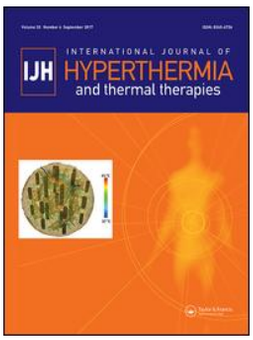

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Complete pathologic response after two-stage cytoreductive surgery with HIPEC for bulky pseudomyxoma peritonei: proof of concept

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ABSTRACT

Introduction: Pseudomyxoma peritonei (PMP) is a rare disease characterized by the progressive accumulation of mucinous ascites and peritoneal implants. The optimal treatment for PMP includes the association of complete cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC). For patients with a large burdensome disease, the completeness of cytoreduction sometimes requires maximal effort surgery. The aim of this article is to provide proof of concept for two stage cytoreductive surgery (CRS) in this category of patients.

Methods and materials: A two stage CRS and HIPEC with oxaliplatin was proposed for patients with bulky PMP including important involvement of the serosal surfaces of the bowel or colon who had an impaired nutritional status. The residual disease at the end of the first stage was less than 5 mm of thickness on several implants. Clinical, surgical and histopathological variables were analyzed.

Results: All eight patients completed the two-stage strategy. Mortality was nil. One Clavien Dindo grade 3 event occurred in each stage. After a median follow up of 29.5 months, all patients were alive and free of recurrence. All of the patients had histopathological complete response on the specimens obtained from the residual sites during the second stage surgery.

Conclusions: Two-stage surgical strategy is feasible for bulky PMP patients and it is associated with little high-grade morbidity and enhanced visceral sparing.

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Pseudomyxoma peritonei; cytoreductive surgery; hyperthermic intraperitoneal chemotherapy; two-stage surgery; oxaliplatin

1. Introduction

Pseudomyxoma peritonei (PMP) is a rare disease characterized by the progressive accumulation of mucinous ascites and peritoneal implants, generally originating from a perforated mucinous tumor of the appendix. This perforation is often due to the obstruction of the lumen due to tumor growth, and leads to the peritoneal spread of mucin-containing epithelial cells [1]. Other origins for PMP such as the ovary, the urachus, the colon, and the pancreas, were also identified but their frequency is even rarer [2].

The optimal treatment for PMP includes the association of complete cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) [1]. Long-term survival data were obtained on large cohort studies and was significantly superior to historical treatment (debulking surgery) making phase III trials ethically unfeasible [3]. Overall survival rates after optimal treatment reach 55% to 63% at 10 years and 50% to 59% at 15 years [3,4]. By contrast, the lack of treatment leads to mucin accumulation in the peritoneal cavity with progressive growth of the abdominal girth, nutritional impairment and eventually occlusion and death [1].

As it is the case for most peritoneal surface malignancies, completeness of cytoreduction represents a major prognostic factor for overall survival whereas non-definitive treatment consisting of debulking surgery is detrimental to the outcome [4]. Another major impact factor is disease differentiation. The most recent consensus classification identifies acellular mucin, low-grade mucinous carcinoma peritonei, high-grade mucinous carcinoma peritonei and high-grade mucinous carcinoma peritonei with signet ring cells [5]. The first two groups have a highly better prognosis than the latter two.

Nevertheless, for patients with a large burdensome disease, with a peritoneal cancer index (PCI) higher than 30 or many implants on the digestive tract (small bowel and colon) making a complete cytoreduction (CCR 0/1) impossible, debulking surgery is the only alternative. Although multiple

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studies have shown that debulking surgery is inferior to complete resection in terms of long term outcome, for patients with a very large disease, any attempt to diminish the tumoral burden may be beneficial [6]. Extensive cytoreductive surgery is associated to important postoperative morbidity especially in patients with impaired nutritional status which may further impact on overall survival [7]. New strategies have to be defined in order to give patients with bulky disease and impaired status access to the prognostic of curatively treated patients.

The present study aims to present a proof of concept of a two-stage organ preserving cytoreductive surgery associated with HIPEC for these patients as to grant them access to a final CCR0-1 status due to the complete pathologic response after the first stage.

