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ORIGINAL ARTICLE – PERITONEAL SURFACE MALIGNANCY

Non-resectable Malignant Peritoneal Mesothelioma Treated with Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) Plus Systemic Chemotherapy Could Lead to Secondary Complete Cytoreductive Surgery: A Cohort Study

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ABSTRACT

Background. Diffuse malignant peritoneal mesothelioma (DMPM) is an aggressive primary peritoneal neoplasia. At diagnosis, few patients are eligible for a recommended cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). Among neoadjuvant strategies, pressurized intraperitoneal aerosol chemotherapy (PIPAC) combined with systemic chemotherapy has been recently proposed. This study evaluated this strategy in a cohort of DMPM patients.

Methods. Patients with DMPM and primary or recurrent non-resectable diseases who received at least one PIPAC procedure in alternation with systemic chemotherapy were included in this retrospective study to analyze oncologic outcomes.

Results. Overall, 26 DMPM patients were treated with at least one PIPAC, including 20 patients with no previous CRS. Of 22 patients (85%) who had symptoms, 9 had perceptible ascites. Overall, 79 PIPAC procedures were performed, with half of the patients receiving three PIPAC procedures or more. Among eight patients (31%), 10 adverse events (13% of procedures) were reported, including two severe complications, both corresponding to digestive perforations. Improvement of symptoms was reported for 32% of the patients, whereas control of ascites was noted in 46%. All but one procedure among 14 patients (54%) secondarily treated by CRS-HIPEC were considered complete resections. After a median follow-up period of 29.6 months (95% confidence interval [CI], 17.6–not reached [NR]), the median overall survival period was 12 months (95% CI 11.1–NR). The median progression-free survival (PFS) was significantly better among the patients who underwent resection than among those who did not (33.5 vs 7.4 months; hazard ratio [HR], 0.18; 95% CI 0.06–0.755; $p < 0.001$).

Conclusions. For patients with initially non-resectable DMPM, PIPAC is feasible for treatment with neoadjuvant intent and could facilitate complete secondary resection.

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Diffuse malignant peritoneal mesothelioma (DMPM) is a rare and aggressive neoplasm arising from the mesothelial cells covering the inside of the abdominal cavity. This

primary peritoneal disease accounts for 7% to 30% of all mesothelioma cases, with an incidence of nearly two cases/million/year, precluding the organization of large prospective randomized trials.[1,2]

The treatment of DMPM is mainly guided by the opportunity to proceed to a radical resection of peritoneal lesions because DMPM is markedly resistant to systemic chemotherapy.[3–10] Thus, at diagnosis, therapeutic strategies are defined according to three main categories: (1) inoperable and/or not resectable, (2) operable and resectable, and (3) borderline resectable disease.[9] The latter group is defined by patients amenable to complete resection at the cost of extensive and highly morbid surgeries with the risk of impaired quality of life.[11–13]

The majority of DMPM patients unfortunately have non-resectable disease at diagnosis.[7,8] The median overall survival (OS) period ranges from 6 months with best supportive care to 11 to 16 months with systemic chemotherapy, and to more than 50 months with the multimodal approach when patients meet all good prognosis factors and are amenable to a complete surgical resection.[5,8, 14–17]

As a primary peritoneal disease, usually limited to this anatomic area, DMPM is a candidate for locoregional treatment.[18] Thanks to the peritoneal-plasma barrier, intraperitoneal chemotherapy (IPC) can be delivered at higher concentrations than intravenous chemotherapy, reaching the threshold of cytotoxic concentrations of otherwise chemoresistant neoplastic cells without increasing the systemic toxicity as much.[19]

Several techniques of IPC are proposed in expert centers. Typically, hyperthermic intraperitoneal chemotherapy (HIPEC) is recommended after a complete cytoreductive surgery (CRS) to eradicate the remnant microscopic disease by taking advantage of the special exposition of all peritoneal surfaces after CRS.[5,6,9,10,15,20–22] The other forms of IPC, based on repetitive administrations of chemotherapy, have been evaluated in retrospective analyses.[11,17,23,24] The differences in the selection criteria and protocols of these studies preclude direct comparisons of oncologic outcomes between them. However, when IPC was used with neoadjuvant intent together with systemic chemotherapy, half of the patients were ultimately amenable to a complete CRS.[11]

