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Survival after complete cytoreductive surgery and HIPEC for extensive pseudomyxoma peritonei

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ABSTRACT

Introduction: The optimal treatment for pseudomyxoma peritonei (PMP) combines complete cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC). Yet, achieving CRS is challenging in the case of extensive involvement of the peritoneal cavity and the survival benefit in this setting remains uncertain. The present study evaluated the surgical outcomes according to the peritoneal extent.

Methods: Between 1992 and 2014, 245 patients underwent CRS and HIPEC for PMP in our institution. Their characteristics were reviewed using a prospective database. Extensive PMP was defined as a peritoneal cancer index (PCI) ≥ 28. Sixty-one patients with extensive PMP were compared to 184 with non-extensive PMP.

Results: Severe complications were more frequent in the extensive group (46% vs. 23%, $p < 0.001$) but the post-operative mortality was not significantly different (8% vs. 3%, $p = 0.1$). The 5-year disease-free survival reached 45% in the extensive and 78% in the non-extensive group ($p < 0.0001$). The 5-year overall survival was 70% and 90% in the extensive and non-extensive group respectively ($p < 0.021$).

Conclusion: CRS with HIPEC offers prolonged survival even in the case of extensive PMP. Because of the high rate of surgical morbidity in the extensive group, patients should be carefully selected.

1. Introduction

Pseudomyxoma peritonei is a rare disease that most commonly originates from the appendix as a result of the rupture of a mucinous neoplasm. When diagnosed at an early stage, PMP shows limited extension, remaining within the area of the appendix. However in about 30% of cases, the accumulation of mucin in the peritoneum extends throughout the abdomen resulting in massive abdominal distention, bowel dysfunction and pain.

The gold standard treatment for PMP combines complete cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC). Complete CRS aims to remove all the visible disease, while the HIPEC ensures the treatment of the remaining microscopic disease. With this approach, the overall survival (OS) reaches 86% at 5-year [1] and the median survival 16.3 years [2] in large series. The main prognostic factors for OS are the completeness of cytoreduction [2], the grade of the disease, and the extent of the peritoneal disease, which is measured by the peritoneal cancer index (PCI comprised between 0 and 39) [3]. There is currently no consensual PCI cut-off to contraindicate surgical resection in PMP patients. Thus, when extensive disease occurs, surgeons are faced with the dilemma of choosing between optimal surgical resection (with the risk of increased morbidity and long-term side-effects arising from multiple visceral resections) and palliative treatments.

Based on our experience, we previously identified a group of PMP patients at higher risk of incomplete CRS due to the large involvement of the peritoneal cavity, termed extensive PMP (also referred as “huge”) [4]. The present study was designed to further analyze short- and long-term outcomes of patients with extensive PMP who underwent CRS plus HIPEC compared to patients with non-extensive PMP.

2. Materials and methods

2.1. Study patients

Between 1992 and 2014, 313 patients operated for PMP at Gustave Roussy Cancer Campus were included in the prospective database. The diagnosis of PMP was confirmed in a multidisciplinary meeting of surgeons, gastroenterologists, medical oncologists, radiologists and pathologists based on the clinical symptoms and the presence of