2. Patients and methods

2.1. Patients

Between June 2014 and June 2018, 52 patients were treated for pseudomyxoma peritonei in the Department of Surgical oncology in Montpellier Cancer Institute. Among them, eight patients with bulky disease were eligible for treatment with two-stage cytoreductive surgery plus HIPEC. The selection was performed during surgery taking into account the extension of the disease as well as the necessary extent of visceral resections. The inclusion criteria were as follows: adult patients considered fitted for surgery who gave their informed consent; PMP with a PCI superior to 20; macroscopic and pathologic aspect suggesting acellular mucin or low grade mucinous neoplasia (LAMN) with mucinous peritoneal implants of gelatinous consistency, easily detachable of the serosal surface except for a thin tissular base superior to 5 mm; involvement of the digestive tract with several implants present on the serosal surface of the small bowel or/and of the colon requiring at least three resections with anastomoses or four long running sutures. An impaired nutritional status was not considered as an exclusion criterion. Patients who were easily resectable under organ-preserving strategies as well as those presenting with infiltrative lesions suggesting a high-grade disease were not eligible for this treatment. The retrospective study was approved by the Institutional Review Board of the investigating center in accordance with the good clinical practice criteria and the ethical standards of the Helsinki declaration of 1975.

2.2. Surgery

The preoperative workup included a contrast enhanced CT-scan and a peritoneal diffusion MRI before operative planning as well as between the two stages. The surgical procedure consisted of a two-stage cytoreductive surgery; each stage associated with HIPEC with oxaliplatin 250 mg/m^2 in a glucose solution 0.5% at 2 l/m^2. The final objective of this therapeutic strategy was to reach a CC-R0/1 resection for these patients at the end of the therapeutic management. The first surgical stage included resection of the whole peritoneal surface and/or of the lesions at risk of obstruction, but carefully excluded all other digestive tract resections. The residual tumor thickness was defined as the maximal thickness of the residual tumor and the cutoff was 5 mm [8–10]. These residual implants were not unique and, usually, more than four, located on the serosal surface of the digestive tube. They would have imposed at least three resections with anastomoses or four long running sutures in the eventuality of a CCR0/1. The second stage included a complete exploration, resection of the macroscopic disease, and resection or biopsy of previously described lesions not performed in the initial surgery, although not always macroscopically visible (Figure 1).

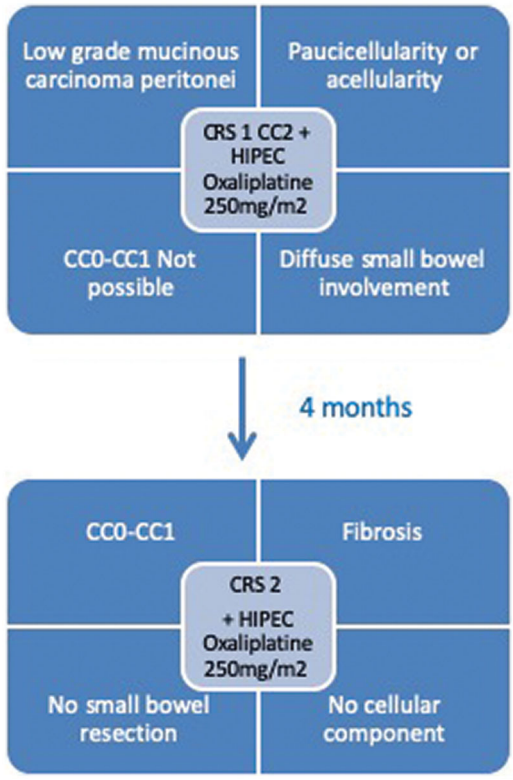

Figure 1. Flowchart of the two-stage treatment strategy.

The histologic evaluation was performed for each step by two pathologists (KL, FB) with conventional Hematoxylin-eosin-saffron stained microscopy using the current pathologic criteria. One of the two pathologist (FB) in an expert in this disease in the National Network of Rare Peritoneal Disease (RENAPE) [11].

All personal, clinical, histological and operative variables were recorded for this pilot cohort. A regular follow-up with clinical examination and contrast-enhanced CT-scan was performed every 4 months during the first two years and every 6 months for the following 3 years then once yearly thereafter. All patients have at least 17 months of postoperative follow-up.