A new technique, pressurized intraperitoneal aerosol chemotherapy (PIPAC), was developed to improve the efficacy and feasibility of IPC while controlling morbidity.[25,26] The PIPAC approach takes advantage of a standard capnoperitoneum at 12 mmHg together with the aerosolization of drugs as microdroplets resulting in a better yield between dose and tissular uptake compared with HIPEC.[27]

Usually, PIPAC is combined with systemic chemotherapy in alternation, allowing periodic laparoscopic tumor assessment, which findings have shown to be more sensitive than cross-sectional imaging for predicting complete resectability.[26] Initially devoted to palliative patients, PIPAC was progressively proposed as an induction treatment to obtain secondary complete CRS, namely in DMPM patients.[28–30] A randomized prospective trial currently is recruiting patients to assess the efficacy and safety of PIPAC in this setting.[12] In the current study, the outcomes for DMPM patients treated with at least one PIPAC procedure in an expert center were reported.

METHODS

This study was a retrospective analysis of a monocentric database (Lyon Sud Hospital, Hospices Civils de Lyon) as part of the RENAPE Observational Registry, prospectively maintained and created in November 2015 when the first PIPAC procedure was performed in the center (NCT02834169). All consecutive patients treated with at least one PIPAC procedure were included in this database. Among these patients, those with a pathologically confirmed DMPM were selected for the current analysis.

The analysis prospectively recorded standard data regarding patient characteristics, treatment history, parameters, and outcomes. All the patients signed an informed consent. The RENAPE Registry has been approved by the Advisory Committee for Data Processing in Health Research at the Research French Ministry (CCTIRS-n°10.257). The study was performed in accordance with the precepts established by the Declaration of Helsinki, and the results were reported according to the Strengthening the Reporting of Cohort Studies in Surgery (STROCSS) criteria.[31]

Treatment Strategy

After a double proofreading, the DMPM diagnosis and subtype determination were confirmed within the French network of peritoneal surface malignancies (PSM) pathologists called RENAPATH, together with Ki-67 and BAP1 expression analysis through immunohistochemistry. The pretreatment workup, aimed at determining the level of resectability, included serum tumor marker dosage (CA125), thoraco-abdominopelvic computed tomography (CT) scan, peritoneal magnetic resonance imaging (MRI), and a staging laparoscopy.

Patients without extraperitoneal disease judged operable and resectable at the cost of limited digestive resections (fewer than 3, leaving more than 1.5 m of the small intestine) were treated with upfront CRS-HIPEC. From

November 2015, the remnant cases were proposed, after three cycles of systemic chemotherapy, for an intensified bi-directional treatment combining PIPAC and systemic chemotherapy provided the abdominal cavity was accessible and the condition involved no digestive obstruction, neither deterioration of the general status (Eastern Cooperative Oncology Group [ECOG] performance status [PS] <3) nor a history of allergic reactions to platinum compounds or doxorubicin.[32]

The typical therapeutic sequence consisted of two systemic chemotherapy cycles alternating with one PIPAC procedure, with the aim to repeat PIPAC every 6 to 8 weeks. Three sequences were scheduled and followed by a tumor assessment workup including a CT scan (interpreted by a PSM expert radiologist), a markers dosage, and a pathologic response analysis of iterative biopsies performed during the PIPAC procedures. If any PIPAC-associated laparoscopic exploration showed a resectable disease, PIPAC was not performed, and the patient was scheduled for CRS-HIPEC. Any therapeutic strategy decision was made in a multidisciplinary team (MDT) meeting including surgeons, medical oncologists, pathologists, and radiologists specialized in PSM.

Adverse events (AEs) were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 per PIPAC and per patient up to 90 days after the last PIPAC.