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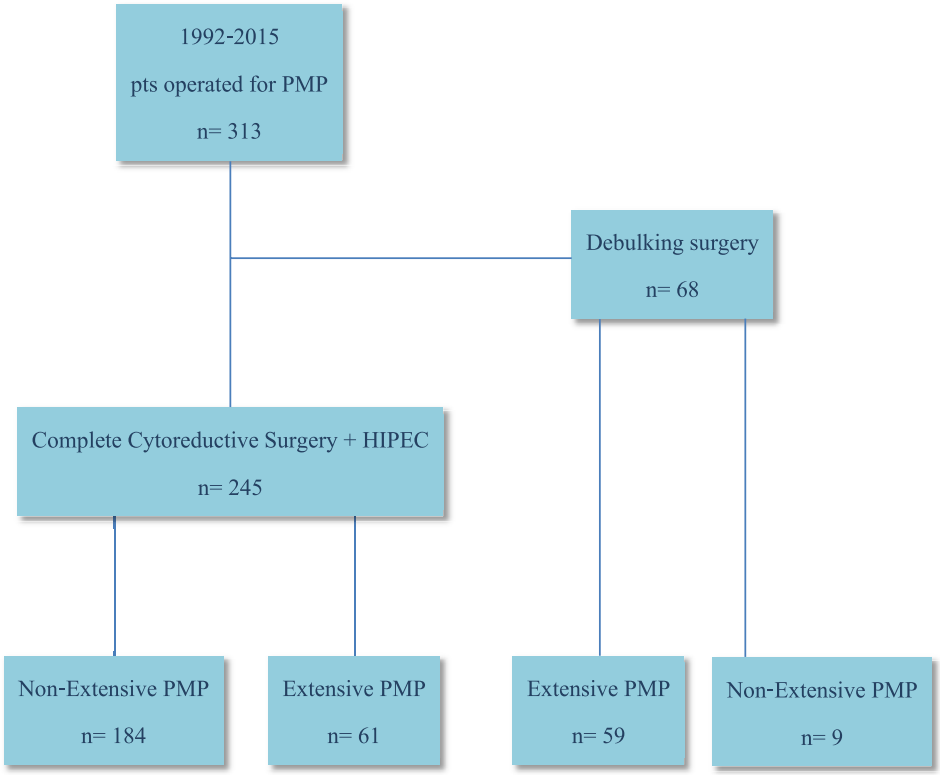

Fig. 1. Flow chart.

abdominal mucin by computed tomography (CT) scan, with or without pathological assessment. The treatment including surgery and pre-operative chemotherapy was collectively discussed. Among these patients, we selected patients who presented with extensive PMP, defined by a peritoneal cancer index (PCI) ≥ 28 calculated intra-operatively. The short- and long-term outcomes were compared to those of patients with non-extensive PMP. Demographic, clinical and operative characteristics were prospectively registered in a database, and surgical specimens were analyzed and graded according to PSOGI consensus [5]. Undernutrition was biologically defined as an albumin level < 30 g/L and/or a pre-album level < 110 mg/L with the level of undernutrition classified as weight loss exceeding 10% overall, exceeding 5% in less than one month and/or a body mass index inferior or equal to 17 kg/m^2 [6]. The short- and long terms morbidity and survival outcomes were also recorded.

Follow-up included clinical examination and thoracic and abdominopelvic CT-scans every 4 months for high-grade PMP (grades 2 and 3) and every 6 months for low-grade PMP (grade 1) for 3 years and then annually for up to 10 years. Recurrences were confirmed after systematic imaging analysis in multidisciplinary meeting.

The study was approved by the institutional review committee and conforms with the guidelines of the French national health agency.

2.2. Surgical procedure

The diagnosis of PMP was confirmed at laparotomy and disease extent was calculated using PCI classification. Surgical procedures were performed by midline laparotomy as previously described [4,7–9]. Complete cytoreductive surgery was defined by the complete macroscopic resection of the disease (R0) with CC0 or CC1 status. The CRS was deemed not feasible in the cases of insufficient length of residual small bowel and/or inability to clear the hepatic pedicle from its tumor involvement (strict limitations). The impossibility to preserve the left gastric vessels in order to preserve the superior third of the stomach was also a relative limitation [4]. HIPEC was performed with the Garmidatech's Sunchip® device using the open coliseum technique with a peritoneal infusion of oxaliplatin and irinotecan for 30 min at 43 °C, associated with systemic 5-fluorouracil [4]. At the end of the procedure, blood loss was measured in the operating theater as well as the duration of surgery.

2.3. Statistical analyses

Categorical variables were compared between groups using the Chi-squared or Fisher's exact tests, as appropriate. Quantitative variable were compared using the *t*-test or Wilcoxon's test as appropriate. Post-operative 30-day morbidity and 90-day mortality were evaluated with the Dindo-Clavien classification [10]. Survival parameters were estimated using the Kaplan–Meier method and compared with the log-rank test. OS was calculated from the date of surgery to the date of death or last follow-up. Disease-free survival (DFS) was calculated from the date of surgery to the date of the first recurrence detected on imaging. The cut-off date for survival analyses was December 15, 2017. Univariate analysis was performed using a single variable Cox proportional hazards model. Any variable achieving $p < 0.1$ in the univariate analysis was included in a multivariate Cox proportional hazards model with backward elimination based on Akaike information criterion [11]. PCI was not included in the Cox regression analysis since it is collinear with the extensive variable. All statistical analyses were performed using R-3.3.2 (The R Foundation for Statistical Computing) and a two-sided *p* value of 0.05 was considered significant.

