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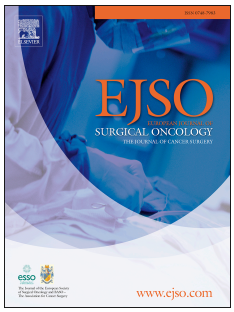

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Peritoneal Mesothelioma: PSOGI/EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up

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49 chemotherapy, Delphi, GRADE

Introduction

Peritoneal mesothelioma (PM) is a rare and aggressive primary peritoneal malignancy characterized by widespread multiple metastatic tumour nodules originating from the peritoneum. The conventional classification distinguishes diffuse malignant peritoneal mesothelioma (DMPM) and border-line forms: multicystic peritoneal mesothelioma (MCPM) and well-differentiated papillary peritoneal mesothelioma (WDPPM). Despite the novel achievements in the management of PM, there is difficulty in conducting randomized trials due to its rarity and aggressive biology in many cases. As there is, a necessity to standardize diagnosis and management of PM, the Peritoneal Surface Oncology Group International (PSOGI) commissioned a steering committee to elaborate clinical guidelines.

The steering committee summarized the literature data and selected 39 panellists on the basis of their experience in treating PM following clear cut criteria for expertise in rare peritoneal disease, established by RENAPE. Those panellists were mainly surgeons treating peritoneal malignancies but additionally medical oncologists and pathologists. According to the Delphi methodology, the voting process completed 3 rounds with 42 questions dedicated to peritoneal mesothelioma management. To rate the recommendations, the GRADE system (Grades of Recommendation Assessment Development and Evaluation) was adopted as it is considered as the most suitable approach for such a rare disease (Table1). The methodology of the consensus process has been outlined elsewhere.[1] We present here the clinical practice guidelines for diagnosis, treatment and follow-up of DMPM, MCPM and WDPPM. The results of this consensus were presented, and discussed, in the plenary session at the PSOGI 2018 international meeting in Paris.

Diffuse Malignant Peritoneal Mesothelioma

Incidence and epidemiology

Malignant mesothelioma is a disease affecting serosal surfaces derived from mesothelium comprising the pleura, peritoneum, pericardium and tunica vaginalis testis. Diffuse Malignant Peritoneal mesothelioma (DMPM) accounts for 7-30% of all cases.[2] The incidence of DMPM varies widely geographically. The highest rates are reported in the UK, Australia, and New Zealand, while some of the lowest reported rates from Japan, Slovenia and other countries in central Europe. The United States (US) has an incidence in the middle range of about 1.94, and 0.41, per 100,000 for men and women respectively.[3,4] It is estimated that there will be approximately 94,000 new cases of pleural and 15,000 cases of DMPM diagnosed between 2005 and 2050 in the US.[2] While there is a significant predominance of men diagnosed with pleural mesothelioma, of the 300-400 new cases of DMPM diagnosed annually, the prevalence is similar in men and women in the US.[5]

The most common carcinogen identified for pleural mesothelioma has been asbestos.[4,6] Although there is a weaker correlation, asbestos is also considered a risk factor for DMPM. About 33-50% of patients diagnosed with DMPM report known prior exposure to asbestos.[4,7] Time and duration of exposure do not directly correlate with disease development, with some long-term asbestos exposures not seemingly resulting in mesothelioma while some short-term exposures leading to significant tumour burden. Many observational and randomized studies using cross sectional imaging with chest CT for lung screening protocols were performed in asbestos exposed workers like the International Early Lung Cancer Action Program (IELCAP),[8] National Lung Screening Trial (NLST),[9] and the Italian Lung Cancer Screening Trial (ITALUNG).[10] No screening programs or protocols have

been proposed for early detection of DMPM, despite the moderately consistent epidemiological correlation with asbestos exposure.

Recommendation 1

Despite a very low level of evidence, individuals with any history of asbestos exposure currently or in the past could be advised to undergo a screening program, with an abdominal ultrasound every year, to improve early detection of DMPM.

Level of evidence: D

Strength of recommendation: II

Consensus: 10/27 (37%)

Diagnosis and pathology

Clinical presentation

The clinical presentation of DMPM is asymptomatic in most cases. Any symptoms are vague and unspecific. Most of the cases are diagnosed at an advanced stage and the median time from symptoms to diagnosis is about 4 months, highlighting the insidious nature of this disease. According to a multicentre cohort study the most frequent symptoms/signs were ascites (77%), abdominal pain (69%), asthenia (43%), weight loss (32%), anorexia (30%), and an abdominal mass (30%).[11] The diagnosis is incidental in many patients, detected during abdominal operations in patients with indolent disease and may be co-incidental to other pathology. The differential diagnoses may include more frequent conditions such as peritoneal metastasis from gastrointestinal tumours or ovarian cancer.

Pathological diagnosis

The pathological diagnosis of DMPM should include consideration of appropriate clinical, radiological, and surgical findings. Mesothelioma often presents with recurrent serous effusions with samples of aspirate submitted for cytologic evaluation. Establishing a definitive diagnosis of DMPM by cytologic examination alone remains controversial, and problematic, as diagnostic sensitivity ranges from 30% to 75%.[12] That broad range of sensitivity (high false-negative rate) is probably related to sampling, rather than interpretation, but one has to acknowledge that there is a broad overlap in atypical features and in immunoreactivity, across benign reactive and malignant mesothelial cell proliferations. Moreover, the malignant cells in sarcomatoid DMPM are not shed into the effusion fluid, which may only contain the overlying reactive epithelioid mesothelial cells that may mislead the pathologist. Inability to assess invasion of pre-existing tissue (not granulation tissue) - one of the key histologic diagnostic features of DMPM - in exfoliative cytology specimens, further hinders definitive cytologic diagnosis and underscores the importance of close correlation with clinical and imaging finding.[13] Furthermore, the cytologic evaluation does not allow the evaluation of proliferative index by means of Ki-67, which could be regarded as a critical prognostic factor with a fundamental role in therapeutic decision making.[14]

Recommendation 2

For the pathological diagnosis of PM, the analysis of adequate tissue specimens obtained from core needle biopsy or explorative laparoscopy is mandatory, rather than a cytologic examination of serosal effusion or material collected by fine needle biopsy.

Level of evidence: A

Strength of recommendation: I

Consensus 27/27 (100%)

Pathological diagnosis

Most DMPM are readily identified or strongly suspected on routine haematoxylin-eosin staining. The DMPM exhibits three major histologic subtypes, divided into epithelioid, sarcomatoid, or mixed (biphasic) categories in the updated 2015 World Health Organization classification.[15] A definitive diagnosis of DMPM requires a workup, including immunohistochemistry (IHC). Positive IHC markers are Calretinin (tight junction-associated protein), Cytokeratin 5/6 (intermediate-sized basic keratins), WT-1 (tumour suppressor gene), Podoplanin (transmembrane mucoprotein), and Thrombomodulin (surface glycoprotein involved in the regulation of intravascular coagulation). Negative IHC markers are Claudin 4, TTF-1, and CEA.[3] According to the International Mesothelioma Interest Group (IMIG) 2017 Pathologic Diagnosis Consensus Statement for an accurate diagnosis, an expert second opinion is advised in difficult cases.[13]

Recommendation 3

A histological review of the diagnosis of a DMPM by a pathologist with expertise in PSM is mandatory.

Level of evidence: A

Strength of recommendation: I

Consensus 27/27 (100%)

Recommendation 4 (4.1 to 4.8)

The pathologic report must mention the histological subtype, the Ki-67 index and the nodal status (if appropriate). The mention of the sub-classification of epithelioid (tubulopapillary

and solid/deciduoid), the invasiveness, the mitotic rate, the nuclear grade and the nuclear size are optional.

4.1 Histological subtype (epithelioid, biphasic and sarcomatoid)

Level of evidence: A

Strength of recommendation: I

Consensus 27/27 (100%)

4.2 Subclassification of epithelioid (tubulopapillary and solid/deciduoid)

Level of evidence: B

Strength of recommendation: II

Consensus 25/27 (92.6%)

4.3 Ki-67 proliferative index

Level of evidence: A

Strength of recommendation: I

Consensus 23/27 (85.2%)

4.4 Invasiveness

Level of evidence: B

Strength of recommendation: II

Consensus 14/27 (51.9%)

4.5 Mitotic rate

Level of evidence: B

Strength of recommendation: II

Consensus 18/27 (66.7%)

4.6 Nuclear grade

Level of evidence: B

Strength of recommendation: II

Consensus 21/27 (7.8%)

4.7 Nuclear size

Level of evidence: C

Strength of recommendation: II

Consensus 23/27 (85.2%)

4.8 Nodal status

Level of evidence: A

Strength of recommendation: I

Consensus 20/27 (74.1%)

Preoperative workup

Imaging

Computed Tomography (CT) Scan

The published literature on imaging assessment of DMPM is scanty. A CT scan is currently regarded as the preferred radiologic method in the preoperative evaluation of this disease. This may be due to accessibility, cost, short acquisition time, and the ease of interpretation by the relatively non-trained radiological eye. Moreover, CT scan is able to detect pleural disease, either malignant disease or plaques that suggest asbestos exposure. Recent data demonstrated that a CT scan could be of assistance in the differential diagnosis between DMPM and other PSM.[16,17] According to a meta-analysis, a CT scan tends to underestimate the disease burden of small volume disease in relation to the small bowel similar to the experience of imaging in peritoneal disease in general.[18-20] However, given that high peritoneal cancer index (PCI) *per se* is not an exclusion criteria for the surgical treatment of DMPM, this caveat might not represent a limitation for the clinical usefulness of CT scan in the preoperative workup of DMPM.

Yan et al conducted a seminal study reporting on CT scan assessment of resectability of DMPM.[21] They analysed the preoperative CT scans of DMPM patients treated with cytoreductive surgery (CRS) and perioperative intraperitoneal chemotherapy. Based on the size of residual tumour nodules after CRS, patients were divided into two groups according to the completeness of CRS. Thirty-nine CT scan parameters were obtained and correlated with adequacy of cytoreduction. Seven patients (64%) in the suboptimal cytoreduction group and 2 patients (11%) in the adequate cytoreduction group had a >5 cm tumour mass in the epigastric region (*P = 0.004*). Nine patients (82%) in the suboptimal group and 2 patients (11%) in the adequate cytoreduction group had CT scans that showed loss of normal

architecture of the small bowel and its mesentery (*P <0.001*). In a composite analysis of these two radiologic features, none of the patients with a >5 cm tumour mass in the epigastric region and loss of normal architecture of the small bowel and its mesentery had an adequate cytoreduction. Patients who lacked these two preoperative CT scan findings had a 94% probability of an adequate cytoreduction (Figure 1).

Recommendation 5

Cross sectional imaging with CT for preoperative evaluation for DMPM should be the preferred diagnostic imaging modality.

Level of evidence: A

Strength of recommendation: I

Consensus 27/27 (100%)

Magnetic Resonance Imaging (MRI)

Magnetic Resonance Imaging (MRI) is an alternative cross-sectional imaging technique and has been suggested to be superior to a CT scan in quantifying the PCI in PSM.[18,22,23] However no data is available reporting the accuracy of MRI in the detection of small lesions, characterization of disease burden, and evaluation of resectability in DMPM.

Recommendation 6

MRI in the diagnostic and preoperative workup of PM patients could be one of the diagnostic imaging modality.

Level of evidence: B

Strength of recommendation: II

Consensus 26/27 (96.3%)

Fluorine-18 fluorodeoxyglucose (18F-FDG)-PET/contrast-enhanced CT (PET/CT)

Recently PET/CT has been introduced in the diagnostic armamentarium of PM with suggestions that it may be a promising tool with sensitivity, specificity and accuracy of 86%, 89%, and 87%, respectively.[24] These data, although encouraging, need confirmation in further studies to define the role and potential of PET/CT in the preoperative workup of DMPM.

Recommendation 7

PET/CT in the diagnostic and preoperative workup of PM patients could be one of the diagnostic imaging modalities.

Level of evidence: C

Strength of recommendation: II

Consensus 18/27 (66.7%)

Laparoscopy

Serum tumour markers

Baratti et al. evaluated the clinical utility of baseline serum tumour markers in 60 DMPM patients selected for CRS and Hyperthermic Intra-Peritoneal Chemotherapy (HIPEC).[25] Forty-six patients underwent adequate cytoreduction. Baseline diagnostic sensitivity of CA125, CEA, CA19.9 and CA15.3 were 53%, 0%, 4%, and 49%, respectively. When CA125 values were expressed as positive or negative according to the 35 U/L cut-off, positive determinations were statistically related to high-grade histological subtype, PCI>25 and no pre-operative systemic chemotherapy. Postoperatively, CA125 became negative in 21/22

patients with elevated baseline levels undergoing adequate CRS-HIPEC, while remained elevated in 9/9 patients with persistent macroscopic disease.

There are conflicting data on the prognostic significance of baseline serum CA125. According to Baratti et al. it did not correlate with overall survival (OS) on multivariable analysis.[25] Others have found such a link and included CA125 in the construction of a preoperative nomogram.[26]

The biological mechanism connecting an elevation of CA125, tumorigenesis and disease progression in DMPM is not fully elucidated. Rump et al. described a mechanism for binding of CA125 to mesothelin, a circulating form of a 40kDa membrane-linked glycoprotein normally present on mesothelial cells. They suggested that this mechanism may contribute to peritoneal dissemination by initiating malignant cell attachment to the mesothelial epithelium.[27] Bruno et al. have recently investigated the performance of mesothelin in the diagnosis of DMPM.[28] In the differential diagnosis of DMPM from other kinds of PSM, according to ROC curve analysis, at a cut off value of 5.21 ng/dl, mesothelin had a sensitivity, specificity, positive and negative predictive values of 70%, 100%, 100%, and 61%, respectively. This data is of particular interest not only for diagnostic utility but also for therapeutic implications as mesothelin represents a valuable target for drug therapy. Amatuximab, a chimeric anti-mesothelin antibody, in combination with Cisplatin/Pemetrexed has recently provided promising oncological outcome in unresectable pleural mesothelioma, in a prospective uncontrolled study.[29] The same combination is currently under evaluation in a randomized phase II study in patients with malignant pleural mesothelioma (NCT02357147). The prognostic significance of mesothelin in PM is still to be defined.