3. Results

Eight patients were included in the study (seven female patients) with a median age of 66.5 years (range 57-76). They

Table 1. Patients' characteristics, medical history, and peritoneal disease evaluation.

Patient	Sex	Age	Medical history	Symptoms	Preoperative imaging	PCI
1	F	62	Appendicitis 18 months prior PMP diagnosis (appendectomy and typhlectomy)	Malnutrition, growth of the abdominal girth, lower limbs edema	CT, DW MRI	39
2	F	76	Mucocele of the appendix in 1995, At the inclusion: mucinous ascites and 6cm pelvic mass, CA 125 = 100UI/ml	Diffuse abdominal pain	CT, pelvic MRI	29
3	F	57	Surgery for pelvic mass with total hysterectomy, bilateral adnexectomy and right hemicolectomy. At the inclusion CA125 = 100UI/ml	Pelvic pain	CT, DW MRI	22
4	F	68	Chronic polyarthritis under treatment Moderate ascites with CA125 = 50UI/ml	Abdominal pain	CT, DW MRI	24
5	F	65	Respiratory deficiency, severe ascites	Dyspnea, abdominal pain	CT, DW MRI	37
6	F	70	Bilateral cataract	Abdominal pain, ascites	CT, US	26
7	M	72	Bilateral inguinal hernias, duodenal ulcer	Abdominal pain	CT	20
8	F	58	2 cesarean sections	Ascites	CT	21

PCI: Peritoneal Carcinomatosis Index; F: Female; PMP: Pseudomyxoma peritonei; CT: Computed Tomography; DW MRI: Diffusion Weighted Magnetic Resonance Imaging; US: Ultrasound.

Table 2. Surgical description of the two stages.

Patient	Stage I	Stage II	Interval
1	Subtotal peritoneal resection, hysterectomy + douglassectomy, splenectomy, omentectomy + HIPEC	Right colectomy, sigmoidectomy + HIPEC	4 months
2	Subtotal peritoneal resection, hysterectomy, douglassectomy, cholecystectomy, omentectomy + HIPEC	Biopsies of the gastric and sigmoid serosal fibrotic nodules + HIPEC	4 months
3	Right phrenic peritoneum resection, hepatic hilum deperitonisation, ileocolic anastomosis resection, omentectomy + HIPEC	Biopsies of the small bowel peritoneum + HIPEC	4 months
4	Subtotal peritonectomy, douglassectomy, bilateral adnexectomy, omentectomy, hepatic hilum peritonectomy, cholecystectomy, appendicectomy + HIPEC	Biopsies of the small bowel peritoneum + HIPEC	3 months
5	Subtotal peritonectomy, hysterectomy with bilateral adnexectomy, douglassectomy, omentectomy, appendectomy + HIPEC	Right colectomy, biopsies of the small bowel peritoneum + HIPEC	3 months
6	Subtotal peritonectomy, hysterectomy with bilateral adnexectomy, douglassectomy, omentectomy, appendectomy, cholecystectomy + HIPEC	Biopsies of mesenteric peritoneum + HIPEC	2.5 months
7	Subtotal peritonectomy, douglassectomy, omentectomy + HIPEC	Biopsies of small bowel and mesenteric peritoneum + HIPEC	4 months
8	Subtotal peritonectomy, hysterectomy with bilateral adnexectomy, douglassectomy, omentectomy, appendectomy, resection of Meckel diverticulum + HIPEC	Biopsies of small bowel and mesenteric peritoneum + HIPEC	4 months

HIPEC: Hyperthermic intraperitoneal chemotherapy.

had a median PCI of 25 (range 20-39) and an impaired nutritional status linked to their oncologic disease (Table 1). All patients were ASA III. The treatment flowchart applied to this small series of patients is detailed in Figure 1.

Cytoreductive surgery during the two stages consisted of various resections (Table 2). Median operative time and length of stay for each stage are presented in Table 3. In all cases, the residual disease after the first surgical stage had the planned maximum thickness of 5 mm and concerned the serosal surface of the small bowel. One patient had residual mucin on the serosal surface of the right colon and another patient on the serosal surface of the sigmoid colon. The placement and spreading of the mucinous lesions on the serosal surface of the digestive tract did not allow electrofulguration for these patients.