3. Results

3.1. Patient characteristics

Among 313 patients operated for PMP between 1992 and 2015, 120 had extensive PMP with a PCI ≥28. Half of the patients with extensive PMP could not undergo CCR0-1 (51%), compared to only 5% of the patients with non-extensive PMP ($p < 0.001$) (Fig. 1). Complete

Table 1
Baseline and surgery characteristics of the patients in the extensive and not-extensive PMP groups undergoing CRS plus HIPEC.

		Non-extensive (PCI < 28) n	Extensive (PCI ≥ 28) n (%)	*p-value*
N		**184**	**61**	
Gender	Male	62 (33)	32 (52)	0.014
	Female	122 (66)	29 (47)	
Age in years, mean ± SD		48 (± 11)	49 (± 11)	0.5
ECOG performance status	0–1	184 (95)	61 (100)	1
Undernutrition		7 (4)	17 (28)	< 0.0001
Histological grade	0-1 (DPAM)	123 (68)	17 (28)	< 0.001
	2 (Hybrid)	31 (17)	26 (44)	
	3 (PMCA)	26 (14)	16 (27)	
	Unknown	4 (2)	2 (3)	
Previous surgery		147 (80)	40 (65)	0.022
Neoadjuvant chemotherapy		38 (20)	36 (59)	< 0.001
Lymph node metastasis		6 (3)	3 (5)	0.69
Blood loss, mean ± SD		572 (± 693)	1826 (± 1465)	< 0.001
Transfusion		13 (7)	36 (59)	< 0.001
Morbidity		168 (91)	61 (100)	0.017
Clavien-Dindo 0-2		119 (65)	28 (46)	0.009
Clavien-Dindo 3-4		43 (23)	28 (46)	< 0.001
Mortality (Clavien-Dindo 5)		6 (3)	5 (8)	0.1
ICU, Mean N days ± SD		10 (± 10)	18 (± 18)	0.002
Hospital stay, mean N days ± SD		23 (± 16)	37 (± 24)	< 0.001

ICU, intensive care unit; *DPAM* disseminated peritoneal adenomucinosis*; PMCA* peritoneal mucinous carcinomatosis, PCI peritoneal cancer index.

cytoreductive surgery (CCR0-1) followed by HIPEC was performed in 245 (78%) patients, including 184 in the non-extensive group and 61 in the extensive group. Reasons for incomplete surgery in patients with extensive PMP were technical impossibility to perform a complete cytoreductive resection (n = 44), elderly patients and/or a poor general status (n = 11), pleural invasion (n = 3) and per-operative bleeding (n = 1).

Patients and surgical characteristics are detailed in Table 1. The PMP originated in the appendix in all but five patients (ovaries n = 2, colon n = 1, pancreas n = 2) in the non-extensive group. High-grade appendiceal mucinous neoplasm (Ronnett's grade 2 and 3) was more frequent in extensive PMP (71%) compared to the non-extensive group (31%) ($p < 0.001$).

3.2. Surgical procedures

The characteristics of surgeries are summarized in Table 1. Before surgery, 74 patients had received preoperative systemic chemotherapy, 36 in extensive PMP patients and 38 in non-extensive PMP ($p < 0.001$). At laparotomy, the median PCI was 16 [1–27] in patients with non-extensive PMP and 37 [28–39] in patients with extensive PMP. A detailed description of the surgical resections performed during CRS plus HIPEC is provided in Table 2. As expected, extensive PMP required significantly more complex resections. Almost half of the patients in the extensive group underwent a total colectomy (43%) and/or a rectal resection (54%). A splenectomy was performed in all patients with extensive PMP except two. The mean per-operative blood loss was higher in the extensive PMP group, reaching 1826 ml vs. 572 ml in the non-extensive group. The rate of peri-operative transfusion was 59% vs. 7% in the non-extensive group. The mean duration of the surgical procedure was significantly longer in patients with extensive PMP (713min ± 119 vs. 432 min ± 122, $p < 0.001$).