Recommendation 8

The determination of baseline serum CA125 level could be included in the preoperative workup of DMPM patients.

Level of evidence: B

Strength of recommendation: II

Consensus 14/27 (51.9%)

Recommendation 9

The determination of baseline serum mesothelin level could be included in the preoperative workup of DMPM patients.

Level of evidence: C

Strength of recommendation: II

Consensus 23/27 (85.2%)

Some studies have explored the clinical utility of laparoscopy in the preoperative evaluation of PSM with the main reported advantages being more accurate evaluation of disease resectability to avoid futile subsequent laparotomies, and low morbidity and mortality associated with laparoscopy.[30-33] Although laparoscopy is inferior to open surgery in the evaluation of PCI in peritoneal metastasis from colorectal cancer,[34] it has been shown to outperform CT scan in the evaluation of limited peritoneal metastasis.[31] The main concerns with laparoscopy regard the feasibility in a patient with a hostile abdomen (due to prior surgery or high tumour burden) leading to incomplete preoperative abdominal cavity

assessment.[35] Moreover, the risk of port site recurrence has been reported by some in the context of PSM.[36,37]

There is one publication that addressed the diagnostic performance of preoperative laparoscopy in DMPM. Laterza et al. reported on 33 DMPM patients who underwent CRS and HIPEC.[38] At laparoscopic evaluation, peritoneal disease was judged resectable in 30 out of 33 patients (91%). In this group, cytoreduction was complete (CC-0/1) in 29 patients and incomplete in one. Three patients were judged not amenable to complete CRS at laparoscopy and they all underwent suboptimal CRS. The sensitivity, specificity, positive predicted value, negative predicted value, and accuracy were 100%, 75%, 97%, 100%, and 96.9%, respectively. Regarding the specific sites of disease involvement, no patients had an epigastric lesion >5 cm diameter at both laparoscopic and surgical exploration. Massive involvement of the small bowel and its mesentery was apparent in three patients at laparoscopy, but at surgical exploration it was confirmed in four. These data supported the utility of laparoscopy in the evaluation of resectability in DMPM.

Of note, as the prediction of a complete cytoreduction is related more to the experience of the operator than to the minimally invasive technique of laparoscopy, one might propose that laparoscopy should be performed by a surgeon acquainted with PSM to ensure an accurate assessment of resectability. But this is controversial as in Laterza's study general surgeons without experience in CRS and HIPEC performed the laparoscopy and the recorded tapes were reviewed by the surgeon who performed the CRS.[38]

Recommendation 10

Laparoscopic evaluation in the preoperative workup of DMPM patients could be performed to better characterize the preoperative peritoneal cancer index and disease resectability.

Level of evidence: B

Strength of recommendation: II

Consensus 13/19 (68.4%)

Recommendation 11 (11.1 to 11.5)

This preoperative laparoscopy should be done by a surgeon with expertise in PSM, with midline placement of trocars to allow excision in a subsequent operation for prevention of port site recurrence, with thorough evaluation of the peritoneal cavity with assessment of PCI, serosal and mesentery. Biopsy of diaphragmatic peritoneum has been associated with local inflammatory reaction and adhesions that hamper the subsequent maneuver of diaphragmatic peritonectomy and therefore should be avoided. A video recording of the procedure could be done.

11.1 Procedure done by a surgeon with expertise in PSM

Level of evidence: A

Strength of recommendation: I

Consensus 24/27 (88.9%)

11.2 Midline placement of trocars

Level of evidence: A

Strength of recommendation: I

Consensus 24/27 (88.9%)

11.3 Throughout evaluation of the peritoneal cavity with assessment of PCI, serosal and mesentery

Level of evidence: A

Strength of recommendation: I

Consensus 26/27 (96.3%)

11.4 The biopsy of diaphragmatic peritoneum

Level of evidence: C

Strength of recommendation: III

Consensus 15/27 (55.6%)

11.5 Video recording of the procedure

Level of evidence: C

Strength of recommendation: II

Consensus 23/27 (85.2%)

DMPM treatment

Therapeutic decision-making

Multidisciplinary team (MDT) management is considered best practice in cancer and is an integral component of coordinated cancer care.[39] Studies about MDT meetings focus on an alliance of all medical and health care professionals involved in treating a specific tumour whose approach to cancer care is guided by their willingness to agree on evidence-based clinical decisions and to co-ordinate the delivery of care at all stages of the process, encouraging patients in turn to take an active role in their care.[40]

Recommendation 12

The selection for the best management strategy for DMPM patients by a Multidisciplinary Team involved or specialized in PSM is mandatory.

Level of evidence: A

Strength of recommendation: I

Consensus 26/27 (96.3%)

Treatment options and strategies

DMPM is a rare serious disease.[41] Due to the rarity, there are no randomized phase III trials evaluating any systemic chemotherapy (SC) regimen in that histology. Most of the reported studies are retrospective with little effectiveness and of poor quality level of evidence.[42-46][47-49] The main SC protocol used in DMPM patients has been evaluated prospectively in pleural mesothelioma patients.[50] Since then, retrospective analysis

suggests that this strategy is also effective in DMPM patients.[46,48] The temptation to extrapolate oncological outcomes from pleural to peritoneal mesothelioma is strong but it would further downrate the supporting evidence by indirectness, according to GRADE. These two pathologies share common characteristics but also true biologic differences. The lack of clear guidelines and the uncertainty of benefit have culminated in SC being offered on an individual basis, and timing of administration is largely dependent on the preference of the oncology team and/or the surgeon's comfort with the procedure.

The main prognostic factors are histological features (epithelioid has a better prognosis than sarcomatoid or biphasic), lymph-node involvement, and the completeness of cytoreduction score (CC-0/1 is better than CC-2 and CC-3), implying that surgery remains the treatment that offers the most prolonged survival for DMPM patients.[51] Complete CRS is usually combined with HIPEC (with various protocols), with good published oncological outcomes. Other parameters were reported to be of prognostic significance, such as the solid subtype (found to be an independent negative prognostic factor for OS)[52] or Ki-67 expression (found to be an independent negative prognostic factor for OS if >9%).[14] Other modalities of intraperitoneal (IP) chemotherapy can also be combined with CRS-HIPEC and systemic chemotherapy, either in a neoadjuvant or adjuvant setting, such as EPIC (early postoperative intraperitoneal chemotherapy) or NIPEC (non hyperthermic intraperitoneal chemotherapy).[53]

Any evaluation of these combinations is difficult because of the differences in the indications and in the protocols used. At diagnosis, treatment strategies are mainly guided by the resectability of the peritoneal metastases (aiming to achieve a complete cytoreduction) and by the patient's general fitness for major intervention. Based on a comprehensive pre-treatment work-up, patients could be categorized into three groups (Figure 2):

- Patients with extra-peritoneal disease, and/or with poor general status not allowing major abdominal surgery, and/or with a clearly non resectable peritoneal metastases at initial assessment;
- Patients with no extra-peritoneal disease, fit for major abdominal surgery, and with disease amenable to complete resection; and
- Patients with no extra-peritoneal disease, and not fit for major abdominal surgery or with disease not fully resectable or resectable at the cost of several bowel resections with higher risk of postoperative morbidity (borderline resectable disease).

In the first group, patients may benefit from palliative treatment, mainly SC and also peritoneal-directed treatment, such as IP chemotherapy. Surgery could be considered in case of intestinal obstruction or uncontrollable abdominal pain.

In the second group, the objective is to propose a curative-intent strategy, based on a complete CRS combined with HIPEC. Ongoing debate persists as to indications for SC, the duration and regimen.

In the third group, preoperative treatment with an attempt to convert to suitability for curative intervention should be discussed. This represents a major challenge in trying to improve the likelihood of curative-intent surgery. Downsizing the extent of the peritoneal disease with a well-tolerated and efficient preoperative treatment represents a key issue for increasing the resectability rate and reducing postoperative morbidity.

Systemic chemotherapy

The combination of cisplatin and pemetrexed is widely accepted as the standard first-line SC protocol for malignant pleural mesothelioma. This strategy is based on the result of a phase III study that included 456 patients (226 received pemetrexed and cisplatin, 222 received

cisplatin alone, and 8 never received therapy).[50] Median survival time in the pemetrexed/cisplatin arm was 12.1 months vs. 9.3 months in the control arm (*P = .020*). Median time to progression was significantly longer in the pemetrexed/cisplatin arm: 5.7 months vs. 3.9 months (*P = .001*). Response rates were 41.3% in the pemetrexed/cisplatin arm vs. 16.7% in the control arm (*P <.0001*). Folic acid and vitamin B12 should be administered routinely with pemetrexed prescription in order to limit myelosuppressive toxicity.[50]

Palliative systemic chemotherapy

No controlled data are available in palliative DMPM patients. Before the Vogelzang et al.'s randomized trial in pleural mesothelioma patients, many protocols were used.[54] In an exhaustive review with meta-analysis, Berghmans et al. compiled results from different SC protocols in pleural and peritoneal mesothelioma.[42] Four groups were compared: cisplatin without doxorubicin (20 trials); doxorubicin without cisplatin (8 trials); combination of cisplatin and doxorubicin (6 trials), and regimens without cisplatin or doxorubicin (54 trials). Trial quality was also evaluated. Overall response rate was better with the combination of cisplatin and doxorubicin. Response rates between cisplatin and carboplatin-containing regimens were significantly different (24.0% vs 11.6%; *P = .004*). The combined agent regimens had a significantly better response rate than single-agent regimens (22.6% vs 11.6%; *P < .001*). After separating the trials into two groups according to trial quality score, the same conclusions on response rates were reported.[42]

Following the Vogelzang et al. randomized trial, but prior to approval of the regimen, there was a demand for patient access to pemetrexed. The International Expanded Access Program (EAP) was created by Eli Lilly and the Food and Drug Administration to facilitate

compassionate use of pemetrexed for patients with mesothelioma prior to approval by regulatory agencies. Two studies evaluated pemetrexed through this non-randomized open study in Europe and in the United States.[45,46] Carteni et al. and Jänne et al. reported outcomes of, respectively, 109 and 98 proven DMPM patients, not resectable, who received at least 1 dose of pemetrexed alone or in combination with cisplatin or carboplatin. Outcomes are summarized in Table 2. In Jänne et al series, 33% of previously treated patients and 21% of chemotherapy-naive patients received a minimum of 6 cycles of therapy. There were no discontinuations due to adverse events or laboratory toxicities in the European series but Jänne et al. reported that one patient died as a result of study drug toxicity.[45]

In the two series response rates were better when pemetrexed was combined with a platinum agent than used as single agent (Table 2). Response was up to 30% with pemetrexed and cisplatin.[45] Median survival for pemetrexed alone was 10.3 months and 8.7 months in the Carteni and Jänne series, respectively. Carteni at al. reported one-year survival rates for pemetrexed/cisplatin and pemetrexed of 57% (10.3-100) and 42% (4.6-78.4), respectively.[46] Jänne et al. showed that median survival was 13.1 months (95% CI, 7.8-13.1 months) for previously treated patients and not reached for chemotherapy-naive patients.[45] So the antitumor activity of pemetrexed in patients with non-resectable DMPM suggests response rates in the range of those observed for pleural disease.

Lastly, a small phase II multicentric trial of pemetrexed combined with gemcitabine was conducted in 20 patients not amenable to curative surgical treatment (Table 2).[47] In this series, 14 were epithelioid, 2 biphasic and 1 multicystic. Before enrolment, 15 patients had at least one disease related surgical procedure and four patients underwent surgery with curative intent. Fifteen patients completed 4 cycles or more. There was one patient death,

518 which occurred after the first treatment as a result of multiple organ failure attributed to
519 study drug treatment. An additional five patients discontinued therapy because of
520 unacceptable toxicities. The most common grade 3 to 4 hematologic toxicity was
521 neutropenia (12 patients; 60%), with eight patients at grade 4 (40%). Two patients (10%)
522 experienced febrile neutropenia and one patient (5%) had grade 4 anaemia. Oncological
523 outcomes are shown in Table 2. The disease control rate was 50% (95% CI, 27% to 73%).
524 Median time to progressive disease was 10.4 months (95% CI, 5% to not reached; 40%
525 censored). Median OS for all patients was 26.8 months (95% CI, 11.7% to not reached; 50%
526 censored).[47] These results are difficult to interpret with the presence in this limited cohort
527 of a multicystic mesothelioma patient of far better prognosis. These promising oncological
528 outcomes are counter-balanced by the observed high morbidity of this combination.
529
530 ***Recommendation 13***
531 In non-operable and/or non resectable DMPM patients (palliative patients), a platinum-
532 based systemic chemotherapy should be proposed rather than best supportive care. The
533 best proposed regimen is the combination of cisplatin and pemetrexed, second choice
534 cisplatin and gemcitabine.
535 Level of evidence: B
536 Strength of recommendation: I
537 Consensus 25/27 (92.6%)
538
539 Perioperative systemic chemotherapy in resectable patients
540 Three retrospective studies on large DMPM cohorts evaluated the influence of a
541 perioperative SC protocol in DMPM curative intent strategy.[55-57] Table 3 and Table 4

show synthetized data from these 3 series, according to the systemic chemotherapy protocol: neoadjuvant (NA), adjuvant (ADJ), pre- and post-operative (PO) and no SC group (NoC). Deraco et al. reported 119 patients, all supposed to have SC, meaning that patients in their NoC group were not fit to receive SC.[55] In a few cases, preoperative chemotherapy was used with neoadjuvant intent (patients with poor general condition or doubtful resectability). No information about criteria for patients allocation to one or other group is available in the Naffouje et al. series, while in the third series it was sometimes a question of centre policy, sometimes for oncological reasons but with no clear data reported.[56,57] Nevertheless, a significant number of this NA group had upfront SC because of the usual policy. Pemetrexed combined with a platinum agent were the most frequently used SC regimens.[55,56]

In two series there was no significant difference between subgroups in terms of oncological outcomes.[55,57] In contrast, Kepenekian et al. showed a significant survival disadvantage with the use of NA chemotherapy, even when adjusting for main prognosis factors.[56] At a median follow-up of 61 months, the 5-year OS was 40%, 67%, 62% and 56%, and the median OS was 37, 82, not reached, and 71 months for NA, PO and NoC groups respectively (*P = .049*). The only factor independently associated with improved OS in multivariate analysis was the absence of neoadjuvant SC (HR, 2.30; 95% CI, 1.07 - 4.94; *P = .033*).[56] This result was also suggested in the Deraco et al. series with NA protocol independently associated with poorer PFS.[55]

Preoperative SC was neither associated with CC-score at CRS nor with grade 3-5 morbidity.[55,56] Deraco et al. reported that NA platinum-pemetrexed combination produced response (complete + partial) and disease control (complete + partial + stable disease) rates of 31% and 86%, while platinum and gemcitabine combination resulted in

responses of 27 and 82%, respectively. The median PFSs were 14.4 months for both combinations. The median OS was not reached for platinum and pemetrexed, and it was 31.4 months for a platinum and gemcitabine combination.