Technical Aspects

The PIPAC surgical technique was performed with the patient under general anesthesia. A balloon trocar (Applied Medical, Paris, France) was placed in the midline according to the open laparoscopic technique, and a capnoperitoneum of 12 mmHg at 37 °C was applied. Another balloon trocar was placed in the midline under visualization. Explorative laparoscopy was performed, and the Peritoneal Carcinomatosis Index (PCI) was determined.[33]

Systematic biopsies of parietal DMPM lesions were performed. Ascites were aspirated, quantified, and sent for peritoneal cytology. A nebulizer (CAPNOPEN; Reger Medizintechnik, GmbH, Villingendorf, Germany) then was connected to a high-pressure injector and positioned within one of the trocars.

The checklist containing all safety aspects was systematically double-checked before administration of cytotoxic agents. A pressurized aerosol containing drugs then was applied, and the system was kept in steady state for 30 min. Next, the capnoperitoneum was exhausted in a closed evacuation system. The trocars were removed, and anti-adhesive gel was applied before standard closure. The drugs administered were cisplatin (7.5 mg/m^2 of body surface in 150 mL of NaCl 0.9%), immediately followed by doxorubicin (1.5 mg/m^2 in 50 mL of NaCl 0.9%). After the results of a phase 1 study in May 2018, doses were increased to 10.5 mg/m^2 of cisplatin and 2.1 mg/m^2 of doxorubicin.[34] The institutional policy was systematically to keep patients hospitalized 2 days after PIPAC.

For each PIPAC procedure, a peritoneal cytologic analysis was performed after centrifugation within the same day and rated as positive or negative (no visible neoplastic cells). The pathologic response was assessed by the percentage of necrosis and viable cancer cells and by the peritoneal regression grading score (PRGS), as described previously.[35] When the patients had received at least three PIPAC procedures, an additional composite score (the combined progression index [CPI]), which combined PRGS and peritoneal cytology evolution from PIPAC 1 to PIPAC 3, was rated as a surrogate of tumor response with a prognostic impact.[36]

When patients were deemed to have resectable disease, CRS was performed as previously described with a dedicated multidisciplinary team.[16] After laparotomy, the PCI was recorded. Then, CRS was performed with the goal of achieving complete resection of the macroscopic disease by a combination of peritonectomies and organ resections, as described by Sugarbaker.[37] The radicality of the CRS was defined according to the completeness of cytoreduction (CC) score according to the size of the larger residual nodule as follows: CC-0 (no macroscopic residual tumor), CC-1 (residual tumor <2.5 mm), CC-2 (residual tumor 2.5 to 25 mm), and CC-3 (residual tumor >25 mm).[33] After CRS, HIPEC was performed by circulating a heated solvent infused with chemotherapeutic agents throughout the abdomen using the closed technique. The protocol for DMPM patients was a combination of cisplatin 50 mg/m^2 and doxorubicin 15 mg/m^2 at 42 °C for 90 min.

Statistical Analysis

Descriptive results are presented as number (%) for qualitative variables and as median (interquartile range [IQR] minimum–maximum) for quantitative variables.

Overall survival (OS) was defined as the time from the date of the first PIPAC procedure to the date of death. Progression-free survival (PFS) was calculated from the date of first PIPAC procedure to progression, relapse, or death, whichever occurred first. If progression, relapse, or death did not occur before the cutoff date, data were censored at the time of the last valid assessment.

Survival distributions were estimated by the Kaplan-Meier method. Differences in survival time were tested using a standard log-rank test, and univariate hazard ratios were estimated in Cox models. The association between

binary variables and response to PIPAC was tested using Fisher's exact test.

RESULTS

Study Population

From January 2016 to May 2020, 26 DMPM patients received at least one PIPAC procedure and were included in this analysis, as shown by the study flowchart in Fig. 1. After a previous complete CRS, 6 of the patients had recurrent diseases, whereas 20 of the patients had upfront borderline or non-resectable diseases.

Table 1 summarizes the patient characteristics. The median age was 64 years (IQR 56–69 years). Most DMPMs (92%) were of the epithelioid subtype. The median Ki-67 expression was 7.5% (IQR 3.0–15.0%). A loss of BAP1 expression was found in 12 tumors (46%), and half of the tumors had a nuclear grade of 2.

At the time of the first PIPAC procedure, 18 patients (82%) had a PS of 0 or 1, and 22 (85%) had at least one clinical symptom of their disease, including 14 patients (54%) with perceptible ascites. Nine patients had previously received one to three systemic chemotherapy lines before the first PIPAC procedure.

