alkylating agent (e.g. oxaliplatin) (20.0%)*
- *Combination of a fluoropyrimidine and a neo-angiogenesis inhibitor (0.0%)*
- *Neo-angiogenesis inhibitor alone (0.0%)*
- *Fluoropyrimidin monotherapy (e.g. 5-FU) (0.0%)*
- *Other (1.8%)*

Follow-up

Despite complete CRS and HIPEC, approximately 25% of patients experience recurrent disease [74,176,177]. Both low and high grade PMP can recur, with increased risk in high grade tumours. In most cases, recurrences are intra-peritoneal [176,177]. According to a recent publication by PMI Basingstoke, an annual CT of the abdomen and pelvis during the first six years appears to be adequate follow-up for low grade PMP. In high grade PMP, additional imaging of the chest and more frequent surveillance during the first three years postoperatively may detect recurrent disease earlier. From year 6 on, reduced frequency of follow-up is proposed, independent of the grade of tumour histology [178].Currently there are no universally accepted guidelines on methodology, intensity and duration of follow-up. Universally accepted follow up guidelines would be beneficial and might incorporate the prognostic features of the disease and individualize the surveillance according to risk stratification of the patients.

Recommendation 69 Follow up:

With which frequency these methods should be proposed in the follow-up of appendiceal PMP patients after CRS and HIPEC

* During the first 2 years

- Physical examination 54.5% strong positive for every 6 months (12.1% every 3 months)
- Thoracic/abdominal/pelvic CT scan: 54,5% strong positive for every 6 months (18,2% every year)

* From 2 years onward

- Physical examination: 36,4% strong positive every 6 months and another 36,4% every year
- Thoracic/abdominal/pelvic CT scan: 66,7% yearly (and 21.2% every 6 months)

Recommendation 70

Do you use tumour markers?

Yes *(90.9%)*

No (9.1%)

At what frequency?

- *Every* 3 months *(15.2%)*
- *Every* 4 months *(12,1%)*
- ***Every* 6 months** *(54,5%)*
- *Every* 12 months *(12,1%)*

Discussion

The modified Delphi process resulted in good consensus on many aspects of PMP. From the first voting round, 98.2% of the PMP expert panel recommended the PSOGI 2016 consensus terminology for histological classification of appendiceal PMP. About two-thirds believe there exists moderate evidence to recommend mandatory inclusion of the following tumour markers in the preoperative workup: CEA, CA19.9 and CA 125. Furthermore, according to the majority an abdomino-pelvic CT scan and colonoscopy should be included in the pre-operative evaluation. An MRI, exploratory laparoscopy and histological confirmation could be obtained prior to definite treatment. Fig. 1 proposes a suggestion for pre-operative evaluation. Fig. 2 provides a treatment algorithm (the need for right hemicolectomy as well as CRS/HIPEC based on voting of the international PMP expert panel) for appendiceal malignancy with or without different subsets of peritoneal disease.

In case of overt appendiceal PMP, a moderate level of evidence exists to support that CRS and HIPEC **should** be performed whenever possible. However, one should bear in mind the contraindications listed in Table 6.

When a patient is not able to undergo CRS/HIPEC (due to morbidity or unresectability) some kind of maximal tumour debulking **could** be offered according to 85% of the experts. The procedure should be as limited as possible and according to half of the panel HIPEC should be added at the same dose and duration. Concerning the HIPEC regimen, the Dutch triple dosing regimen seems to be preferred by 42.9% of the experts, followed by the Glehen medium dose oxaliplatin regimen suggested by 28.6% of the expert panel.

With curative intent, the use of systemic chemotherapy in patients with low grade appendiceal PMP was discouraged by the vast majority of experts on the basis of the available evidence. On the other hand, in the presence of high grade or signet ring cell histology most experts considered administration of systemic chemotherapy, especially in the adjuvant setting. Whether neo-adjuvant or adjuvant therapy is used, 87.3% of the experts voted for the use of a fluoropyrimidin and an alkylating agent (e.g. oxaliplatin). In a palliative setting, most experts consider systemic chemotherapy, in this case even more so in low grade (89.1%) than high grade or signet ring cell histology (67.3%). Currently the majority (78.2%) favours combination chemotherapy together with a neo-angiogenesis inhibitor (e.g. bevacizumab) (78.2%)

The fact that there do not exist universally accepted guidelines on methodology, intensity and duration of follow-up was reflected in our voting with consensus agreement.

Conclusion

The current modified Delphi exercise provides valuable consensus on many aspects of the management of appendiceal tumours and pseudomyxoma peritonei. The conclusions and recommendations help to inform best practice and optimal treatment strategies to improve outcomes. Further work is needed to clarify a number of other important aspects such as methodology, intensity and duration of follow-up.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2020.02.012.

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Please cite this article as: Govaerts K et al., Appendiceal tumours and pseudomyxoma peritonei: Literature review with PSOGI/EURACAN clinical practice guidelines for diagnosis and treatment, European Journal of Surgical Oncology, https://doi.org/10.1016/j.ejso.2020.02.012

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Please cite this article as: Govaerts K et al., Appendiceal tumours and pseudomyxoma peritonei: Literature review with PSOGI/EURACAN clinical practice guidelines for diagnosis and treatment, European Journal of Surgical Oncology, https://doi.org/10.1016/j.ejso.2020.02.012

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Glossary

CA 125: cancer antigen 125
CA 19.9: cancer antigen 19.9
CC0: no visible disease after CRS
CC1: remaining nodules <2.5 mm after CRS
CCRS: complete cytoreductive surgery
CEA: carcino-embryonic antigen
CPM: colorectal peritoneal metastases
CRS: cytoreductive surgery
DFS: disease free survival
EPIC: Early postoperative intra-peritoneal chemotherapy
GCC: goblet cell carcinoid
HAMN: high grade appendiceal mucinous neoplasms
HIPEC: Hyperthermic Intra Peritoneal Chemotherapy
LAMN: low grade appendiceal mucinous neoplasms
LoE: Level of Evidence
MTD: maximum tumour debulking
OS: overall survival
PFS: progression free survival
PMP: pseudomyxoma peritonei
RHC: right hemicolectomy
SoR: Strength of Recommendation
SRC: signet ring cell

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