Recommendation 14

Adjuvant combined systemic chemotherapy should be proposed rather than direct follow-up, in DMPM patients treated with CRS-HIPEC, and with at least one bad prognosis factor (CC-score > 1, sarcomatoid or biphasic subtype, lymph node involvement, Ki67>9%, PCI>17).

Level of evidence: B

Strength of recommendation: I

Consensus 24/27 (88.9%)

Recommendation 15

DMPM patients treated with CRS-HIPEC and with a favorable prognostic profile (complete cytoreduction and epithelioid subtype and no lymph node involvement and Ki67 ≤ 9% and PCI ≤ 17) could be managed by follow-up alone. The benefit from adjuvant systemic chemotherapy is uncertain in these patients.

Level of evidence: B/C (48.1% each)

Strength of recommendation: II

Consensus 20/27 (74.1%)

Intraperitoneal chemotherapy

EPIC and NIPEC

CRS-HIPEC has been associated with the best oncological outcomes in DMPM patients. To consolidate the results of this comprehensive treatment, Sugarbaker proposed the addition of postoperative intraperitoneal chemotherapy. [58] Two main modalities exist: namely EPIC (early postoperative intraperitoneal chemotherapy) and NIPEC (non hyperthermic intraperitoneal chemotherapy).

Multiple studies have used EPIC in varying amounts as shown in Table 5.[26,51,59-61] In most cohorts, EPIC was performed in selected patients who received CRS-HIPEC without clear selection criteria. The lack of characterization and uniformity of the chemotherapeutic agents used, number of days and mechanism by which EPIC is administered, combined with the small numbers of patients who receive therapy, do not allow readers to draw a consistent conclusion.

Recently, EPIC and NIPEC were compared retrospectively in 129 epithelioid DMPM patients after exclusion of low grade and poorly differentiated disease. Three groups comprised the following: CRS-HIPEC (42 patients), CRS-HIPEC-EPIC (58 patients) and CRS-HIPEC-EPIC-NIPEC (29 patients). HIPEC was performed with cisplatin and doxorubicin, EPIC with paclitaxel and NIPEC with paclitaxel or pemetrexed. All patients treated by NIPEC completed at least 5 of the 6 cycles. Group statistical comparisons reported a significantly better survival in favour of the NIPEC group (*P = .037*). A comparison of patients without NIPEC, and with NIPEC, showed a P-value of 0.011.[53] Adding EPIC to HIPEC showed no significant difference; however, a statistically significantly better survival was reported when multiple cycles of NIPEC were utilized. This lack of difference with the addition of EPIC over time, with marked

benefit as repeated cycles of regional chemotherapy were introduced, supports the concept of a long-term IP-directed treatment.

Bijelic et al. reported a phase II study of bidirectional chemotherapy with IP pemetrexed combined with IV cisplatin after CRS-HIPEC (and EPIC in 90% of the patients).[62] Of 10 patients, 8 were epithelioid and 2 biphasic, 4 patients were CC-0/1, 4 were CC-2 and 2 CC-3. Nine of 10 patients completed all 6 cycles of therapy without treatment delays or dose modifications. One patient developed a catheter infection after cycle 3 and required catheter removal. The median survival for all 10 patients was 33.5 months.[62]

Recommendation 16

Locoregional adjuvant therapy (EPIC and/or NIPEC), in association with systemic chemotherapy, could be proposed in DMPM patients submitted to CRS-HIPEC, as long as postoperative clinical conditions are sufficient.

Level of evidence: C

Strength of recommendation: II

Consensus 22/27 voters (81.5%)

Combination of systemic and intraperitoneal chemotherapy in borderline/not resectable patients

As CRS-HIPEC is the most effective treatment in DMPM patients, but associated with procedure related morbidity and mortality correlated to the extent of CRS and the number of digestive tract resections, the management of DMPM with a high tumour burden is challenging. Reducing the extent of peritoneal disease could render patients with DMPM resectable and/or to limit the extent of CRS and thus the related morbidity. With limited

response rates, SC usually does not achieve sufficient downsizing to convert DMPM patients to resectability. Several approaches have been proposed to reduce the tumour burden via peritoneal-directed treatments, notably the combination of intraperitoneal and systemic chemotherapy.

Le Roy et al. reported the experience of 20 patients with epithelioid DMPM, either unresectable or borderline resectable, treated with neo-adjuvant bidirectional chemotherapy.[63] A pre-treatment staging laparoscopy was performed to define unresectability as an impossibility in performing a complete resection mainly due to extensive involvement of the mesentery and/ or serosa of small bowel. ‘‘Borderline’’ resectability was defined as the disease potentially resectable but with multiple visceral resections at high risk for postoperative complications and impaired quality of life. Staging laparoscopy was performed again after 4 IP cycles to reassess resectability. Two IP-CT regimens were used: pemetrexed combined with IV cisplatin or carboplatin simultaneously on day 1 of a 21-day cycle; and oxaliplatin IP combined with IV gemcitabine on day 1 of a 14-day cycle. The choice of IP-CT regimen between pemetrexed and oxaliplatin was determined in accordance with previous treatments, potential side effects, and toxicity.[63] In patients with resectability confirmed after restaging laparoscopy, CRS-HIPEC was performed with oxaliplatin, with or without irinotecan and IV systemic 5-fluorouracil.

Fourteen patients had previous SC (3 with objective response): pemetrexed plus carboplatin or cisplatin (median, 4 cycles). The median PCI before treatment was 27 (15-39) with 95% of patients having a PCI>20. Disease was classified as borderline in 12 patients and unresectable in 8 patients, with median PCI scores of 24 (range 15-34) and 34 (range 25-39), respectively (*P = .002*). First-line IP-CT was pemetrexed combined with systemic cisplatin (or carboplatin) for 19 of the 20 patients and oxaliplatin combined with systemic gemcitabine

for 1 patient. As progressive disease persisted after six (2 patients) and four (2 patients) cycles of bidirectional chemotherapy, pemetrexed was replaced by IP oxaliplatin for these four patients. A total of 118 cycles were administered IP with no adverse event related to the catheter after a median of 5 (range 1–15) cycles per patient. One patient had to discontinue IP-CT because of an inadequate solute distribution in the peritoneal cavity, shown by the scintigraphic control performed after eight cycles. A clinical response to bidirectional chemotherapy was observed in 12 patients (60%), with resolution of ascites (n=10), relief of abdominal pain (n=1), or both (n=1) after a median of 3 (range 2–5) cycles. Laparoscopic re-evaluation in 15 patients showed a median variation in PCI score at first laparoscopic re-evaluation of minus -5 (range minus -26 to +2). Eleven patients finally had CRS-HIPEC with 9 having CC-0 and 1 a CC-1. The patient who had CC-2 was due to extensive involvement of the right diaphragmatic area. The median PCI score in the patients who underwent CRS-HIPEC decreased from 27 (range 15–39) before bidirectional chemotherapy to 14 (range 6–30) at the time of surgery (*P =.036*). Major complications (grades 3 to 4) occurred in four patients (early peritoneal haemorrhage requiring reintervention in 4 cases and severe acute respiratory distress syndrome in 1 case).[63]

For the entire cohort, after a median follow-up period of 18.5 months, 2-years OS was 68.5% and median OS not reached. Two-years OS was 83% and 44% for patients treated with CRS-HIPEC and for the patients treated with bidirectional chemotherapy alone, respectively (*P = .02*, log-rank test). Median disease-free survival rate was 25.5 months for the group treated with curative intent.

Recommendation 17

Bidirectional chemotherapy could be proposed in DMPM patients with good general condition, no extra-peritoneal metastases and, after staging laparoscopy, unresectable disease or with borderline resectability (large extent of the disease potentially resectable, with multiple visceral resections at high risk for postoperative complications and impaired quality of life), rather than an induction systemic chemotherapy with conversion intent. The proposed regimen is pemetrexed IP and cisplatin IV.

Level of evidence: C

Strength of recommendation: II

Consensus 25/27 (92.6%)

Surgical management of local-regional disease: CRS and HIPEC

Data reporting outcomes of DMPM patients treated with CRS and HIPEC are derived from single centre institutional reviews, two large multicentre reviews, and a recent meta-analysis.[41,51,64-66] These data are uncontrolled and retrospective. Nonetheless, CRS-HIPEC has emerged as the preferred initial treatment in selected DMPM patients with median OS ranging from 34 to 92 months. CRS-HIPEC carries rates of severe complications that range from 30% to 41% and rates of postoperative mortality ranging from 2.0% to 2.6%.[11,41,45,46,51,55,65]

Prognostic factors and patient selection for CRS and HIPEC

The process of patient selection is complex and requires careful evaluation of patient operability,[67] resectability (see section preoperative workup), and a wise and sensible interpretation of prognostic profiles. Several authors have reported prognostic factors in DMPM. The most well-established ones are age, histological subtype, completeness of

cytoreduction, and disease extent.[51,65,68,69] Recently the proliferative index measured by Ki-67 has been shown to be of strong prognostic importance.[70] Another factor, namely the expression of PD-L1 level, has also been suggested as a good candidate prognosticator.[52] (Table 6)

The current literature lacks prognostic tools able to provide personalized prediction of survival in DMPM. Yan et al. proposed a tumour, node, and metastasis staging system based on review of 294 patients with DMPM undergoing CRS-HIPEC.[71] However, such staging system relies on lymph node status, which is a parameter that is available only after surgery, and thus of no assistance for preoperative prognostic estimation as part of patient selection for CRS-HIPEC. Schaub et al. developed a preoperative nomogram that predicts survival in DMPM, using machine-learned Bayesian belief networks with stepwise training, testing, and cross-validation. The nomogram relies on histological subtype, pre-CRS PCI and preoperative serum CA-125.[26] This nomogram has a good discriminative capacity with mean areas under the receiver operating characteristic curve for the 10-fold cross-validation of the 3- and 5-year models being 0.77 and 0.74, respectively (Figure 3).

More recently Kusamura et al. developed an algorithm by means of a conditional inference tree model.[14] This user friendly and easy to understand graphic output assists the surgeon in patient selection for CRS and HIPEC in the preoperative phase. This model relies on pre-cytoreduction PCI and tumour proliferative index measured by Ki-67 using immunohistochemistry. Three prognostic subsets were defined: (I) Ki-67 ≤ 9 % with whatever PCI; (II) Ki-67 >9 % and PCI ≤17; and (III) Ki-67 >9 % and PCI >17. The median OS for subsets I, II, and III were, 86.6, 63.2, and 10.3 months, respectively. The model had an acceptable discriminant capacity with a bootstrap corrected Harrel c-index of 0.74. (Figure 4)

Biphasic mesothelioma represents a distinct and rare histologic subtype that has traditionally been grouped together with sarcomatoid variant and analysed separately from epithelioid mesothelioma. This practice stemmed predominantly from the rarity of biphasic and sarcomatoid mesotheliomas. Given the extremely dismal prognosis related to sarcomatoid variant, biphasic mesotheliomas have also been considered as a contraindication for CRS-HIPEC. To clarify what is the outcome of biphasic peritoneal mesotheliomas after complete CRS-HIPEC, data from an International Registry on Peritoneal Mesothelioma was analysed. From a cohort comprising 484 DMPM cases treated with complete CRS-HIPEC, 34 biphasic PM were identified. For patients with CC-0 resection, 5-year survival was 64.5% and 50.2% (median 7.8 and 6.8 years; *P = .015*) for epithelioid and biphasic mesotheliomas, respectively, while inclusion of CC-1 resections in the analysis resulted in inferior 5-year survival of 62.9% and 41.6% (median 7.8 and 2.8 years; *P =.0012*), respectively.[72]

Recommendation 18

CRS-HIPEC is recommended in DMPM patients rather than palliative SC, provided that the patient has a sufficient clinical condition for a major operation, has resectable disease, and that the treatment is done in a specialized PSM center.

Level of evidence: B

Balance of benefits and harms: favorable (96.3%), uncertain (favorable) (3.7%), uncertain (unfavorable) (0%) and unfavorable (0%)

Strength of recommendation: I

Consensus 26/27 (96.3%)

Recommendation 19 (19.1 to 19.11)

Four factors are judged to constitute an absolute contra-indication for CRS-HIPEC in DMPM patients: sarcomatoid histology, massive small bowel serosa involvement, concomitant pleural disease and/or a retroperitoneal and/or cardiophrenic lymph node involvement.

A biphasic histology, a disease not amenable by cytoreduction down to CC-0/1, a Ki-67 >9% in the preoperative pathological report, a PCI>17 in the pre-cytoreduction evaluation, the combination of a high risk subset with Ki-67 >9% and PCI>17 according to preoperative workup, massive small bowel mesentery involvement, and/or massive diaphragmatic involvement are judged to constitute relative contra-indications for CRS-HIPEC in DMPM patients.