PIPAC Treatment

Table 2 presents that PIPAC outcomes. All but one of the patients received systemic chemotherapy alternating with PIPAC. The one patient had previously received three lines of chemotherapy elsewhere, and then only one PIPAC procedure. Overall, 79 PIPAC procedures were performed, leading to a median of 3 PIPAC (IQR 1–3; range 1–15) procedures per patient, with half of the patients receiving three PIPAC procedures or more.

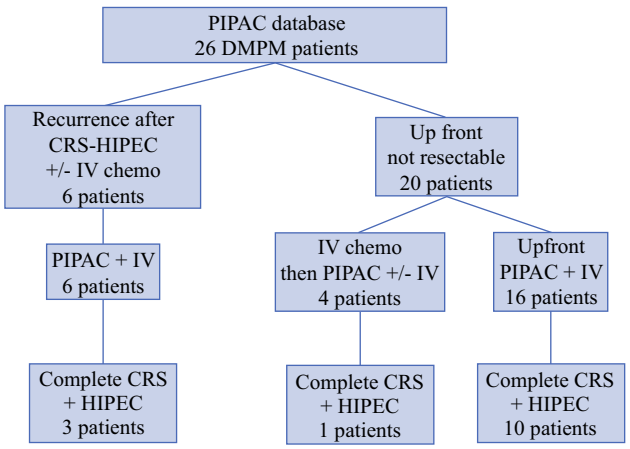

FIG. 1 Study flowchart. PIPAC, pressurized intraperitoneal aerosol chemotherapy; DMPM, diffuse malignant peritoneal mesothelioma; CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy, IV, intravenous chemotherapy

TABLE 1 Patients characteristics

	Overall population (n = 26) n (%)	No previous CRS (n = 20) n (%)
Median age: years (IQR)	64 (56–69)	66 (59–69)
Median BMI: kg/m^2 (IQR)	23.1 (21.3–26.3)	23.4 (21.7–26.5)
Sex		
Male	14 (54)	13 (65)
Female	12 (46)	7 (35)
Ethnicity		
Caucasian	25 (96)	19 (95)
Black	1 (4)	1 (5)
ECOG PS score	(NA = 4)	(NA = 3)
0	5 (23)	3 (18)
1	13 (59)	11 (65)
2	4 (18)	3 (18)
Pathologic subtype		
Epithelioid	24 (92)	19 (95)
Biphasic	2 (8)	1 (5)
Nuclear grade	(NA = 6)	(NA = 5)
1	7 (27)	3 (15)
2	13 (50)	12 (60)
BAP1	(NA = 5)	(NA = 4)
Lost	12 (46)	8 (40)
Present	9 (35)	8 (40)
Median Ki-67: % (IQR)	(NA = 6)	(NA = 5)
	7.5 (3.0–15.0)	11 (7.5–17.5)
Previous cytoreduction	6 (24)	–
Previous chemotherapy		
One line	5 (19)	2 (10)
Two lines	3 (12)	2 (10)
Three lines	1 (4)	0
Previous IV platinum	9 (35)	4 (20)
Previous IV pemetrexed	8 (31)	4 (20)
Symptomatic patients	22 (85)	17 (85)
Clinical presentation		
Abdominal pain	11 (42)	9 (40)
Ascites	14 (54)	11 (55)
Dysphagia	2 (8)	1 (5)
Obstructive symptoms	5 (19)	3 (15)
Nausea	2 (8)	1 (5)
Median CA125: IU/mL	(NA = 2)	(NA = 4)
(IQR)	30.0 (19.0–38.0)	30.6 (20.7–30.8)

CRS, cytoreductive surgery; IQR, Interquartile range; BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; NA, not applicable; IV, intravenous