3.3. Post-operative outcomes

Almost all patients experienced complications in both groups. These complications were more severe in the extensive group with a higher rate of grade 3–4 complications (46% vs. 23%, $p < 0.001$). There was a trend toward a higher mortality rate in the extensive group (8% vs. 3%; $p = 0.1$). Five patients (8%) died post-operatively in the extensive group, due to anastomotic leakage with peritonitis (n = 1), acute renal failure (n = 2), cerebral hemorrhage (n = 1) and acute multi-visceral deficiency (n = 1). Six patients (3%) died in the non-extensive group, due to acute respiratory failure (n = 1), post-operative sepsis from unknown origin with aplasia (n = 1), peritoneal hemorrhage (n = 1), aplasia with acute vascular cerebral embolism (n = 1), respiratory failure (n = 2). The mean hospital stay was significantly longer in the extensive PMP group (37 vs. 23 days, $p < 0.001$). Post-operative chemotherapy proposed to all patients with high-grade PMP and was received by 21% of patients in the extensive group vs. 13% of patients in the not-extensive group ($p = 0.15$).

Table 2
Organ resection performed in the extensive and not-extensive groups.

	Non-Extensive N (%) (N = 184)	Extensive N (%) (N = 61)	*p-value*
Gastrectomy	15 (8)	39 (64)	< 0.001
Antrectomy	15 (8)	37 (60)	< 0.001
Total gastrectomy	0 (0)	2 (3)	0.01
Colectomy	154 (84)	61 (100)	< 0.001
Total	4 (2)	26 (43)	< 0.001
Bifocal	18 (10)	17 (28)	< 0.001
Right	94 (51)	11 (18)	< 0.001
Caecum	15 (8)	0 (0)	0.02
Extended right	14 (8)	6 (10)	0.58
Left	7 (4)	1 (1)	0.4
Transverse	2 (1)	0 (0)	0.4
Rectal resection	27 (14)	33 (54)	< 0.001
Ileal resection	47 (25)	57 (93)	< 0.001
Stoma	10 (5)	18 (29)	< 0.001
Number of anastomosis,	1 [0–4]	2 [0–5]	0.09
Splenectomy	90 (49)	59 (97)	< 0.001
Omentectomy	180 (98)	61 (100)	0.24
Cholecystectomy	172 (93)	59 (97)	0.34
Hysterectomy (% of females)	27 (14)	13 (21)	0.22
Oophorectomy (% of females)	61 (33)	14 (23)	0.13
Liver wedge resection	2 (1)	6 (10)	< 0.001
Urinary bladder	1 (0.5)	2 (3)	0.09
Ureteral resection	1 (0.5)	1 (1)	0.4
Douglassectomy	130 (70)	60 (98)	< 0.001
Diaphragm peritoneum	109 (59)	59 (97)	< 0.001

Median[range].

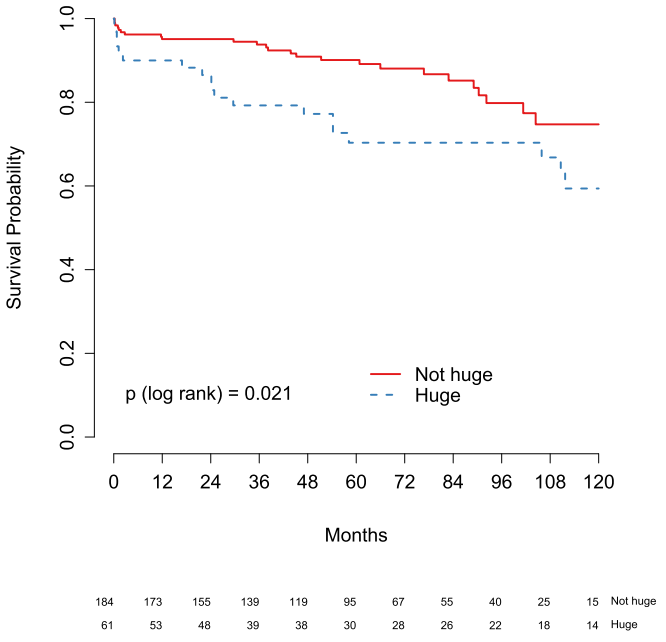

Fig. 2. Overall survival in the extensive and non-extensive groups.