No macroscopically-visible residual disease was found in the second stage of CRS (Figure 2). Fibrotic scars were sometimes present on the peritoneal surface. They were all resected and sent for pathological examination. The sites of the residual disease described at the end of the first stage were also either resected or sampled during the second stage, depending on their report with the digestive serosa. All biopsies and specimens were free of residual disease at the pathology examination and presented signs of fibrosis suggesting a complete histologic response to HIPEC (Figure 3). The median time interval between the two stages was 4 months (range 2,5-4).

One patient had bowel resection during the first stage and two patients had isolated bowel resections in the second stage. Morbidity of the two stages consisted of one grade 3 event under the Clavien-Dindo classification [12] in each stage (Table 3). Mortality was nil. All patients are presently alive, without any evidence of recurrent disease. The median follow-up was of 31.5 months (range 17–65) at the time of analysis (November 2019).

4. Discussion

The present study is the first to show a proof of concept for two stage surgical treatment of bulky PMP on a small series of patients.

Most patients with pseudomyxoma peritonei are currently eligible for a complete cytoreductive surgery associated with HIPEC. This treatment offers the best chance of survival

Table 3. Operative and postoperative outcomes.

Patients	Operative stage I	Operative stage II	Length of stay I (days)	Clavien Dindo complications I	Length of stay II (days)	Clavien Dindo complications II	Follow-up interval (months)
1	10h	5h	31	Grade 3A pleural effusion; Grade 2 (fatigue, ileus)	13	Grade 2 (fatigue)	65
2	8h	4h	18	Grade 2 (ileus, respiratory)	15	Grade 3B (bowel perforation)	45
3	6h	3h	12	Grade 2 (pneumopathy)	10	–	38
4	7h	4h	15	Grade 2 (fatigue)	13	–	32
5	9h	4h	14	Grade 1 (fatigue)	10	–	31
6	9h	6h	21	Grade 2 (ileus, venous catheter infection)	30	Grade 2 (ileus)	21
7	10h	5h	23	Grade 2 (ileus, fatigue)	10	–	19
8	8h	6h	13	Grade 2 (ileus)	8	–	17
Median	8.5	4.5	16.5		11.5		29.5