TABLE 2 Treatment by PIPAC characteristics

	Overall population (n = 26) n (%)	No previous CRS (n = 20) n (%)
Alternation with IV chemotherapy		
No	1 (4)	1 (5)
Platinum + pemetrexed	19 (73)	16 (80)
Platinum alone	1 (4)	0
Pemetrexed alone	2 (8)	1 (5)
Gemcitabine	3 (12)	2 (10)
No. of PIPAC		
Total	79	66
Median no. per patient[a]	3 (1–3; 1–15)	2.5 (1–3.5; 1–15)
No. of patients who accomplished n PIPAC		
1	9 (34)	7 (35)
2	4 (15)	3 (15)
3	8 (31)	5 (25)
> 3	5 (19)	5 (25)
Complications		
Total	10 (13)	9 (14)
Severe (grades 3–4)	2 (3)	2 (3)
Reoperation	1 (1)	1 (2)
Parietal	1 (1)	1 (2)

PIPAC, pressurized intraperitoneal aerosol chemotherapy; CRS, cytoreductive surgery; IV, intravenous
[a]IQR (min–max)

No PIPAC-related death was recorded. Eight patients (31%) experienced 10 PIPAC-related AEs (13% of the PIPAC procedures). The vast majority had low-grade AEs, with one patient having a parietal abscess treated medically. Two severe AEs were reported, consisting of digestive perforations linked to tumor shrinkage diagnosed 19 and 27 days after the second PIPAC procedure. The one AE gave rise to an abscess, medically treated in an altered patient with a PCI of 39, whereas the other AE required a re-intervention with creation of a stoma. With these 2 patients excepted, PIPAC was interrupted so CRS-HIPEC could be performed for 14 patients (54%) because of a small intestine loop injury efficiently fixed during the PIPAC procedure for 1 patient (4%), because an abdominal cavity was no longer accessible in 3 patients (12%) (at the second PIPAC procedure for the 1 patient and at the third PIPAC procedure for the 2 remaining patients), and because of disease progression or death for 5 patients (19%).

CRS and HIPEC

Overall, 14 patients (54%) were ultimately treated via CRS-HIPEC with curative intent, including 11 (55%) of the 20 patients with non-resectable disease at diagnosis. Only one of these patients treated surgically finally had unresectable disease due to an infiltration of the mesentery root undetected during laparoscopy or CT scan.

Efficacy Outcomes

The main efficacy outcomes are summarized in Table 3. Improvement of baseline symptoms was reported for 7 (32%) of the 22 patients who were symptomatic at the time of the first PIPAC procedure, whereas a response of ascites was noted in 6 (46%) of 14 patients.

The mean PCI evolved from 27 (range 20–34) before PIPAC to 25 (range 20–39) after two or three PIPAC sequences (p = 0.21, Wilcoxon signed-rank test) (Fig. 2). Overall, 15% of the patients showed a response on imaging after three PIPAC procedures, whereas pathologic examinations showed a significant decrease in the PRGS, from 3.0 to 2.0 (p = 0.014), for the 14 patients who had at least three PIPAC procedures. The serum tumor marker remained low.

The survival analyses are presented in Fig. 3. After a median follow-up period of 29.6 months (95% CI 17.6–not reached [NR]), 17 patients presented with a progression or death leading to a median PFS of 12 months (95% CI 11.1–NR) and a 1-year PFS of 48.3% (95% CI 31.4–74.5%). The

TABLE 3 Short-term oncologic outcomes

Outcomes	Overall population (n = 26) n (%)	No previous CRS (n = 20) n (%)
Subsequent cytoreduction: CC-score	14 (54)	11 (55)
CC-0	4 (15)	4 (20)
CC-1	9 (35)	6 (30)
CC-2/3	1 (4)	1 (5)
PRGS[a]		
(n = 14–10 with ≥ 3 PIPAC)		
Before PIPAC (NA = 0)	3.0 (2.2–4.0)	3.5 (2.2–4.0)
After 3 PIPAC (NA = 0)	2.0 (2.0–3.0)	2.0 (2.0–3.0)
p Value (Wilcoxon signed-rank test)	0.014	0.065
CPI[a]	(NA = 6)	(NA = 5)
2	18 (69)	14 (70)
3	2 (8)	1 (5)
Response on symptoms (n = 22–17 with symptoms, NA = 1–0)	7 (32)	5 (29)
Response on ascites (n = 14–9 with ascites, NA = 1–0)	6 (46)	5 (56)
Partial or complete response on imaging after 3 PIPAC	(NA = 10)	(NA = 8)
	4 (15)	4 (20)
CA125 after 2 or 3 PIPAC[a]	(NA = 16)	(NA=12)
	20.9 (14.9–38.0)	20.9 (16.4–36.0)
PCI[b]		
Before PIPAC (NA = 1)	27 (20–34)	28 (21–37)
After 2 or 3 PIPAC (NA = 15)	25 (20–39)	27 (22–32)
p Value (Wilcoxon signed-rank test)	0.21	