3.4. Long-term outcomes

The median follow-up for patients undergoing CRS plus HIPEC was 69 months. After CRS plus HIPEC, 5-year OS was respectively 70% [95%CI: 0.57–0.81] and 90% [95%CI 0.84–0.93] in the extensive and non-extensive PMP groups ($p = 0.021$) (Fig. 2). Five-year DFS was 45% [95%CI: 0.32–0.59] in the extensive group and 78% [95%CI: 0.70–0.84] in the non-extensive group ($p < 0.0001$) (Fig. 3). After recurrence, 16 patients underwent iterative CRS in the non-extensive group (including 5 patients with grade 3 tumor). In the extensive group and 5 patients underwent iterative CRS (including 1 patient with grade 3 tumor).

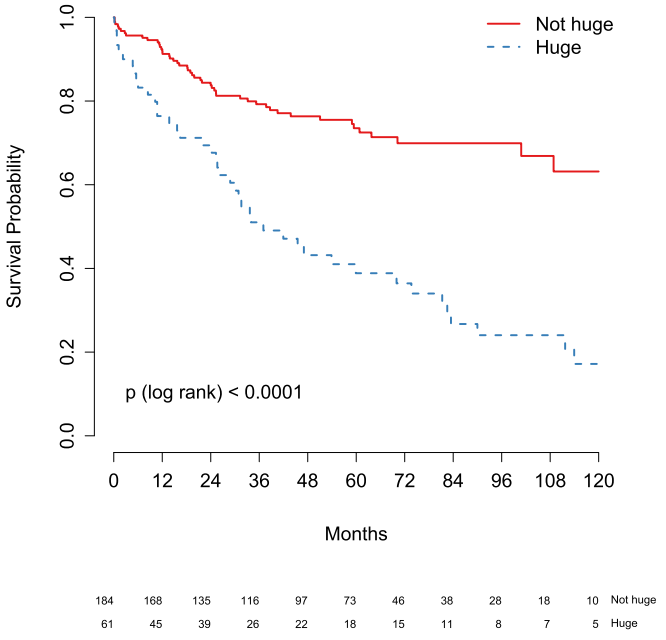

Fig. 3. Disease-free survival in the extensive and non-extensive groups.

3.5. Prognostic factor analysis

Univariate analysis showed that factors associated with lower OS were high-grade disease, pre-operative chemotherapy, extensive PMP, PCI and per-operative transfusion (Table 3). In the multivariate analysis, high-grade was the only factor significantly associated with OS. Univariate analysis also showed poorer DFS was significantly associated with high-grade disease, pre-operative chemotherapy, extensive PMP, PCI, gender and peri-operative transfusion (Table 3). In the multivariate analysis, gender, high-grade and extensive PMP remained significantly associated with DFS.

A sensitivity analysis did not identify any predictive factors for shorter OS or PFS in the sub-group of extensive PMP. The small number of patients may limit the reliability of this sub-group analysis.

4. Discussion

This is the first published report dedicated to the outcome of patients with extensive PMP and aiming to clarify the balance between surgical risk and expected survival in these patients. The first step is to determine a PCI cut-off to define extensive PMPs. Although high PCI (> 20) has already been linked to shorter OS in multicentric studies [1,2] the ideal cut-off defining extensive abdominal spread is yet to be defined. The three main surgical conditions identified to achieve complete resection were the possibility of: (a) conserving at least the upper part of the stomach, (b) clearing the hepatic pedicle, and (c) conserving a sufficient length of small bowel to avoid short-bowel syndrome [4]. Exceptions can be made for the total gastrectomy which can be performed in selected patients in specialized centers [12,13]. Based on our surgical experience, we therefore observe that extensive peritoneal spread is more likely to correspond to disease that invades at least all 13 areas of the abdomen with a PCI score ≥2 for each area (peritoneal implants ≥5 mm) plus a minimum score of 3 (peritoneal implants > 5 cm) in the locations for difficult clearance corresponding to the hepatic pedicle and the upper part of the stomach. The evaluation of the technical surgical aspects of this setting has been reported [4]. We acknowledge that our definition may not be consensual and this threshold might not be perfect. However, in the present study, the rates of CCR0-1 in patients with or without extensive PMP, confirmed that a PCI cut-off of 28 was adequate to define extensive PMP which is difficult to resect in totality, with only 51% of our patients' population able to undergo CRS plus HIPEC in the extensive group compared to 95% for the rest of the PMP population. In peritoneal extension from colorectal cancer, the relation between PCI and survival is linear and no threshold can be formally drawn [14]. Likewise, we agree that the PCI in this publication should be regarded as an indicator for outcomes and not as a perfect crossroad.