For the following recommendations (19.1 to 19.11), the statement was:

Strong positive - Absolute contra-indication.

Weak positive - Relative contra-indication.

Strong negative - Not contra-indication.

19.1 Biphasic histology

Level of evidence: B

Strength of recommendation: II

Consensus 24/27 (88.9%)

19.2 Sarcomatoid histology

Level of evidence: B

Strength of recommendation: I

Consensus 20/27 (74.1%)

19.3 Disease not amenable by cytoreduction down to CC-0/1

Level of evidence: B

Strength of recommendation: II

Consensus 15/27 (55.6%)

19.4 Ki-67 >9% in the preoperative pathological report

Level of evidence: C

Strength of recommendation: II

Consensus 21/27 (77.8%)

19.5 PCI >17 in the pre-cytoreduction evaluation

Level of evidence: B

Strength of recommendation: II

Consensus 19/27 (70.4%)

19.6 High risk subset with Ki-67 >9% and PCI>17 according to preoperative workup

Level of evidence: B

Strength of recommendation: II

Consensus 17/27 (63.0%)

19.7 Massive small bowel mesentery involvement

Level of evidence: B

Strength of recommendation: II

Consensus 23/27 (85.2%)

19.8 Massive small bowel serosa involvement

Level of evidence: B

Strength of recommendation: I

Consensus 26/27 (96.3%)

19.9 Massive diaphragmatic involvement

Level of evidence: B

Strength of recommendation: II

Consensus 18/27 (66.7%)

19.10 Concomitant pleural disease

Level of evidence: B

Strength of recommendation: I

Consensus 14/27 (51.9%)

19.11 Retroperitoneal and/or cardiophrenic lymph node involvement

Level of evidence: B

Strength of recommendation: I

Consensus 14/27 (51.9%)

825

826 Technical aspects of CRS

827 Complete vs partial parietal peritonectomy

828 CRS is a standardized surgical strategy that comprises an ordered sequence of surgical
829 manoeuvres. The extent of CRS varies, according to the type of PSM, as the extent of surgical
830 effort should intuitively be modulated according to the biological aggressiveness of the
831 tumour. One of the disputed issues regarding the extent of cytoreduction is the surgical
832 policy with regards to resection of the parietal peritoneum. Investigators from Milan have
833 proposed a more aggressive cytoreduction with complete parietal peritonectomy, even if
834 the peritoneum is macroscopically normal.

835 The argument against this is that the parietal peritoneum corresponds to only 18% of the
836 total peritoneal surface area (visceral and parietal combined),[73] and that a limited increase
837 in the amount resected by total parietal peritoneal resection is unlikely to produce an impact
838 on prognosis. In favour of complete parietal peritonectomy is the fact that the peritoneal
839 surface is heterogeneous from the ultrastructural and biological point of view, with some
840 areas, such as the parietal peritoneum, more prone to develop neoplastic implants than
841 others, such as the serosa of the small bowel.[74]

842 A retrospective controlled study was performed involving 30 patients with DMPM
843 undergoing selective parietal peritonectomy of macroscopically involved regions, and 30
844 matched patients undergoing routine complete parietal peritonectomy, regardless of
845 disease distribution. Groups were comparable for the main prognostic factors. The complete
846 parietal peritonectomy group was associated with a 5-year overall survival of 63.9% (vs
847 40.0% of selective, *P = .027*). At multivariate analysis, the type of peritonectomy was an
848 independent prognostic factor, along with complete cytoreduction, negative lymph nodes,

epithelial histology, and lower MIB-1 labelling index. Morbidity and reoperation rates were not different between groups. No operative mortality occurred. In 12 of 24 patients undergoing complete parietal peritonectomy, pathologic examination detected microscopic disease involvement on parietal surfaces with no evident tumour at surgical exploration.[75]

Recommendation 20

A complete parietal peritonectomy during CRS for DMPM patients could be considered, as an option to selective parietal peritonectomy, regardless of PCI, in order to maximize locoregional disease control and eventually the long-term oncological outcomes.

Level of evidence: C

Strength of recommendation: II

Consensus 17/27 (63%)

Retroperitoneal lymph node dissection

Although the prognostic role of lymph node metastasis has been recognized in the most important DMPM cohorts,[51,76,77] the assessment of retroperitoneal lymph node status does not seem to be systematically and uniformly performed across international PSM centers.

From the multi-institutional data registry comprising 405 DMPM cases,[51] variables associated with improved survival were identified on univariate analysis and included: age ≥50, female gender, epithelial subtype, absence of lymph node metastasis, absence of extra-

abdominal metastasis, CC-0 or CC-1 cytoreduction, peritoneal cancer index of ≥20, use of HIPEC, transfusion of ≤5 units, and absence of cardiac complications. Only epithelial subtype, absence of lymph node metastasis, completeness of cytoreduction and use of HIPEC were independently associated with improved outcomes in multivariate analysis.

In the Washington cancer centre experience, seven out of 100 DMPM patients were lymph node positive and all 7 died of disease within 2 years of surgery. The remaining 93 patients had a 5-year survival of 50%. Multivariate analysis demonstrated that female gender, lymph node metastasis not detected, epithelial type, and adequate cytoreduction were independently associated with an improved survival.[76]

Baratti et al. reported on surgical specimens from 83 consecutive patients with DMPM undergoing CRS and HIPEC submitted to pathological examination. Lymph nodes were examined in 38 patients, being positive in 11 and negative in 27. Lymph nodes were not clinically suspicious and not sampled in 45 patients. Iliac (n=7) and paracolic (n=2) nodes were the most commonly involved nodes. OS was 18% for patients with pathologically positive nodes and 82.5% for those with pathologically negative nodes (*P = .0024*). On multivariate analysis, pathologically negative (versus positive/not assessed) nodes [hazard ratio (HR) = 2.81; 95% confidence interval (CI) = 1.12-7.05; *P =.027*], was independently correlated with increased OS. Positive nodes (versus negative/not assessed) did not significantly correlate with survival. The authors concluded that careful node sampling when performing surgical cytoreduction for DMPM patients is advisable.[77]

The exact anatomic sites for lymphadenectomy have not been clearly defined. Lymph node groups that have been suggested for histopathological assessment include the deep epigastric lymph nodes, external iliac lymph nodes at the internal inguinal ring, common iliac lymph nodes, lymph nodes at the origin of the gastroepiploic vessels, or accessible lymph

nodes present in the mediastinum immediately above the superior surface of the diaphragm.[76,77]

Recommendation 21

The dissection of suspicious retroperitoneal lymph nodes, and the sampling of non suspicious nodes, could be considered during CRS for DMPM, in order to enhance the prognostic characterization of the patient.

Level of evidence: C

Strength of recommendation: II

Consensus 20/27 (74.1%)

HIPEC drug schedules

HIPEC with platinum drugs such as cisplatin, and carboplatin either alone or in combination with doxorubicin, pemetrexed, ifosfamide and mitomycin have been used according to a recently published systematic review and meta-analysis of 20 publications with data on outcomes of over 1000 DMPM patients treated with operative CRS.[41] The outcomes related to each HIPEC drug option are outlined in Table 7. Single agent mitomycin has also been used with similar efficacy, although slightly inferior survival rate. In a previous study on 211 DMPM cases treated with the combined approach in three internationally recognized US institutions (University of Maryland School of Medicine, Baltimore; University of Pittsburgh Medical Centre, Pittsburgh; and the National Cancer Institute, Bethesda) patients receiving cisplatin based HIPEC had a better outcome as compared with mitomycin-C based HIPEC, according to multivariable Cox regression analysis.[65] However such apparent survival

advantage in favour of cisplatin was not observed when the cytoreduction was not optimal (CC-2/3).

Recommendation 22

Platinum-based HIPEC should always be considered after a complete cytoreduction down to residual disease <2.5 mm in DMPM patients, rather than other HIPEC drug combinations.

Level of evidence: B

Strength of recommendation: I

Consensus 25/27 (92.6%)

Recommendation 23

HIPEC after an incomplete cytoreduction down to residual disease >2.5 mm could be considered in DMPM patients as an option to systemic treatment.

Level of evidence: B

Strength of recommendation: II

Consensus 20/27 (74.1%)

Recommendation 24

Cisplatin and Doxorubicin is judged to be the best drug regimen recommended for HIPEC in DMPM patients.

Level of evidence: C

Strength of recommendation: I

Consensus 23/27 (85.2%)

Follow-up, long-term implications and survivorship

Follow-up

The goals of a post treatment follow-up program should be the identification of potentially resectable recurrences and a continuous evaluation of early and long-term treatment related sequelae. Due to the heterogeneity and scarcity of the available studies on this topic, it is hard to define precisely what are the best combination of follow up examinations, their frequency, and the total duration of surveillance. According to the main PSM centre's experiences the follow-up policy could consist of physical examination, thoracic/abdominal CT-scan and serum tumour marker measurements every 3-4 months during the first 2 years, then every 6 months for 3 years and annually thereafter.[56,65,66]

A more intense post treatment surveillance policy is appealing as it could detect potentially resectable recurrence amenable to a limited surgical resection. However there are no data confirming that increased frequency of visits is associated with improved survival. Moreover, should the recurrence be unresectable, as in most cases, there is no standardized second line treatment option, as in general, DMPM is well known to be chemo-resistant.

DMPM patients after CRS-HIPEC, usually have a median progression free survival ranging between 13.9 to 25.1 months.[26,56,65,68] As nearly 70% of recurrences occur within the first two years after treatment, the follow-up varies and is usually different in two periods (before and after two years from the initial therapy) with more frequent evaluations in the first period.

Another important issue is the duration of surveillance. Baratti et al. reported on 108 patients with DMPM undergoing complete CRS-HIPEC with cisplatin and doxorubicin or mitomycin-C.[66] After a median follow-up of 48.8 months the 5- and 10-year OS were

52.4% and 44.6%, respectively. The 5- and 10-year PFS were 38.4% and 35.9%. The survival curve reached a plateau after 7 years. This plateau represents 19 actual 7-year survivors out of 39 patients (43.6%), who had the potential for more than 7 years of follow-up. In these 19 long-term survivors, median survival was 104.2 months (95% CI = 91.4–133.6).

The US National Cancer Data Base has recently been interrogated for newly diagnosed non-metastatic DMPM.[69] 1,514 patients were selected and divided into five cohorts: observation (25%), chemotherapy alone (24%), CRS alone (13%), CRS/chemotherapy (23%), and CRS-HIPEC (14%). At median follow-up of 50 months, median OS in the CRS and HIPEC was 61 months. Similar to Baratti's data, the number of deaths decreased consistently after approximately 85 months of follow-up. Even though DMPM is known to have a high propensity to remain inside the peritoneal cavity for most of its natural history, a number of cases relapse outside the peritoneal cavity during post treatment surveillance. Baratti et al. analysed the pattern of recurrence in 70 DMPM and observed that in nearly 18.4% of cases the treatment failure occurred outside the peritoneal cavity and included pleura, and retroperitoneal lymph nodes, so that the follow-up imaging evaluation should consider not only the abdominal cavity but also the thorax.[78]

Recommendation 25

The length of follow-up extended to 7 years could be considered, after CRS-HIPEC in DMPM patients, in contrast to 5 years defined for other peritoneal metastatic disease (like colorectal cancer).

Level of evidence: B

Strength of recommendation: II

Consensus 18/27 (66.7%)

Recommendation 26 (26.1 to 26.6)

The follow-up of DMPM patients during the 2 first years and onward after CRS-HIPEC is proposed to be performed every 6 months and to include every 6 months:

- a physical examination,
- a thoracic/abdominal/pelvic CT scan,
- and a biomarker CA125 dosage.

26.1 Physical examination: 0-2 years

Physical examination during follow-up between 0 and 2 years should be should be done every 6 months

Level of evidence: C

Strength of recommendation: I

Consensus 8/19 (42%)

26.2 Physical examination: 2 years onward

Physical examination during follow-up from 2 years onward should be done every 6 months

Level of evidence: C

Strength of recommendation: I

Consensus 10/19 (52.6%)

26.3 Thoracic/abdominal/pelvic CT scan: 0-2 years

Thoracic/abdominal/pelvic CT scan during follow-up between 0 and 2 years should be done every 6 months.

Level of evidence: C

Strength of recommendation: I

Consensus 7/19 voters (36.8%)

26.4 Thoracic/abdominal/pelvic CT scan: 2 years onward

Thoracic/abdominal/pelvic CT scan during follow-up from 2 years onward should be done every 6 months.

Level of evidence: C

Strength of recommendation: I

Consensus 9/19 (47.4%)

26.5 Biomarker CA125: 0-2 years

CA125 assessment during follow-up between 0 and 2 years should be done every 6 months.

Level of evidence: C

Strength of recommendation: I

Consensus 7/19 (36.8%)

26.6 Biomarker CA125: 2 years onward

CA125 assessment during follow-up from 2 years onward should be done every 6 months.