CRS, cytoreductive surgery; PRGS, peritoneal regression grading score; ; PIPAC, pressurized intraperitoneal aerosol chemotherapy; NA, not applicable; CIP, combined progression index; PCI, Peritoneal Carcinomatosis Index

[a]Median (IQR)

[b]Mean (IQR)

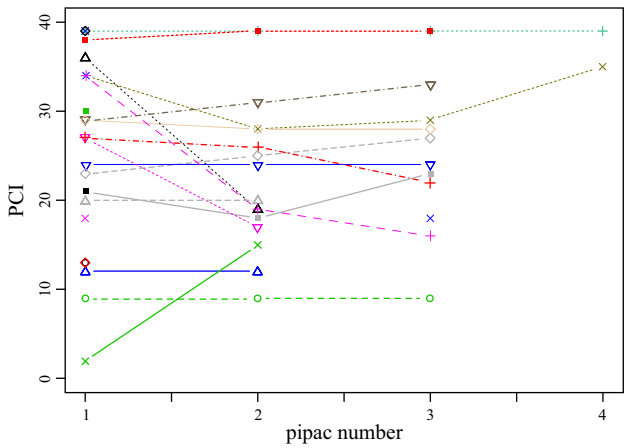

FIG. 2 Peritoneal Carcinomatosis Index (PCI) evolution along pressurized intraperitoneal aerosol chemotherapy (PIPAC).

median OS was evaluated at 17.1 months (95% CI 13.6–NR), with a 1-year OS at 75.8% (95% CI 60.7–94.7%). The patients amenable to CRS-HIPEC exhibited significantly better oncologic outcomes, with a median PFS of 33.5 months (95% CI 12.0–NA) versus 7.4 months (95% CI 3.3–NA) for those without resection (HR 0.18; 95% CI 0.06–0.755; $p < 0.001$).

No correlation was observed between survival and the response to treatment on imaging, the combined score (p = 0.23, Fisher's exact test), the nuclear grade (p = 1.0), the PRGS (p = 1.0), or the CPI (p = 0.22).

In the subgroup of 20 patients with a unresectable DMPM at diagnosis, the long-term oncologic outcomes were consistent, with a median PFS of 12 months (95% CI 7.8–NR), a 1-year PFS of 45.6% (95% CI 27.1–77.1%), a median OS of 17.1 months (95% CI 12.0–NR), and a 1-year OS of 70% (95% CI 52.0–93.2%).