The study being retrospective, numerous limitations and selection biases are acknowledged. The data from only one center were analyzed over two decades during which surgical technics, imaging, drugs management evolved. The number of patients is also too limited to perform a perfect comparison within an heterogeneous population of patients.

This study nonetheless confirms the technical challenge associated with extensive PMP resection, with higher rates of organ resection, bleeding, blood transfusion, and long operation duration. As expected, these substantial procedures resulted in a higher rate of severe complications - twice that of patients with non-extensive PMP. The rate of postoperative mortality did not significantly differ between the two groups; however there was a trend towards a higher mortality rate in the extensive group. This highlights the key role of the center's experience, which allows for early recognition of complications and appropriate treatment [15–17].

High-grade PMP histology is identified as a more aggressive and more invasive disease, and may result in specific technical difficulties for achieving CCR0, independent of the PCI. Extensive PMP were more

Table 3
Univariate and multivariate analysis for overall and disease-free survival.

Variables	Categories	Overall Survival		Disease-Free Survival	
		HR	*p-value*	HR	*p-value*
Univariate					
Gender	Female	1	0.17	1	0.0014
	Male	0.67 [0.37–1.19]		0.51 [0.37–1.19]	
Age (per year)		1.01 [0.98–1.04]	0.47	1 [0.98–1.02]	0.8
Performance status	0	1	0.21	1	0.67
	1	0.68 [0.37–1.25]		1.09 [0.72–1.66]	
Undernutrition	No	1	0.87	1	0.14
	Yes	1.08 [0.43–2.75]		1.57 [0.86–2.89]	
Grade	0–1	1	< 0.001	1	< 0.0001
	2	4.46 [2.08–9.55]		4.41 [2.67–7.27]	
	3	4.44 [1.94–10.16]		3.71 [2.14–6.45]	
Lymph node metastasis	No	1	0.039	1	0.36
	Yes	2.82 [1.01–7.89]		1.51 [0.61–3.73]	
Pre-operative chemo	No	1 [1.57–5.02]	0.00026	1	< 0.0001
	Yes	2.81 [1.57–5.02]		3.34 [2.21–5.06]	
PCI		1.05 [1.01–1.09]	0.0065	1.08 [1.05–1.11]	< 0.0001
Group	Non-Extensive	1	0.021	1	< 0.0001
	Extensive	2 [1.01–3.63]		3.80 [2.04–4.66]	
Transfusion	No	1	0.0086	1	< 0.0001
	Yes	2.24 [1.21–4.15]		2.22 [1.42–3.47]	
Clavien-dindo	0–2	1	0.72	1	0.53
	3–5	0.89 [0.47–1.69]		1.15 [0.74–1.78]	
Multivariate					
Grade	0–1	1	< 0.001	1	< 0.001
	2	4.46 [2.08–9.55]		3.36 [1.95–5.77]	
	3	4.44 [1.94–10.16]		3.1 [1.72–5.56]	
Sex	Female		ns	1	0.0045
	Male			0.53 [0.34–0.82]	
Extensive	Non-Extensive		ns	1	0.018
	Extensive			1.75 [1.1–2.78]	

PCI: peritoneal cancer index.

likely to be high-grade, confirming the aggressiveness of this histological subtype, and may represent biases for survival analysis. In addition, patients with extensive PMP received preoperative chemotherapy more frequently. Our center's policy is to perform preoperative systemic chemotherapy in patients with confirmed high-grade peritoneal carcinomatosis and/or CA 19–9 > 200 UI/L. This policy could nonetheless be questioned as the true benefit of this preoperative chemotherapy and the tumor response that can be expected, are still unclear.