Level of evidence:

Strength of recommendation:

Consensus 9/19 (47.4%)

Management of recurrent disease: the role of iterative CRS and HIPEC

Despite encouraging survival outcomes obtained with first-line CRS-HIPEC, DMPM does recur and represents a therapeutic challenge. The options can range from best supportive care, palliative systemic chemotherapy, and repeat surgery in an attempt to prolong a good quality of life and survival benefits. Some authors have proposed iterative CRS and HIPEC if a patient meets defined eligibility criteria. Ihemelandu et al. reported on recurrent DMPM cases who had undergone iterative CRS and HIPEC.[79]

The criteria for patient selection included good general condition to withstand major surgery and resectable disease, according to Yan's criteria (see section on preoperative workup). The exclusion criteria were an unfavourable tumour biology, as suggested by early disease recurrence (<1 year after the first treatment), and unresectable disease. Overall 10/54 patients had unsuccessful exploration with an inability to perform a repeat CRS and HIPEC. Forty-four patients underwent a successful iterative procedure and were compared to 161 DMPM patients who had just one CRS and HIPEC. There was no 30-day mortality following an iterative procedure, and the grade III–V morbidity was 2.3%. The median overall survival of patients undergoing an iterative CRS and HIPEC was 54 months versus 77 months following an initial CRS and HIPEC (*P = 0.96*). Patients undergoing iterative surgery had a 3- and 5-year survival of 61 and 46 %, respectively, versus 60 and 52 % following an initial CRS and HIPEC. Incomplete cytoreduction was significantly more frequent in the iterative group

(65.9% vs. 53.4%, *P = .000*). Independent prognostic factors in the iterative group were histological subtype, gender, completeness of cytoreduction, HIPEC regimen utilized, postoperative complication, and age at diagnosis. Wong et al. performed iterative CRS and cisplatin based HIPEC in 8 out of 29 DMPM cases. The majority were male (62%) and the median age was 66 years. Complication rates were 65% and 50%, respectively in the initial iterative HIPEC. Reoperation rate was far higher (4% initial and 25% iterative), and perioperative death was low (4% initial, 0% iterative). Median treatment-free time (time from initial to repeat HIPEC or chemotherapy) was not different between initial and iterative HIPEC (8.8 and 6.3 months, respectively, *P = 0.92*). Median OS for the cohort was 41.2 months. Patients who underwent iterative HIPEC had a median OS of 80 months versus those who had one CRS and HIPEC intervention (27.2 months; *P = .007*). A lower PCI and optimal residual disease were associated with better survival.

The retrospective nature of these studies does not allow us to conclude whether these outstanding short-term surgical and long-term survival outcomes associated with iterative combined procedures are a result of selection bias or derived from an actual treatment effect.

Recommendation 27

In recurrent DMPM patients with good general condition, resectable disease, and favourable prognostic profile (young age, epithelioid subtype, time to recurrence > 1 year, limited PCI), iterative CRS and HIPEC could be considered.

Level of evidence: B

Strength of recommendation: II

Consensus 15/27 (55.6%)

Conclusion on DMPM

As a conclusion, these guidelines can be considered to be consensus guidelines for the management of DMPM patients, with 80% of experts voting. Recommendations are listed in Table 8. Such patients should be referred promptly to PSM specialized centers to complete the workup and determine the most appropriate treatment strategy.

Peritoneal mesothelioma with low malignant potential: MCPM and WDPPM

In patients with peritoneal mesothelioma, a subset have a less aggressive form of the disease: multicystic peritoneal mesothelioma (MCPM) and well-differentiated papillary peritoneal mesothelioma (WDPPM). Both these disease entities generally affect reproductive age women with no history of asbestos exposure and show indolent clinical behaviours.

Multicystic Peritoneal Mesothelioma (MCPM)

Introduction

MCPM was first macroscopically described in 1928 by Plaut after surgery for uterine leiomyomas, but the histological description was published in 1979 by Mennemeyer and Smith who defined the lesion as “multicystic peritoneal mesothelioma”.[80] MCPM is a rare tumour, accounting for 3-5% of all cases of all cases of abdominal mesothelioma.[81] Consequently the reported literature data is only from case-reports and short series, summarized in Table 9.

Although the peritoneum is the most common tissue of origin, multicystic mesothelioma can also originate on other serosal membranes (pleura, spermatic cord, tunica vaginalis, and pericardium).[82] MCPM affects predominantly women of reproductive age with a mean age at diagnosis of approximately 42 years, lower than for DMPM patients. The female to male ratio is around 4.7:1 (Table 9). The most common presenting complaints are abdominal

pain, abdominal tenderness and infertility.[83,84] The duration of symptoms ranges from a few days to several months and in some cases years. Incidental diagnosis is the norm.[85]

Pathology and natural history

The intra-abdominal cystic lesion dissemination behaviour is typical, and similar to that of peritoneal metastases, with diaphragmatic peritoneal implants, involvement of the greater omentum, right iliac fossa, the parietal peritoneum, ovaries, mesentery and the small bowel serosa.[86] The pathogenesis remains unclear. Studies vary as to the proportion of patients with a history of previous surgery, pelvic inflammatory disease or endometriosis, suggesting that chronic peritoneal irritation could be a precipitating factor.[87-90]

Histologically, the tumour has border-line features: MCPM usually lacks cellular atypia or increased number of mitoses, however squamous cell metaplasia has been reported in some lesions.[91] Typically MCPM consists of small cysts composed of mesothelial epithelium with benign histologically bland appearing cuboidal cells and clear fluid. Between the cysts, a variable stromal and inflammatory component exists. As the histological findings could be concordant with peritoneal irritation, it was suggested that MCPM may be related to conditions with chronic peritoneal etiology.[91] Kurisu et al. reported, for example, two cases of MCPM associated with endometriosis.[90] This issue of whether MCPM is a reactive inflammatory or neoplastic origin is contentious. The female predominance could be related to a repetitive/chronic irritation of pelvic peritoneum rather than a consequence of hormonal secretion. A variable number of MCPM patients have a history of previous abdominal surgery but it could also be co-incidental rather than causative. It is of interest that there are two authenticated cases of malignant transformation of MCPM after multiple

surgical procedures and recurrences, suggesting a role of repetitive/chronic inflammation in the behaviour of such tumours.[82,92]

Pathological differential diagnosis includes a number of benign and malignant lesions that present as cystic or multicystic abdominal masses. Benign lesions include cystic lymphangioma, cystic forms of endosalpingosis, endometriosis, mullerian cysts involving the retroperitoneum, cystic adenomatoid tumours and cystic mesonephric duct remnants. Malignant lesions include malignant mesothelioma and serous tumours involving the peritoneum.[93]

Immunohistochemistry may help to clarify the diagnosis. Baratti et al. studied the level of Ki-67 expression and mitotic rate in 12 MCPM patients and found them to be low in all patients, as compared with the truly malignant counterpart, suggesting that poor proliferative activity may be related to the indolent MCMP behaviour.[83] Due to the predominant incidence in women, the influence of hormonal secretion was investigated.[91] Ravindranauth et al. studied the expression of oestrogen and progesterone receptors (ER and PR) in 17 MCPM patients and did not find any over-expression (one case was diffusely positive for ER only, one case was focally positive for PR only, and one case was focally positive for both ER and PR).[94]

Thus, two points have been established in the field of MCPM: the high rate of recurrence and the possibility of malignant transformation.

Based on previous reported data, Van Ruth et al. evaluated the recurrence rate at approximately 50% with a mean interval of 32 months.[95] Ross et al. reported outcomes in 25 women with MCPM with a median follow-up of 92.4 months (20.4 - 253.2), and found that 12 patients had postoperative local recurrence, of which 4 had multiple recurrences. Intervals between occurrences ranged from *5* months to 9 years (median 2.5 years). Very

late recurrences, one at 36 years, have also been described.[96] In the absence of treatment, disease is slow growing in the majority of cases. One case report in a patient who did not receive treatment died from the disease 12 years after diagnosis.[89]

Three cases of possible malignant transformation of MCPM have been reported in the literature. The first was in a 6 month-old child.[97] The second, more typical, concerned a young women, whose successive pathological analysis, along 6 surgical procedures, allowed to confirm the transition between a MCPM and a DMPM (with lymph nodes and abdominal wall invasion).[82] The clinical history of the third case is uncertain with 10 years of repeated conservative treatment leading to a DMPM.[92] Two more case-reports mentioned MCPM presenting as large multicystic masses and histologic features of associated malignant mesothelioma. The first concerned a young man with an initial diagnosis of MCPM, reviewed and confirmed at the time of early recurrence.[98] The second report is a 73 year-old woman with a diagnosis of a cystic malignant mesothelioma.[99] These small numbers are not enough to determine the incidence of MCPM malignant transformation but this in conjunction with the high risk of recurrence, justifies removing the “benign” from the previously accepted term “benign multicystic mesothelioma” and warrants classification as a low-grade or borderline disease.[82,84,85,92,100]

Recommendation 1

In a case of histologic diagnosis of MCPM, an histopathological review by an expert pathologist in PSM is mandatory.

Level of evidence: A

Strength of recommendation: I

Consensus 26/27 (96.3%)

Diagnosis

Kemp et al. reported a case diagnosed from a needle core biopsy with touch preparation of a gross pelvic mass. This case suggests that this allows for assessment of both the architectural, cytomorphologic, and immunohistochemical features, necessary to confirm a diagnosis with more certainty than is achievable through cytomorphologic characteristics alone.[101] More recently, analogous to other PSM management, some have proposed a staging laparoscopy to evaluate the disease extension and perform an adequate biopsy.[100] From a radiological point of view, MCPM is usually described as having an appearance of cystic structures in close association with the peritoneal surface.[102] In women, cysts often adhere closely to the uterus and the ovaries.[103-105] An ultrasound usually shows anechoic to mildly echogenic, multi-septated cystic structures in the pelvis with a varying number of lobulations and cysts. In rare occasions, intraabdominal fluid or haemorrhage is also reported.[103-105] On occasions wall calcifications have been noted.[105] On CT, MCPM usually appears as low-density, multiloculated, multi-cystic, thin walled lesions that may engulf the surrounding soft tissue; however, invasion has not been reported. On MRI, they appear as multiloculated cystic masses that are hypointense on T1 weighted images and hyper to intermediate intensity on T2 weighted sequences. The walls may demonstrate mild enhancement with contrast. Fat within the cysts has not been demonstrated.[102-105]

Treatment

Traditionally there were no uniform treatment strategies for MCPM. Complete surgical excision of localized lesions or debulking procedures for more extensive disease have been

described.[89] Some patients received adjuvant systemic chemotherapy and/or radiation therapy, with uncertain results.[91] Laser vaporization, percutaneous cystic drainage, hormonal therapy, sclerotherapy with anthracycline, or simple observation have been also proposed.[106] Due to the rarity of the disease, no randomized trial is conceivable for MCPM. The high recurrence rates and potential for malignant transformation support an aggressive approach to this disease at the time of diagnosis, with a systematic clinical follow-up of these patients for prolonged periods of time, probably for life. Following that idea, a comprehensive treatment with CRS and HIPEC has been proposed to MCPM patients, rather than expectant management, even in asymptomatic patients.

Five series, including 5, 12, 26, 19 and 28 MCPM patients (with cross inclusions), reported excellent results of CRS-HIPEC (Table 9). The high rates of complete CRS resulted in 5-year PFS of more than 80% and 10-year OS rates close to 100%. The main HIPEC protocol used was the combination of cisplatin and doxorubicin (Table 9). Interestingly, in a series of 12 women (4 with MCPM and 8 with WDPPM) treated with CRS-HIPEC, Baratti et al. showed that PFS following previous debulking surgery (median 24 months; range 2-87) was statistically worse than PFS after upfront CRS-HIPEC ($P = .0156$).[85] This result was confirmed later with 12 MCPM patients that were all alive at a median follow-up of 64 months after CRS-HIPEC, with no evidence of disease, including 2 patients who underwent the procedure twice, due to locoregional recurrence. Median PFS was not reached in patients with upfront CRS-HIPEC, while it was 11 months (range, 2-31) in case of previous debulking surgery ($P < 0.0001$).[83]

Nizri et al. reported 19 MCPM patients treated with 20 CRS-HIPEC procedures. The median PCI was 11 (3-39) and all patients underwent a complete CRS with a total number of procedures at the CRS operation being 6.7 (± 2.6) per patient. The recurrence rate was 21%

with a mean PFS of 159 months (± 27 months). After 10 years of follow-up, about 80% of the patients remained disease free.[84] Patients who underwent "complete peritonectomy" (resection of all peritoneum, even if macroscopically uninvolved) (n=13) had comparable PFS to the ones that underwent peritonectomy on demand (only if involved) (n=6), (*P = .61*).[84] Mean PFS time was 106.4 ± 6.6 months for the high PCI group (>11) vs. 125.6 ± 34.1 months for the low PCI group (*P = .03*). This suggest that as disease progresses and the PCI increases, the extent of the operations and consequently the complications, increase and ultimately, higher PCI results in shorter PFS.[84]

Major postoperative complication rates varied from 7% to 60% (Table 9). The possibility that CRS-HIPEC, as a potentially life-threatening procedure, might represent an over-treatment warrants consideration. Particularly, the higher incidence in reproductive age women raises the question of fertility protection. Complete surgical resection should be favoured but considering the risk of infertility deriving from extensive pelvic surgery, less aggressive surgical approaches could also be considered. In Nizri et al. series all patients underwent a complete CRS with 90% having pelvic peritonectomy.[84] Preservation of the uterus and ovaries was undertaken in 3 young patients who expressed a wish to conceive. This strategy seemed to increase the recurrence rate and decrease PFS, although not statistically significant. Laparoscopic CRS-HIPEC has also been described.[107-111] However PCI underestimation with laparoscopic assessment is documented with the risk of missing peritoneal lesions resulting in recurrence.[34]

Recommendation 2

In a case of histological diagnosis of MCPM, patients should be referred to a PSM specialized center.

Level of evidence: A

Strength of recommendation: I

Consensus 27/27 (100%)

Recommendation 3

In a case of confirmed MCPM, after expert pathologic review and comprehensive preoperative assessment, complete CRS followed by HIPEC should be advocated rather than a complete CRS alone **(I-B)**.

Level of evidence: B

Strength of recommendation: I

Consensus 18/27 (66.7%)

Recommendation 4

In a case of confirmed MCPM, after expert pathologic review and comprehensive preoperative assessment, complete CRS followed by HIPEC could be proposed to patient rather than a follow-up.

Level of evidence: B

Strength of recommendation: II

Consensus 19/27 (70.4%)

Recommendation 5

In pre-menopausal women, affected by MCPM, and deemed candidates for CRS-HIPEC, fertility specialist counseling and consideration of cryopreservation of oocytes should be done routinely.