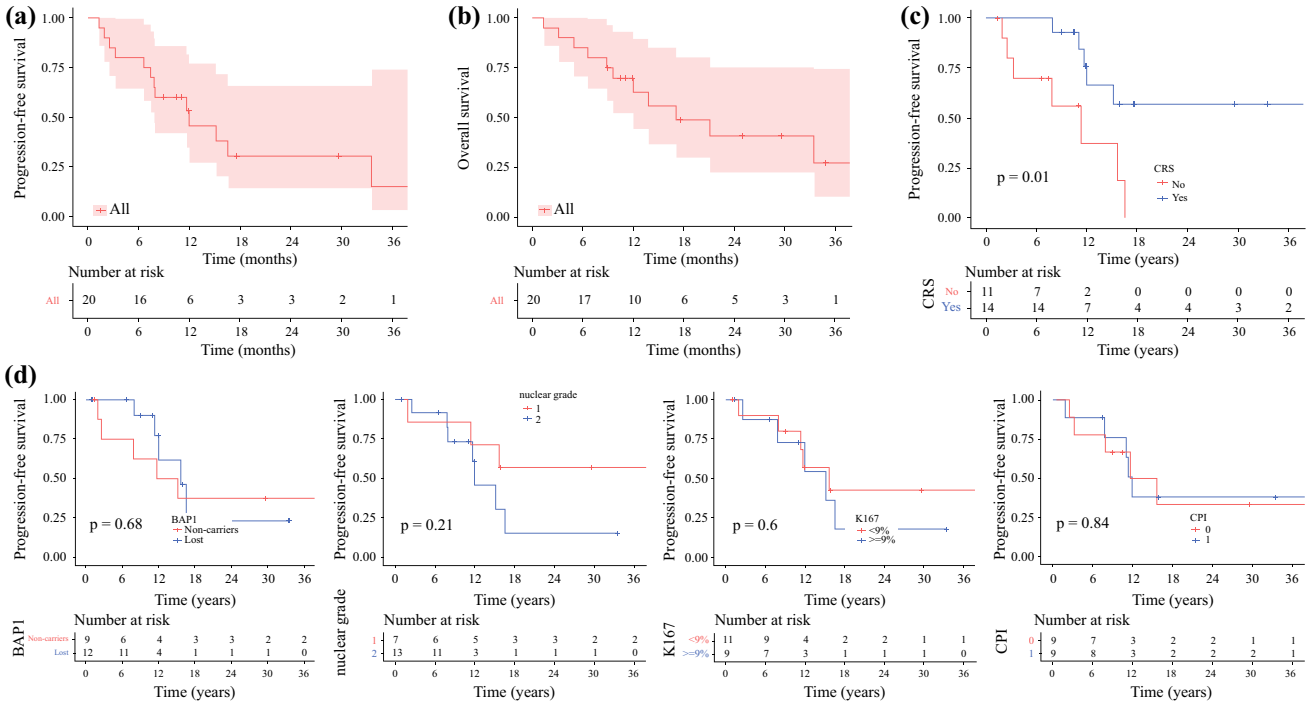

FIG. 3 Long-term oncologic outcomes. Oncologic outcomes of patients not resectable upfront and treated with pressurized intraperitoneal aerosol chemotherapy (PIPAC) plus systemic chemotherapy. **A** Progression-free survival. **B** Overall survival. **C** Progression-free survival of patients ultimately treated with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) after PIPAC and systemic chemotherapy vs patients not treated with resection according to BAP1 expression (conserved vs lost), nuclear grade (1 vs 2), Ki67 (<9% vs >9%), and combined peritoneal index (0 vs 1).

DISCUSSION

In this monocentric series of patients with non-resectable DMPM, PIPAC combined with systemic chemotherapy allowed a secondary complete CRS for half of the patients, leading to a clear survival advantage with a good safety profile.

Malignant peritoneal mesothelioma is an aggressive and chemo-resistant disease whose prognosis has been transformed by the development of the comprehensive CRS described by Sugarbaker.[3,5,21,33,37] Complete CRS currently is considered the treatment strategy associated with the best long-term outcomes.[5,15,16] In parallel, the development of the intraperitoneal drug delivery as part of a multimodal approach has been proposed to improve prognosis.[38] In this last quarter of a century, several independent observational series have reported consistent results of CRS-HIPEC, sometimes followed by early postoperative intraperitoneal chemotherapy, with a median OS of about 50 months.[3,5,15,16] During the same period, patients treated with systemic chemotherapy exhibited limited improvement, from 5 to 11 months in large retrospective series and up to 15 months in smaller series.[7,8,14]

Unfortunately, at diagnosis, less than half of patients fulfil the tied selection criteria for CRS.[7,8] Miura et al.[7] analyzed the evolution of the therapeutic strategies proposed to peritoneal mesothelioma patients through the Surveillance, Epidemiology, and End Results (SEER) cancer registry, with 1591 patients included during a 40-year period. Overall, 62% of the patients did not undergo any kind of surgery, and the median OS for the entire cohort was 9 months.[7] Interestingly, the proportion of patients without surgery remained stable, at about 56% between 1991 and 1995 and between 2006 and 2010, whereas the proportion of mesothelioma patients treated with radical/debulking surgery slightly decreased, from 30% to 25%.[7] Bijelic et al.[8] prolonged that study through the National Cancer Database during the 2003–2014 period, including 2062 patients. Similarly, 51% of the patients did not undergo surgery, and only 34% underwent a radical treatment.[8] Once again, the rate of patients radically treated did not change during the study period.[8] Numerous biases should balance these analyses, but they highlight the necessity for neoadjuvant strategies aimed at downstaging the peritoneal tumor load and increasing the proportion of DMPM patients amenable to CRS.