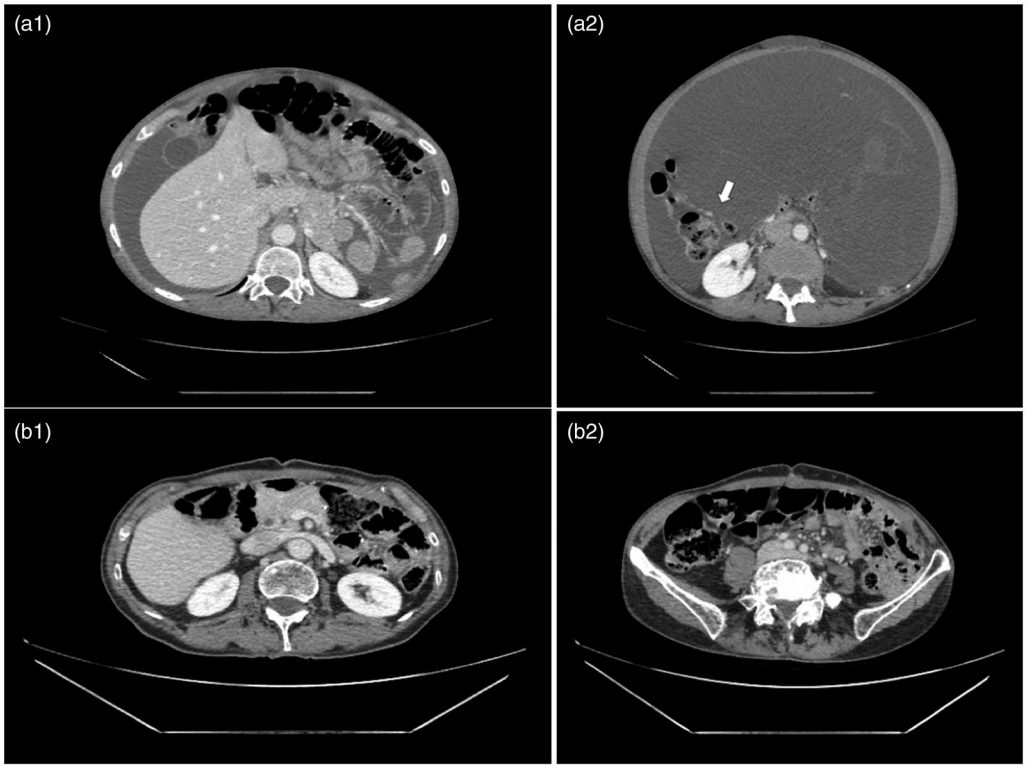

Figure 2. Radiological evaluation before surgery. (a) Axial contrast-enhanced CT images prior first stage surgery shows ascites (a1) and a large ill-defined multicystic mass within the abdominal cavity (a2). This complex cystic mass is seen repressing the intraperitoneal organ such as the right colon (a2 arrow). (b) Axial contrast-enhanced CT images performed just before the second time surgery show in comparison to images a1 and a2 the complete disappearance of ascites and of the complex cystic mass with the intraperitoneal organ back in their proper position in the abdominal cavity. Those results are in keeping with a complete radiological response of the first stage CRS/HIPEC oxaliplatin 250mg/m2

when compared to serial debulking surgery or medical treatment [3,4,13]. However, some of these patients present with a very extensive disease or with an impaired general status, which does not allow extensive surgery [14]. In a standard situation, these patients are thus usually treated in a palliative setting.

In a retrospective comparative study of debulking *versus* cytoreductive surgery [6], the benefit in overall survival rate of complete cytoreductive surgery (CC-R0/1) over debulking surgery (CC-R2) was 75% at 5 years and 70% at 10 years. Debulking surgery had initial benefits, but this has rapidly decreased in time as a very high recurrence rate was reported. However, in this study, little information was delivered on the residual disease in the R2 resections and on the interval between the different successive debulking surgeries.

Even for teams specialized in the treatment of large pseudomyxoma, achieving a CC-R0/1 resection is conditioned by the limited involvement of the small bowel, the capacity of conservation of the upper part of the stomach, the resectability of the hepatic pedicle involvement and the general status of the patient [15]. In expert centers, 29% of all large pseudomyxoma remain unresectable despite advanced multidisciplinary approaches; this percentage is irrespective of the grade [15].

Under the current definitions, CCR0 indicates the absence of any macroscopic residual disease while CCR1 indicates that the maximum diameter of any remaining nodule is