Level of evidence: B

Strength of recommendation: I

Consensus 24/27 (88.9%)

Recommendation 6

In women of reproductive age, with MCPM, deemed candidates for surgery, with a desire for childbearing, the preservation of uterus and ovaries should be offered after careful counseling about risks and prognostic implications.

Level of evidence: B

Strength of recommendation: I

Consensus 22/27 (81.5%)

Recommendation 7

The systemic chemotherapy in MCPM patients is not indicated.

Level of evidence: C

Strength of recommendation: IV

Consensus 17/27 (63%)

Recommendations related to MCPM management are summarized in Table 10.

Well-differentiated papillary peritoneal mesothelioma

Introduction

The first case of well-differentiated papillary peritoneal mesothelioma (WDPPM) was discovered incidentally in 1958 in a 41-year-old woman during a laparotomy published by JB Hanrahan.[112] As for MCPM, WDPPM is rare with an unclear pathogenesis and uncertain behaviour. Most WDPPMs are found in the peritoneum, but may also occur in the pleural cavity, pericardium, and tunica vaginalis.[113] WDPPM affects women predominantly (female to male ratio of 5:1 from the selected series in Table 11), usually in the reproductive years, with a mean age of 42 years (7-75) at diagnosis.[85, 100, 113-116] WDPPM demonstrates a wide spectrum of clinical behaviour, ranging from an indolent course to disseminated disease resulting in death. It is often discovered as an incidental finding, but may present with abdominal pain or symptoms of chronic pelvic inflammatory disease.[114-117] Most patients do not have a history of asbestos exposure.[115-117]

Pathology and natural history

As for MCPM, the origin remains unclear. Malpica et al. noticed that endometriosis was seen in 6 (23%) of 26 cases and judged this was probably coincidental rather than pathogenic, as in many of these cases the endometriosis had prompted the surgery in which the WDPPM was incidentally detected. In addition, in none of their cases was WDPPM found in the immediate vicinity of endometriosis. Nevertheless Malpica et al. could not exclude a possible association between peritoneal hyperplasia, iterative peritoneal irritations and WDPPM.[115]

WDPPM can manifest as single or multiple lesions, usually of small size (a few millimeter to a few centimeters), though lesions larger than 10 cm have been described.[113-115,117] Recent histopathologic descriptions of WDPPM have emphasized the specific papillary component with more or less myxoid and typically fairly plump cores with a single layer of overlying bland mesothelial cells as the essential feature of WDPM.[113] Chen et al. demonstrated the possibility of composite WDPPM with adenomatoid tumour, and with MCPM.[116]

As a result WDPPM diagnosis can be challenging. Even if a cytologic diagnosis is suspected, histopathologic analysis of a tissue specimen is mandatory to confirm WDPPM and help eliminate a malignant differential diagnosis.[118] The identification of a mesothelial-based papillary proliferation mandates cautious pathological examination in order to prevent both "under-diagnosis" (resulting in failure to treat the patient) or "over- diagnosis" (resulting in aggressive treatment for malignant mesothelioma perhaps not necessary for this rare variant). The differential diagnosis of WDPPM includes mesothelial hyperplasia, malignant mesothelioma, and serous tumour of low malignant potential.

The papillae in mesothelial hyperplasia differs from those in WDPPM in that they are composed exclusively of mesothelial cells or contain a very small amount of fibro-connective tissue. In addition, mesothelial hyperplasia has reactive/inflammatory changes in the adjacent serosa, which are absent in WDPPM.[115]

The distinction of malignant mesothelioma from WDPPM can represent a major challenge, considering that malignant mesothelioma can exhibit areas that resemble WDPPM. To solve this diagnostic dilemma, accurate clinical and radiological correlation is required to ensure that the tissue available for microscopic examination is truly representative. Subsequently, special emphasis should be placed on the need for examining the tissue underlying the

lesion to ensure the absence of invasion.[119] Ultimately, immunocytochemical analysis clarifies the differential diagnosis.[113,115] Eventually, in doubtful cases, BAP1 loss could be a solution to distinguish malignant mesothelioma with papillary component from WDPPM in which such a deletion is usually absent.[120]

A major issue with WDPPM management is that its neoplastic nature cannot be excluded. In an old reported series of 19 mesothelioma cases (localized and diffuse), which were difficult to interpret from an histological point of view, Goldblum et al. suspected that a number of cases were WDPPM that evolved to malignant mesothelioma.[121] Torii et al. presented a case considered as a pleural well-differentiated mesothelioma with malignant potential (with no recurrence reported up to 8 months)[122] and Costanzo et al. mentioned another case of WDPPM transformation in an old man.[123] Bürrig et al. described a man with multiple WDPPM on biopsies who developed ascites 1 year later and died from a DMPM 5 years later.[124] Butnor et al reported a man with a WDPPM who developed progressive disease and died 3 years later but without autopsy confirmation of the diagnosis.[125]

As mentioned by Churg et al. these reports are equivocal.[113] Two other cases are more substantiated and supported by pathological examination.

Through a series of 8 WDPPM treated with CRS-HIPEC, Baratti et al. presented the case of a 41-year-old woman who underwent an initial debulking surgery without HIPEC.[85] She recurred 58 months later and underwent CRS-HIPEC, unfortunately with an incomplete CRS (scored CC-3) due to disease extensively infiltrating the diaphragm and the subpyloric region. HIPEC was performed for palliation of intractable ascites. Pathological examination showed coexistence of typical WDPPM and biphasic mesothelioma. Post-operative disease progression occurred after 9 months and the patient died 4 months later.[85]

Washimi et al. reported the case of a 58-year-old woman, operated on for a rectal carcinoid tumour.[126] A large number of white miliary nodules were identified on the mesentery and peritoneum, histologically diagnosed as WDPPM. A wait-and-see approach was adopted. Seven years later, the biopsy of an abdominal wall mass diagnosed a malignant mesothelioma. Mesothelioma similar to papillary proliferation was present on the outer layer of the peritoneum. Review of ascites and tissue biopsy from the first surgery confirmed a WDPPM. At the time of recurrence, the papillary lesion on the peritoneal surface was adjacent to the invasive lesion. Immunohistochemically, the results were almost identical between 2004 and 2011, except with regard to glucose transporter 1 (GLUT-1), known to be over-expressed in a variety of human tumors. Positive staining for p53 and Ki-67 was much more frequent in the invasive lesion (12.7% and 12.2%, respectively), than in the surface lesion (6.8% and 5.6%, respectively).[126]

To investigate this possible relationship between WDPPM and malignant mesothelioma, Churg et al. explored outcomes of 20 patients with well-differentiated mesothelioma (3 of pleural origin and 17 WDPPM), selected due to the presence of invasion foci on histologic analysis.[113] In 15 cases the lesions were multifocal. Invasive foci always constituted a small area of the lesion. For the most part, the invasive foci tended to be superficial and were confined to the polyp that constituted the WDPPM lesion, but in 1 case foci invaded fat (this case was unfortunately lost to follow-up). In 1 case several separate invasive foci were present. p16 FISH testing was performed on the invasive foci in 5 cases, and none showed p16 deletion. Karyotyping was successfully performed on 3 WDPPM cases, derived from the whole WDPPM lesions. Of these, 2 cases revealed clonal abnormalities, whereas the third case yielded a normal karyotype.[113] In this series, 8 out of 20 patients recurred (4 patients multiple times), while other authors reported less tendency to recurrence for WDPPM: 1

patient out of 22 in the Malpica et al. series for example.[115] This suggests that WDPPM with invasive foci may be particularly prone to recurrence, and that this histologic characteristic is important to take into account for stratifying the treatment strategy.

Recommendation 1.1

In a case of histologic diagnosis of WDPPM, histopathological review by an expert pathologist in PSM is mandatory.

Level of evidence: A

Strength of recommendation: I

Consensus 26/27 (96.3%)%

Recommendation 1.2

In a case of histological diagnosis of WDPPM, patient should be addressed to a PSM specialized center.

Level of evidence: B

Strength of recommendation: I

Consensus 27/27 (100%)

Treatment

Due to rarity and uncertainty a treatment strategy is difficult to define for WDPPM. As for MCPM, no clinical trials are possible due to the rarity of the disease. Some WDPPM patients underwent various local and systemic treatments, while other patients were regularly followed up without any treatment.[115,117,119]

Lee at al. explored different treatments performed in 15 WDPPM patients, clustered into 8 patients with a single lesions and 7 with multiple.[117] For the single lesion patients, complete tumour excision was performed. Four of these 8 patients had adjuvant 5-fluorouracil-based chemotherapy. None of them experienced recurrence, and 6 patients are alive while two died of other causes. In the remaining 7 cases with multiple lesions, 2 had no, or partial surgery, without adjuvant therapy for their residual tumors, and were still alive with disease at the end of follow-up. The other 5 patients had chemotherapy and one a further extensive CRS. Among 4 evaluable patients, two complete responses and two partial responses were observed. One patient with massive ascites and a pleural effusion received 3 cycles of intraperitoneal chemotherapy. A partial response was initially obtained, but he died of tumour progression 9 years after the initial diagnosis. Two are alive with disease at 48 and 145 months, while 2 are alive without recurrence at 18 and 96 months.[117] The authors concluded that when WDPPM tumours were completely excised, recurrence was rare even without adjuvant therapy. They suggested that if complete excision is not available, platinum-based chemotherapy seems to be effective.[117]

Malpica et al. also reported 26 patients with WDPPM who underwent complete resection without adjuvant therapy, and only one patient experienced recurrence, which was surgically curable.[115] However, some patients experienced disease progression, with death attributed to disease burden and others had malignant transformation.[85,100,113] Therefore, WDPPM should be considered a disease with malignant potential, which requires active treatment. Two series reported outcomes of CRS-HIPEC in 8 and 11 WDPPM patients.[85,100] Baratti et al. could perform complete CRS in 87.5% with a median time-to-progression of 24 months (11-31) and an estimated 5-year PFS and OS of 80% and 90%, respectively. As mentioned earlier, one case previously debulked, presented with malignant

transformation.[85] Gilani et al. reported 11 cases who were included in a cohort of low-grade peritoneal mesothelioma (MCPM + WDPPM). All patients who underwent a complete CRS were alive at the end of follow-up, while 4 out of 5 patients with incomplete CRS died of the disease.[100]

WDPPM continues to be a complex and unknown entity. Two entities are perhaps distinguishable based on the presence of a single or multiple lesions at diagnosis. Another prognostic factor, helpful for treatment decision-making, might be the presence of invasive foci on pathologic examination. WDPPM has a propensity for recurrence and could evolve to malignant peritoneal mesothelioma suggesting active treatment may be warranted from the outset.

Recommendation 2

In case of WDPPM, confirmed by pathologist from a PSM expert center, with a unique lesion after comprehensive assessment, without invasive foci on biopsy obtained by laparoscopy, a complete CRS followed by HIPEC should be advocated rather than a complete CRS alone.

Level of evidence: C

Strength of recommendation: I

Consensus 16/27 (59.3%)

Recommendation 3

In case of WDPPM, confirmed by pathologist from a PSM expert center, with a unique lesion after comprehensive assessment, without invasive foci on biopsy obtained by laparoscopy, a complete CRS-HIPEC could be proposed rather than a follow-up.

Level of evidence: C

Strength of recommendation: II

Consensus 19/27 (70.4%)

Recommendation 4

In case of WDPPM, confirmed by pathologist from a PSM expert center, with multiple lesions, and/or invasive foci, a complete CRS-HIPEC should be proposed to patient rather than a complete CRS alone.

Level of evidence: B

Strength of recommendation: I

Consensus 24/27 (88.9%)

Recommendation 5

In case of WDPPM, confirmed by pathologist from a PSM expert center, with multiple lesions, and/or invasive foci, a complete CRS-HIPEC should be proposed to patient rather than a follow-up.

Level of evidence: B

Strength of recommendation: I

Consensus 25/27 (92.6%)

Recommendation 6

In pre-menopausal women, affected by WDPPM, and deemed candidates for CRS with/without HIPEC, fertility specialist counseling and consideration of cryopreservation of oocytes should be done routinely.

Level of evidence: B

Strength of recommendation: I

Consensus 27/27 (100%)

Recommendation 7

In women of reproductive age, with WDPPM, without other adverse prognostic factor, deemed candidates for CRS with/without HIPEC, with a desire for childbearing, the preservation of uterus and ovaries should be offered after careful counseling about risks and prognostic implications.

Level of evidence: B

Strength of recommendation: I

Consensus 24/27 (88.9%)

Recommendation 8

The systemic chemotherapy in WDPPM should not be considered.

Level of evidence: C

Strength of recommendation: III

Consensus 14/27 (51.9%)

All recommendations related to WDPPM management are summarized in Table 12.

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Table 1. Levels of evidence and grades of recommendation

Table 1. Levels of evidence and grades of recommendation		
Levels 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
Grades 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

Table 10. Summary of recommendations regarding MCPM

Table 10. Summary of recommendations regarding MCPM

Recommendations	Grade
Diagnosis and pathology	
• In a case of histologic diagnosis of MCPM, an histopathological review by an expert pathologist in PSM is mandatory.	I-A
Treatment	
• In a case of histological diagnosis of MCPM, patients should be addressed to a PSM specialized center.	I-A
• In a case of confirmed MCPM, after expert pathologic review and comprehensive preoperative assessment, complete CRS-HIPEC, as an alternative to complete cytoreductive surgery alone should be advocated.	I-B
• In a case of confirmed MCPM, after expert pathologic review and comprehensive preoperative assessment, complete CRS-HIPEC, as an alternative to follow-up could be proposed to patient.	II-B
• In pre-menopausal women, affected by MCPM, and deemed candidates for CRS-HIPEC, fertility specialist counseling and consideration of cryopreservation of oocytes should be done routinely.	I-B
• In women of reproductive age, with MCPM, deemed candidates for surgery, with a desire for childbearing, the preservation of uterus and ovaries should be offered after careful counseling about risks and prognostic implications.	I-B
• The systemic chemotherapy in MCPM patients is not indicated.	IV-C

MCPM, multicystic peritoneal mesothelioma; PSM, Peritoneal Surface Malignancies; CRS-HIPEC, cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy.