Long-term outcomes in our population were impressive. Despite the considerable disease extension, almost half of the patients were alive without recurrence 5 years after the surgery and OS reached 70%. This 5-year OS rate is clearly superior to what can be expected after incompletely resected disease. For extensive PMP not accessible to complete resection, median OS is currently between 15 and 30 months [18–20]. We recently reported the outcomes of the group of patients with extensive PMP who could not undergo CCR0-1 surgery. In the case of major debulking surgery without HIPEC the 5-year OS was 46% [18]. While the patients in these two studies are not directly comparable, this point supports the approach of performing CCR0-1 in patients with extensive PMP who can sustain this aggressive strategy. In our center, the choice between CRS with HIPEC versus tumor debulking is usually made pre-operatively. Patients at high risk for surgical complications with a performance status score ≥2, undernutrition and/or who are > 75 years-old are typically considered unsuitable for CRS and HIPEC.

When CRS appears unachievable for technical reasons or poor performance status, most patients are eligible for palliative debulking, which has demonstrated safety and efficacy in decreasing symptoms [18]. For those difficult cases, long term function preservation and symptoms management is sometimes the best choice [21]. Other criteria for selection may also be taken into consideration, including tumor grading, tumor marker levels and mucinous diffusion in the peritoneal space. Tumor marker levels including CEA, CA 125 and CA 19-9 have been linked to survival outcomes in patients with PMP, and can be considered a prognostic factor for CRS [22–25]. Histological grade is another main prognostic factor, as confirmed in the present study that may balance the decision to proceed or not with extensive PMP resection. Interestingly, in the extensive PMP group, the grade was not predictive for survival. The “group” characteristic appears to override the “grade”, although the reliability of this sub-group analysis remains limited by the small number of patients. We have demonstrated that selected patients with high-grade extensive PMP can benefit from CRS plus HIPEC. The patients’ selection is clearly an important part of the surgical expertise to obtain acceptable morbidity rate and to achieve long-term survival.

Beyond patient selection, other pertinent aspects play a role in decreasing the risk related to these extensive surgeries. Future treatments are expected to induce pre-operative tumor shrinkage to limit the extent of the surgical resections. Depletion of mucin with local application of bromelain and *N*-acetylcysteine is a promising alternative to chemotherapy and is currently being tested in animal models [26]. The risk related to these extensive surgeries could also be limited by alternate strategies. A two-step surgery has been proposed, mirroring the multistep strategy employed to treat patients for liver metastasis of colorectal origin. This strategy could be used to increase the possibility for resection and/or to decrease the morbidity rate. Nonetheless this option comes with several limitations including an increased rate of technical complications related to iterative dissection or disturbed distribution of the chemotherapy within a previously dissected abdomen. Moreover in patients with non-resectable disease, it is unlikely that two-stage surgery will offer any possibility for CRS at second laparotomy. In our practice this option remains limited to very specific situations where

surgery has to be interrupted for acute per-operative problem (medical issue, bleeding …). In Miner et al. the ability to achieve CRS was associated to the number of previous surgey for PMP [21]. Although related with an increased morbidity the role of HIPEC in this strategy is unknown and its practice diverse across surgical teams. The modality of chemotherapy administration varies from open to closed technics and regimens are based on mitomycine C, cisplatin or oxapliplatin, with or without irinotecan. The choice for Oxaliplatin and Irinotecan in this trial could be debated as it is related with higher rate of post-operative hemorrhage than Mitomycine C. This could be compared in a dedicated trial. Finally, the direct comparison between CRS alone and CRS + HIPEC has never been performed.

In conclusion, these results confirm that CRS plus HIPEC for PMP allow prolonged survival even in cases of extensive PMP. Future efforts should focus on reducing the extent of extensive PMP surgery, with lower postoperative complication rates, better patient selection, and effective pre-operative treatment.

Disclosures and funding sources

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.suronc.2019.03.004.

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