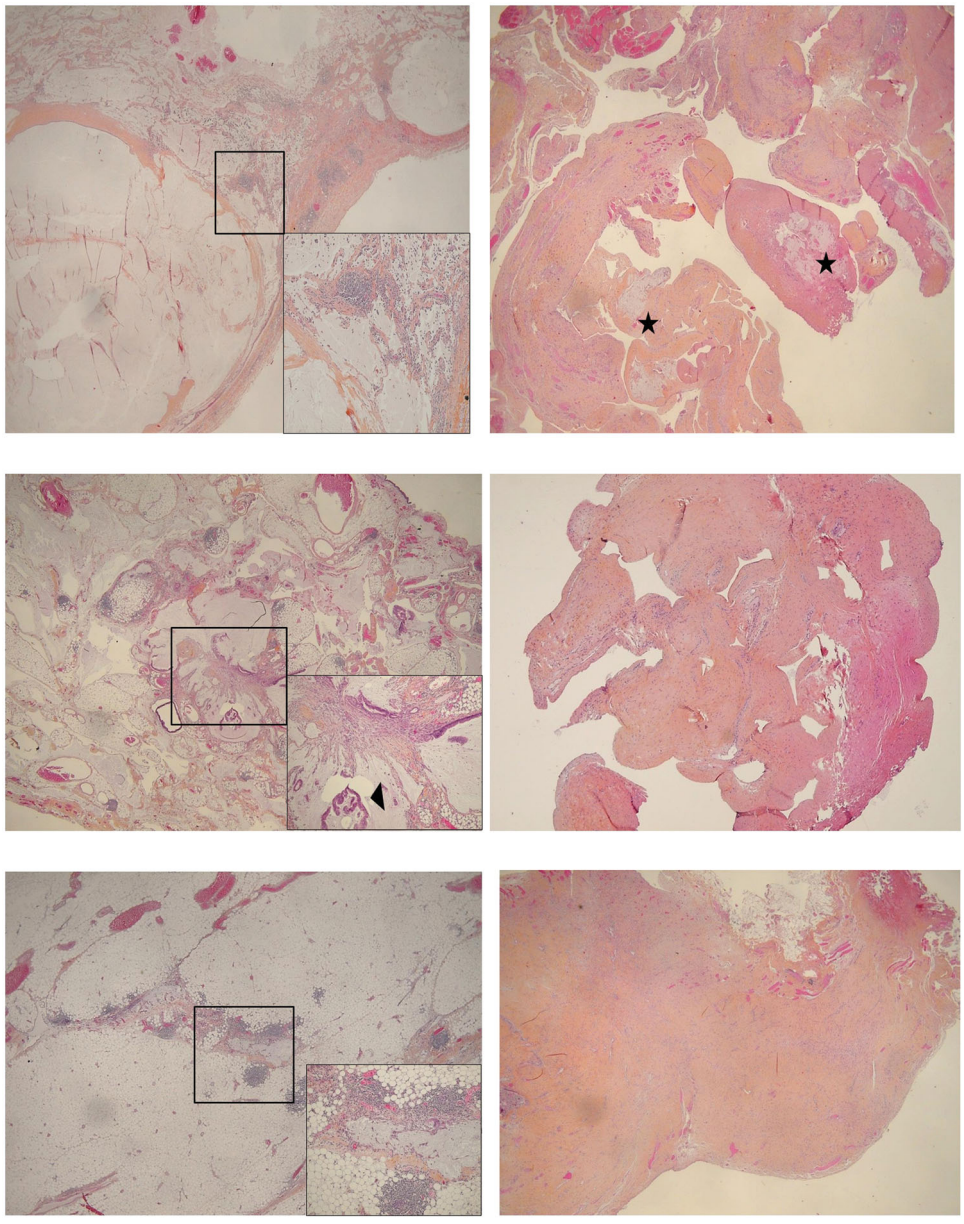

Figure 3. Example of histological samples from the two-stages.. (a) Patient 5 (a1) Stage I, parietal peritoneum involved by pools of acellular mucin, assessed as low-grade mucinous carcinoma peritonei (pseudomyxoma peritonei). HES, magnification × 20. Insert: evidence of acellular mucin with a reactive lymphocytic infiltrate. HES, × 100. (a2) Stage II, mesenteric peritoneum sampling showing a fibrous scar tissue embedding inconspicuous residual acellular mucin (asterisks). HES, × 20. (b) Patient 6 (b1) Stage I, parietal peritoneum involved by pools of extracellular mucin along with low grade neoplastic epithelium, assessed as low-grade mucinous carcinoma peritonei. HES, × 20. Insert: neoplastic epithelium highlighted by arrowheads. HES, × 100. (b2) Stage II, mesenteric peritoneum sampling showing merely fibrous scar tissue. HES, × 40. (b) Patient 8 (c1) Stage I, parietal peritoneum involved by pools of acellular mucin (low-grade mucinous carcinoma peritonei). HES, × 20. Insert: evidence of acellular mucin with a reactive lymphocytic infiltrate. HES, × 100. (c2) Stage II, mesenteric peritoneum sampling showing merely fibrous scar tissue. HES, × 40. HES: Hematoxylin eosin saffron.

2.5 mm [4]. These two terms characterize complete cytoreductive surgery. CCR2 indicates that nodules between 2.5 mm and 2.5 cm in diameter remained while for patients with CCR3 resections, nodules larger than 2.5 cm in diameter remained. These two terms characterize debulking surgery and have a significantly less favorable prognosis when compared with the first two for many peritoneal diseases including PMP [4]. While there is a high discrepancy in prognosis between CCR1 and CCR2, the range of size for CCR2 is very large justifying further research. For the present study, we chose a cutoff point of 5 mm which is a CCR2 status but within the initial range. In our technique, this threshold represents the residual thickness, not the maximal diameter of the remaining disease at the end of stage 1. This parameter was arbitrarily chosen based on the fact that previous studies pointed out a tissue penetration rate of 3-5 mm during the hyperthermic intraperitoneal chemotherapy [16].