Table 11. Main WDPPM series in medical literature

Table 11. Main WDPPM series in medical literature											
Authors	**Year**	**Cases**	**F/M**	**Age**	**Treatment**	**PCI**	**CC-score**	**FU (mo)**	**Complications**	**PFS**	**OS**
Daya D et al.	1990	22	18/4	41 (25-69)		N/A	N/A		N/A		
Baratti D et al.	2007	8	8/0	37,8 (25-69)	CRS-HIPEC	10 (3-23)	CC-0: 6 CC-1: 1 CC-3: 1	25,5 (6-66)	G IV: 1	Median TTP: 24 mo (11-31) 5-year PFS: 80%[£]	5-year OS: 90%[£]
Malpica A et al.	2012	26	26/0	48,6 (23-75)	Surgery	N/A	N/A	32 (4-192)	N/A	22 p alive after FU of 5-144 mo	
Chen X et al.	2013	18*	14/4	37 (18-60)		N/A	N/A	59,5 (5-136)	N/A		
Lee YK et al.	2013	15	9/6	53 (23-76)	6p: no specific treatment or (limited) surgery, 8p : IV chemotherapy, 1p : IP chemotherapy	N/A	N/A	6-146	N/A		
Churg A et al.	2014	20°	16/4	43,4 (7-74)	Surgery, chemotherapy, 1p : IP chemotherapy	N/A	N/A	42 (6-72)	N/A		
Gilani SNS et al.	2018	11	N/A	44 (21-69)[£]	CRS-HIPEC	9 (3-39)[£]	CC-0/1: 56%	34 (6-152)[$]	7%		CC0/1: all alive[£] Others: 4/5 died of disease[£]

* peritoneal: 14 cases, pleura 2 cases, testicular tunica vaginalis 2 cases
° peritoneal: 17, pleural 3 cases
[£] cohort of low-grade peritoneal mesothelioma (MCPM and WDPPM)
[$] For the entire cohort of low and high-grade peritoneal mesothelioma (76 patients)

CRS-HIPEC, cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy; TTP: time-to-progression; mo, months; p, patient; IP: intraperitoneal, IV: intravenous.

Table 12. Summary of recommendations regarding WDPPM

Table 12. Summary of recommendations regarding WDPPM

Recommendations	Grade
Diagnosis and pathology	
• In a case of histologic diagnosis of WDPPM, an histopathological review by an expert pathologist in PSM is mandatory.	I-A
Treatment	
• In a case of histological diagnosis of WDPPM, patient should be addressed to a PSM specialized center.	I-B
• In case of WDPPM, confirmed by pathologist from a PSM expert center, with a unique lesion after comprehensive assessment, without invasive foci on biopsy obtained by laparoscopy, a complete CRS followed by HIPEC, as an alternative to complete CRS alone should be advocated.	I-C
• In case of WDPPM, confirmed by pathologist from a PSM expert center, with a unique lesion after comprehensive assessment, without invasive foci on biopsy obtained by laparoscopy, a complete CRS followed by HIPEC, as an alternative to follow-up, could be proposed to patient.	II-C
• In case of WDPPM, confirmed by pathologist from a PSM expert center, with multiple lesions, and/or invasive foci, a complete CRS-HIPEC, as an alternative to complete CRS alone should be proposed.	I-B
• In case of WDPPM, confirmed by pathologist from a PSM expert center, with multiple lesions, and/or invasive foci, a complete CRS-HIPEC, as an alternative to follow-up should be proposed.	I-B
• In pre-menopausal women deemed candidates for CRS with/without HIPEC, fertility specialist counseling and consideration of cryopreservation of oocytes should be done routinely.	I-B
• In women of reproductive age without other adverse prognostic factor, deemed candidates for CRS with/without HIPEC, with a desire for childbearing, the preservation of uterus and ovaries should be offered after careful counseling about risks and prognostic implications.	I-B
• The systemic chemotherapy in WDPPM should not be considered.	III-C

WDPPM, well-differentiated papillary peritoneal mesothelioma; PSM, Peritoneal Surface Malignancies; CRS-HIPEC, cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy.

Table 2. Literature data evaluating palliative systemic chemotherapy in DMPM patients

Table 2. Literature data evaluating palliative systemic chemotherapy in DMPM patients

Authors	Study type	N	Regimen (%CN)	Med. age	Response rates	DCR (95% CI)	TtDP	OS
Carteni G et al. 2009	Non randomized open-label	109	PEM-CIS : 37 (65%) PEM-CARBO : 34 (50%) PEM : 38 (21%)	56.0 58.5 62.0	20% (7.7-38.6) 24% (10.3-43.5) 13% (3.5-29.0)	76% (56.5-89.7) 50% (31.9-68.1) 80% (61.4-92.3)	na na 6,2 mo	**1-year OS** 57% (10.3-100) na 42% (4.6-78.4) **Med OS** PEM: 10,3 mo
Jänne PA et al. 2005	Non randomized open-label	98	PEM-CIS : 47 PEM : 26 Prev Treat. : 43 Chemo-naïve : 28	na na 58 65	29.8% (17.3-44.9) 19.2% (6.6-39.4) 23.3% (11.8-38.6) 25% (10.7-44.9)	70% 73% 72% 68%	na	**Med OS** PEM-CIS: 13.1 (8.6-13.1) PEM: 8.7 mo (5.4-*)
Simon GR et al. 2008	Phase 2 trial	20	Gemcitabine + Pemetrexed	67,5	CR: 0 PR: 15% (3.2-37.9) SD: 35% (15.4- 59.2) P: 25%	50% (27.2-72.8)	10,4 mo (5.3%-nr)	**Med OS** 26,8 mo (11.7%-nr; 50% censored) 1-year OS 67.5% (46.0-89.0)

DMPM, diffuse malignant peritoneal mesothelioma; N, number of cases; %CN, percentage of chemotherapy naïve patients; DCR, Disease control rate (complete response + partial response + stable disease); P, progression; OS, overall survival; PEM, pemetrexed, PEM-CIS, combination of intravenous pemetrexed and cisplatin; PEM-CARBO, combination of intravenous pemetrexed and carboplatin; na, not available; TtPD, time to progressive disease; mo, months; nr, not reached.
* Not known as a result of censorship

Table 3. Three studies evaluating perioperative systemic chemotherapy in DMPM patients

Table 3. Studies evaluating perioperative systemic chemotherapy in DMPM patients							
Authors	**Study type**	**N**	**N**	**Med FU**	**Med OS**	**OS**	**Prognosis factors**
Deraco M et al. 2013	Monocentric retrospective	116	NA: 60 ADJ: 30 NoC: 26	33 mo	PEM-CIS: nr PEM-GEM: 31.4 mo		CC-score NA ECOG>2 PCI>20
Kepenekian V et al. 2016	Multicentric retrospective	126	NA: 42 ADJ: 16 PO: 20 NoC: 48	61 mo	37 82 Nr 71	40% 67% 62% 56%	CC-score NA
Naffouje SA et al. 2018	National databse analysis	1740	NA: 55 ADJ: 228 NoC: 169 SC: 684 NoT: 604	N/A	52,3 55,0 57,4 11,1 3,6	50% 55%	

NA, neoadjuvant; ADJ, adjuvant; NoC, no systemic chemotherapy; PO, perioperative systemic chemotherapy; NoT, no treatment at all; mo, months; N/A, not applicable, N/n: number of cases.

Table 5. Main data related to EPIC used for peritoneal mesothelioma

Table 5. Main data related to EPIC used for peritoneal mesothelioma							
	N / n	**Pathology**	**EPIC protocol**	**Duration**	**Med FU (months)**	**Morbidity**	**Survival results (months)**
Feldman AL et al. 2003	49/35	Epith: 26 Sarcom: 4 LGPM: 17	5-FU (800 mg/m2) + paclitaxel (125 mg/m^2)	1 time between POD7 and POD10	28.3 (1-106)	18 in 12 p	Med OS: 92 Med PFS: 17
Elias D et al. 2007	26/2	Epith: 13 Biphas: 1 LGPM: 12	Cisplatin	5 days POD 0 to 4	54 (6-129)	G3-4 : 54%	Med OS nr (>100) Med PFS: 40
Yano H et al. 2009	17/8	Epith: 5 Biphas: 4 LGMP: 8	Doxorubicin (3 mg/m^2) + Cisplatin (20 mg/m^2)	4 days	13.2 (1.2-82.8)	7 p (41%)	Med OS Complete CRS : 44.4 y (21-207) MTD: 1 y (10-171)
Yan TD et al. 2009	401 p HIPEC: 372 EPIC without HIPEC: 12 HIPEC + EPIC: 94	Epith: 318 Sarcom/biphas: 48	Cisplatin + Doxorubicin: 16 Paclitaxel: 77 Other: 1	5 days POD 1 to 5	33 (1-235)	G3-4: 127p	Med OS: 53 EPIC was not an independent factor of better survival
Schaub NP et al. 2013	104/69	Epith: 90 Sarcom/biph: 14	5-FU (800 mg/m^2) + Paclitaxel (125 mg/m^2)	5 days POD 7 to 12	49.4 mo (1-195)	N/A	Med OS: with EPIC: 67 without EPIC: 35 P=0,345

EPIC, early post-operative intraperitoneal chemotherapy; N / n, number of peritoneal mesothelioma patients treated on with CRS-HIPEC / with CRS-HIPEC and EPIC; MTD, maximal tumor debulking; Epith: mesothelioma epithelioid; Sarcom, mesothelioma sarcomatoid; Biph, mesothelioma biphasic; POD, postoperative day; y, year(s); mo, month(s); p, patient; G3-4: Grade 3 or 4 postoperative complications.

Table 6. Independent prognostic factors in DMPM according to multivariable analysis

Table 6. Independent prognostic factors in DMPM according to multivariable analysis									
Prognostic factors	***Feldman AL et al.*** **2003**	***Deraco M et al.*** **2006**	***Yan TD et al.*** **2006**	***Yan TD et al.*** **2009**	***Alexander RH et al.*** **2013**	***Schaub NP et al.*** **2013**	***Magge D et al.*** **2014**	***Kusamura S et al.*** **2016**	***Verma V et al.*** **2017**
	N=49	N=49	N=62	N=405	N=211	N=104	N=65	N=117	N=1514
Previous debulking surgery	x								
Gender									x
Age	x				x		x		x
Invasiveness	x								
Nuclear size			x						
Nuclear grade					x				
Mitotic rate		x							
Baseline Ca125						x			
Histological subtype				x		x	x	x	x
Percentage of epithelioid solid component						x			
Ki-67								x	
Lymph nodes				x					
Disease extent						x	x	x	
Completeness of cytoreduction	x	x		x	x		x		
HIPEC				x					
HIPEC drug schedule					x				
Severe morbidity							X sepsis		
Insurance coverage									x

Table 7. Most frequently used drug schedules for HIPEC in DMPM with the respective survival outcomes

Table 7. Most frequently used drug schedules for HIPEC in DMPM with the respective survival outcomes

Chemotherapy agents	Expected 1-year survival (%)	Expected 5-year survival (%)
Mitomycin-C only	78	30
Cisplatin only	87	49
Doxorubicin + cisplatin	79	32
Docetaxel + cisplatin	70	17
Drug combinations including doxorubicin, mitomycin-C, cisplatin	85	45

DMPM: diffuse malignant peritoneal mesothelioma

Table 8. Summary of recommendations regarding DMPM

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Recommendations	**Grade**
Diagnosis and pathology	
• Individuals with any history of asbestos exposure, currently or in the past, could be advised to undergo a screening program to improve early detection of DMPM, with an abdominal ultrasound every year.	II-D
• For the pathological diagnosis of DMPM, the analysis of an adequate tissue specimens obtained from core needle biopsy or explorative laparoscopy is mandatory, rather than a cytologic examination of serosal effusion or material collected by fine needle biopsy.	I-A
• A histological review of the diagnosis of a DMPM, by a pathologist with expertise in PSM, is mandatory.	I-A
• The pathologic report must mention:	
- the histological subtype,	I-A
- the Ki-67 index,	I-A
- the nodal status (if appropriate).	I-A
• The following mentions are optional:	
- the sub-classification of epithelioid (tubulopapillary and solid/deciduoid),	II-B
- the invasiveness,	II-B
- the mitotic rate,	II-B
- the nuclear grade,	II-B
- the nuclear size.	II-C
Preoperative workup	
• Cross sectional imaging with CT should be the preferred diagnostic imaging modality.	I-A
• MRI could be one of the diagnostic imaging modality.	II-B
• PET/CT could be one of the diagnostic imaging modality.	II-C
• The determination of baseline serum CA125 level could be included in the preoperative workup.	II-B
• The determination of baseline serum mesothelin level could be included.	II-C
• The laparoscopic evaluation of DMPM patients in the preoperative workup could be performed to better characterize the preoperative PCI and disease resectability.	II-B
• If performed, a preoperative laparoscopy should be :	I-A
- done by a surgeon with expertise in PSM,	
- with midline placement of trocars: allow excision in a future surgery to prevent port site recurrence,	I-A
- with throughout evaluation of the peritoneal cavity with assessment of PCI, serosal and mesentery.	
• The biopsy of diaphragmatic peritoneum has been associated with local inflammatory reaction and adhesions that hamper the subsequent maneuver of diaphragmatic peritonectomy and therefore should be avoid.	I-A
• The video recording of the procedure could be done.	III-C II-C
Treatment	
• The selection for the best management strategy by a Multidisciplinary Team specialized in PSM is mandatory.	I-A
• In non-operable and/or non resectable DMPM patients (palliative patients), a platinum-based systemic chemotherapy should be proposed as an option to best supportive care. The best proposed regimen is the combination of cisplatin and pemetrexed, second choice cisplatin and gemcitabine.	I-B
• Adjuvant combined systemic chemotherapy should be proposed, as an option to direct follow-up, in DMPM patients treated with CRS-HIPEC, and with at least one bad prognosis factor (CC-score > 1, sarcomatoid or biphasic subtype, lymph node involvement, Ki67>9%, PCI>17).	I-B
• DMPM patients treated with CRS-HIPEC with a favorable prognostic profile (complete CRS and epithelioid subtype and no lymph node involvement and Ki67 ≤ 9% and PCI ≤ 17) could be addressed directly to follow-up. The benefit from an adjuvant systemic chemotherapy is uncertain in these	II-B/C

patients.	
• Locoregional adjuvant therapy (EPIC and/or NIPEC), in association to systemic chemotherapy, could be proposed in patients submitted to CRS-HIPEC, as long as postoperative clinical conditions are sufficient.	II-C
• Bidirectional chemotherapy could be proposed in patients with good general condition, no extra-peritoneal metastases and, after staging laparoscopy, unresectable disease or with borderline resectability (large extent of the disease potentially resectable, with multiple visceral resections at high risk for postoperative complications and impaired quality of life), as an option to induction systemic chemotherapy with conversion intent. The proposed regimen is pemetrexed IP and cisplatin IV.	II-C
• CRS-HIPEC is recommended in DMPM, as an option to palliative systemic chemotherapy, provided that the patient has a sufficient clinical condition for a major surgery, has a resectable disease, and that the treatment is done in a specialized PSM center.	I-B
• Four factors are judged to constitute an absolute contra-indication for CRS-HIPEC in DMPM patients:	
- sarcomatoid histology,	I-B
- a massive small bowel serosa involvement,	I-B
- a concomitant pleural disease,	I-B
- and/or a retroperitoneal and/or cardiophrenic lymph node involvement.	I-B
• Seven factors are judged to constitute a relative contra-indication for CRS-HIPEC in DMPM patients:	
- a biphasic histology,	II-B
- a disease not amenable by cytoreduction down to CC-0/1,	II-B
- a Ki-67 >9% in the preoperative pathological report,	II-C
- a PCI>17 in the pre-cytoreduction evaluation,	II-B
- the combination of a high risk subset with Ki-67 >9% and PCI>17 according to preoperative workup,	II-B
- a massive small bowel mesentery involvement,	II-B
- and/or a massive diaphragmatic involvement.	II-B
• A complete parietal peritonectomy during CRS for DMPM patients could be considered, as an option to selective parietal peritonectomy, regardless of PCI, in order to maximize locoregional disease control and eventually the long-term oncological outcomes.	II-C
• The dissection of suspicious retroperitoneal lymph nodes, and the sampling of non suspicious nodes, could be considered during CRS, in order to enhance the prognostic characterization of the patient.	II-C
• Platinum-based HIPEC after a complete CRS down to residual disease <2.5 mm should always be considered, as an option to other HIPEC drug combinations.	I-B
• HIPEC after an incomplete cytoreduction down to residual disease >2.5 mm, could be considered in DMPM patients as an option to systemic treatment.	II-B
• Cisplatin and Doxorubicin is judged to be the best drug regimen recommended for HIPEC.	I-C
Follow up	
• A follow-up extended to 7 years after CRS-HIPEC could be considered in DMPM patients.	II-B
• The follow-up during the first 2 years and onward after CRS-HIPEC is proposed to be performed every 6 months and to include:	
- a physical examination,	I-C
- a thoracic/abdominal/pelvic CT scan,	I-C
- and a biomarker CA125 dosage.	I-C
• In recurrent DMPM patients with good general condition, resectable disease, and favourable prognostic profile (young age, epithelioid subtype, time to recurrence > 1 year, limited PCI), iterative CRS-HIPEC could be considered.	II-B

DMPM, Diffuse Malignant Peritoneal Mesothelioma; PSM, Peritoneal Surface Malignancies; PCI, peritoneal Cancer Index; CRS-HIPEC, cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy; EPIC, early postoperative intraperitoneal chemotherapy; NIPEC, normothermic intraperitoneal chemoperfusion.

Table 9. Main multicystic peritoneal mesothelioma series in medical literature

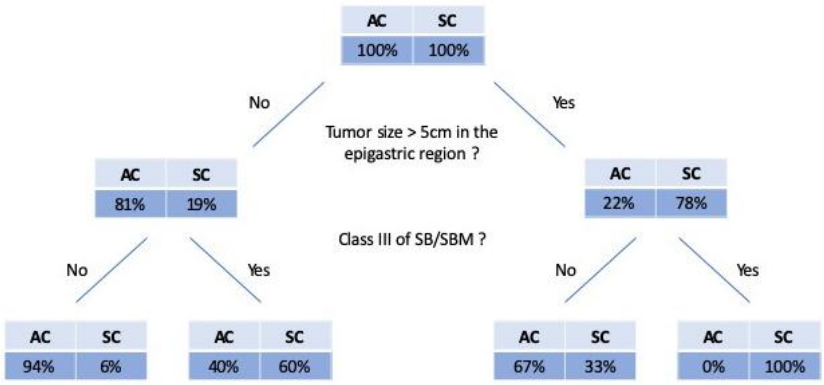
Table 9. Main multicystic peritoneal mesothelioma series in medical literature

Authors	Year	Cases	F/M	Age	Treatment	Med PCI	CC-0/1	FU (months)	Complications	DFS	OS
Weiss SA et al.	1988	37	31/6	W: 38 M: 47	Surgery 2 p: + radiation 1 p: + chemotherap	6 solitary lesions 15 localized 16 diffuse	N/A	37 (5-372)		N/A	N/A
Ross MJ et al.	1989	25	25/0	33	Surgery +/- hormonal therapy / radiation / melphalan	N/A	7	92,4 (20,4-253,2)		12 p recurred (4 p multiple recurrence) 11 p without recurrence (FU: 31,2 – 201,6 m)	
Sethna K et al.	2003	5	4/1	35,8	CRS-HIPEC Cisplatin - doxorubicin	N/A	100%	30,8	G III-IV: 3 (60%)		All alive 1 with disease
Baratti D et al.	2010	12	11/1	40,9	CRS-HIPEC Cisplat-doxo: 10 Cisplat: 2 Cisplat-mito: 1 mito: 1	10 (4-26)	100%	64 (5-148)	G IV: 1	5-y PFS: 90% 10-y PFS: 72%	
Chua TC et al.	2011	26	20/6	42	CRS-HIPEC Cisplatin +/- doxorubicin 3 p: + EPIC paclitaxel	14 (6-39)	92%	54 (5-129)	G III-IV: 23%	1 p recurred	All alive
Nizri E et al.	2018	19	16/3	42	CRS-HIPEC	11 (3-39)	100%	69 (4-220)	G III-IV: 15%	Median PFS: NR Mean RFS: 159,4 +/- 27 m 5-y PFS: 84% 10-y PFS: 79%	
Gilani SNS et al.	2018	28	22/17*	44*	CRS-HIPEC Cisplat-doxo 11 p: + EPIC cisplat-doxo[$]	9 (3-39)*	93%	34 (6-152)[$]	G III-IV: 7% 90-days mortality: 2,6%[$]	Mean PFS: 74,7 m 5-y PFS: 83,3%	Mean OS: 152 m 5-y OS: 100%

* Upon the cohort of low-grade peritoneal mesothelioma (39 patients: 28 MCPM and 11 WDPPM)
[$] For the entire cohort of low and high-grade peritoneal mesothelioma (76 patients)

F/M, female/male, CC-0/1, completeness of cytoreduction score of 0 or 1; DFS, disease-free survival, OS, overall survival; p, patient; G, grade; PCI, peritoneal carcinomatosis index; CRS-HIPEC, cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy; EPIC, early postoperative intraperitoneal chemotherapy; MCPM, multicystic peritoneal mesothelioma; WDPPM, well-differentiated papillary peritoneal mesothelioma.

Figure 1. Predictive value of computed tomography findings by tree-structured diagram.



AC, adequate cytoreduction; SC, suboptimal cytoreduction; SB, small bowel; SBM, small bowel mesentery.

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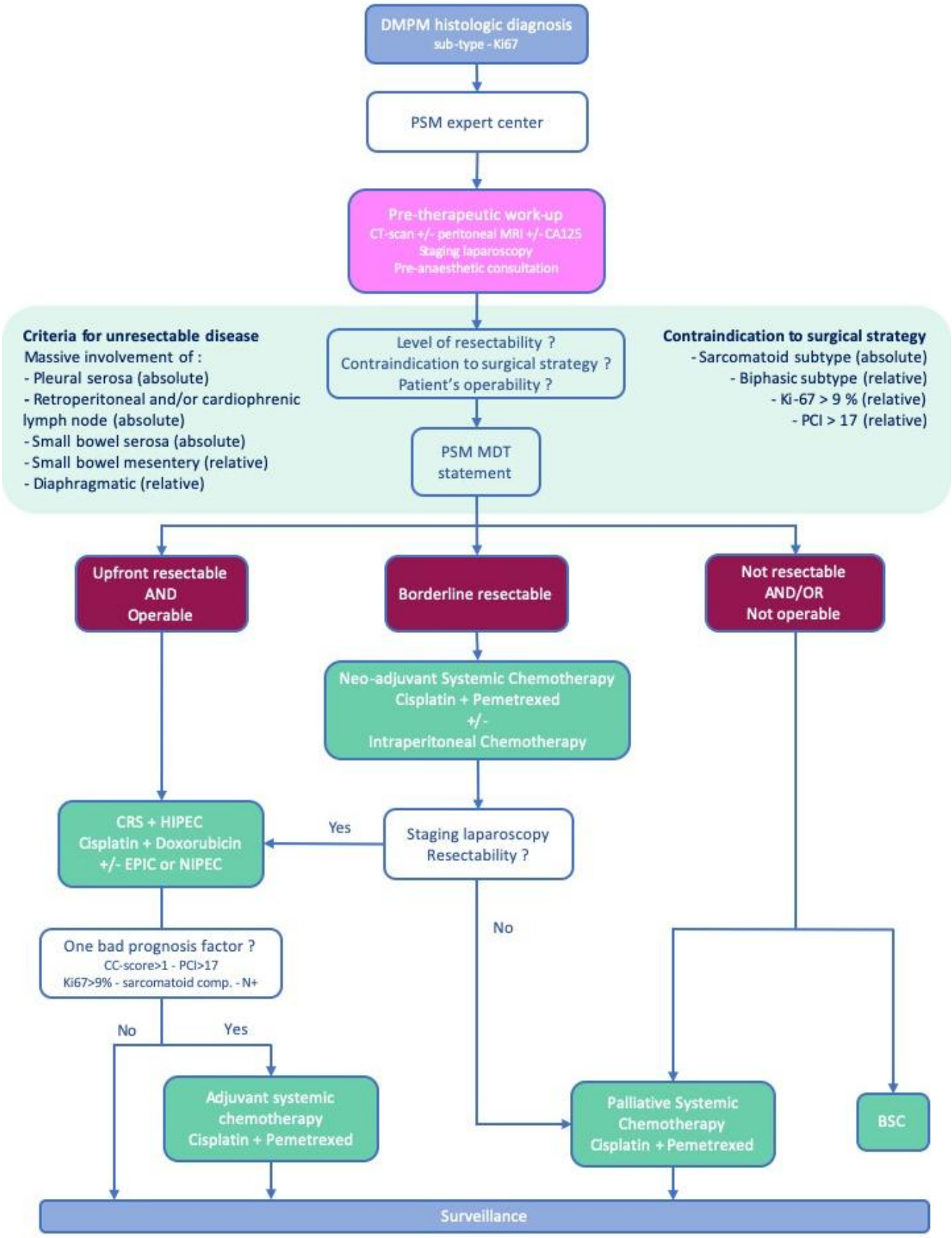
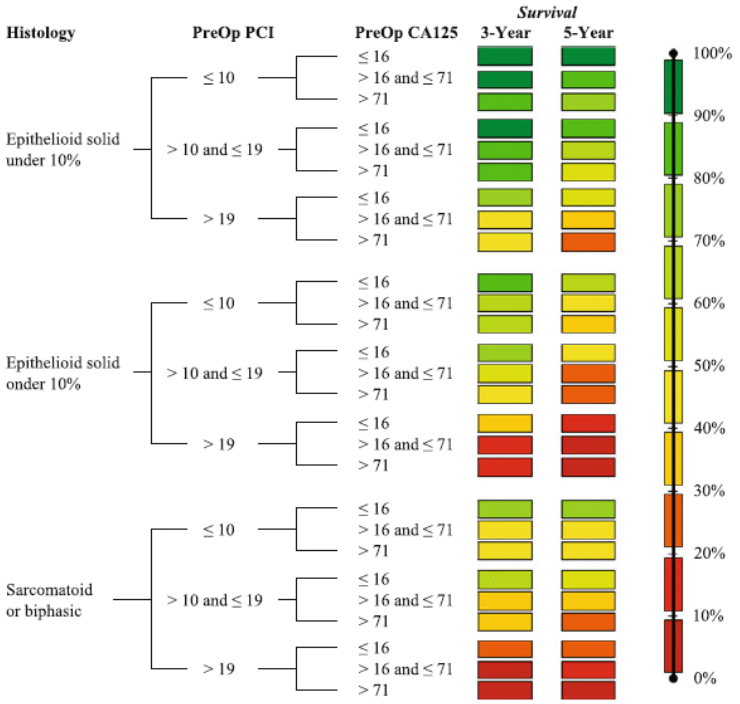
Figure 2. Flowchart of DMPM management



PSM, peritoneal surface malignancies; CT, computed tomography; MRI, magnetic resonance imaging; MDT, multidisciplinary team; CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy; EPIC, early postoperative intraperitoneal chemotherapy; NIPEC, non hyperthermic intraperitoneal chemotherapy; PCI, peritoneal carcinomatosis index; CC-score, completeness of cytoreduction score, N+, positive lymph node(s); BSC, best supportive care.

Figure 3. Preoperative nomogram that predicts survival in DMPM patients



PCI, peritoneal carcinomatosis index.
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Figure legends

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