Our strategy, the two-stage cytoreductive surgery associated with HIPEC for PMP, targets patients with an important tumoral burden and a too fragile condition for very extensive surgery. The CC-R0/1 resection may theoretically be obtained at the end of the second stage but, in this experience, a

complete pathologic response to HIPEC was already observed during the second surgical stage, as a result of the treatment applied in the first stage. This finding opens the door for future refining of the CCR2 category and of the real necessity for the second stage.

This two-stage surgical strategy had already been tested without the use of HIPEC in the first stage but the initial results in three patients were not encouraging [17]. Our improved results are probably due to the acquired knowledge concerning LAMN, the limited residual tumoral thickness of less than 5 mm, the response to the hyperthermic intraperitoneal chemotherapy at the end of the first surgical stage and, eventually, the administration of local treatment also during the second surgical stage.

Several cytotoxic drugs are used for HIPEC in pseudomyxoma peritonei with interesting results [13,18]. A recent short-term *ex vivo* assay aimed to evaluate the tumor cell sensitivity to different local chemotherapy drugs in samples from patients with PMP. The study found that IC50 values for cisplatin and oxaliplatin were almost identical in PMP subgroups [19]. Given that a higher dose of oxaliplatin compared to cisplatin can be administered intraperitoneally, oxaliplatin was preferred to achieve a maximum effect in this setting. That was consistent with the choice of oxaliplatin in our two-stage surgical strategy. However, we favored a less aggressive dose of 250 mg/m^2 [20] over our usual high dose of 460 mg/m^2 [21] as to reduce the risk of morbidity at the end of the first stage, thus ensuring completion of the two stages for the selected patients. This choice translated into a 100% completion rate of the two-stage strategy with an important visceral sparing.

Although there is little clinical consensus about the use of oxaliplatin over mitomycin C for HIPEC in the PMP setting, both the quality of the surgery and the drug choice remain important. In the *ex vivo* study pre-cited [19], drug sensitivity had a prognostic impact on progression-free survival but not on overall survival suggesting that qualified surgery was crucial for good long-term outcomes. A recent systematic review in the setting of peritoneal metastases of colorectal origin failed to show any superiority of one drug over the other in terms of both disease-free and overall survival [22].

The patients included in this proof of concept cohort had a reasonable morbidity when compared to other extensive disease cohorts [7] with only one Clavien Dindo grade 3 event in each stage. Small or large bowel resections were avoided in seven cases in the first stage and in six cases in the second stage which probably contributes extensively to the diminished morbidity. Even more so, the two resections performed in the second-stage concerned specimens with complete response to the first stage HIPEC and they were performed in order to secure CCR0 at the end of the treatment given the nature of our innovative strategy.

The interval between the two surgical stages was planned to be of 3 to 4 months. The rationale for this interval was based on the association of estimated postoperative recovery (1 month), the kinetics of the intraperitoneal adhesions [23] and the preparation for the iterative surgery.

A complete pathologic response was found, during the second CRS stage in all patients included in our study. This result is essential for the future management of large PMP especially in frail patients [24]. Also, our results only concern low-grade carcinoma PMP and may not be applicable to peritoneal diseases of higher grades. Finally, a score for histopathologic response assessment was recently proposed but it is difficult to use it in the setting of low-grade PMP as acellular mucin is a marker of the presence of the disease and not of the response to therapy in this clinical entity [25].

The limitations of the current study are related to the low number of patients and to the lack of comparative strategy. Large number of patients are difficult to assemble for testing new strategies in a relatively rare disease. However, these results are very encouraging for the future treatment of patients with voluminous tumoral burden of low-grade PMP and an impaired general status. We show that two-stage strategy is feasible and safe in these patients as it has a low morbidity, enhanced visceral sparing and promising long-term survival outcome. Confirmation of these preliminary results is needed in a future clinical trial and other de-escalating strategies will be consequently developed.

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Disclosure statement

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