Tailoring such treatment options is rendered difficult by the scarcity of data. Data regarding systemic chemotherapy used in DMPM chemo-naïve patients, usually combining pemetrexed and platinum, are heterogeneous. Response rates of 46% to 83% have been reported, but the potential secondary resectability have not been described.[14,39] As a result, the related conversion rate remains unclear. Le Roy et al.[11] proposed a bi-directional multi-drug protocol, with intraperitoneal pemetrexed or oxaliplatin and intravenous cisplatin or gemcitabine. The authors reported a conversion rate for completion of CRS at 50% of patients who reach a DFS in 25.5 months. Interestingly, our results were closed, with resection completed for 54% of patients after neoadjuvant cisplatin-doxorubicin PIPAC and systemic chemotherapy, leading to a median DFS of 33.5 months. That result could be correlated with the significant pathologic response according to the PRGS decrease in patients with at least three PIPAC procedures. This reinforces the idea that locoregional treatments are a valid option for DMPM not amenable to upfront CRS.

The use of PIPAC as neoadjuvant treatment has been proposed for different types of cancer, with conversion rates varying from 5 to 14%.[28,40] Giger-Pabst et al.[29] first reported a consistent experience of PIPAC for epithelioid mesothelioma patients. They reported 79 procedures performed for 29 patients, including 5 patients treated for pleural mesothelioma extended to the abdominal cavity and 3 patients who failed to get one PIPAC procedure for an abdominal access failure unsolvable by adhesiolysis.[29] Of the 24 peritoneal patients, 63% had previous CRS, and 41% had three PIPAC procedures or more. A pathologic tumor regression was described for 52% of the patients, and the median OS was estimated to be 26.6 months (95% CI 9.5–43.7 months), which was associated with a significant quality-of-life improvement, specifically for gastrointestinal toxicity-related items.[29] No patients had secondary CRS, but it is unclear whether that option was proposed to the patients, rendering any comparison difficult. Indeed, the treatment strategy differed from ours because 76% of the patients had PIPAC without systemic chemotherapy.

Interestingly, in our series, whereas a pathologic response was noted, the good conversion rate did not reflect a significant PCI decrease or radiologic response, questioning the evaluation of the resectability. The combined resectability and operability assessment is complex for PSM, particularly for DMPM patients. Because CC-1 resection offers good survival outcomes and because large retrospective analyses tend to show a deleterious effect of neoadjuvant systemic chemotherapy on long-term oncologic results, we always aim for an upfront CRS where possible. Consequently, the surgical quote resulting from the initial workup, including a systematic staging laparoscopy, allows consideration of extensive CRS including partial gastrectomy, pancreatectomy, and extensive intestine resections.

Objectively, the advent of bi-directional neoadjuvant treatment strategies puts the aforementioned paradigm into perspective. Previously, certain boundaries of resectability would have been pushed back to favor upfront CRS over neoadjuvant systemic chemotherapy, whereas the availability of bi-directional strategies currently makes it logical to postpone CRS when it is borderline and at very high risk of severe complications. The disadvantage of this development is that it makes comparison of outcomes difficult, especially because data on the conversion rate of the standard treatment by systemic chemotherapy remain unclear. However, obtaining a locoregional and systemic control makes it possible to ensure the absence of progression and allows prehabilitation of the patient, which tends to decrease the rate of postoperative complications. Moreover, the relationship between PCI and resectability is not linear. Sometimes, a two-point decrease in PCI translates into a less extensive digestive resection. This could be particularly true for the small bowel whose involvement is decisive in determining resectability and which is one of the organs that benefits most from exposure to aerosolized chemotherapy.

In a comparison of treatment options for potentially palliative patients, the morbidity assessment is of primary importance. In the Giger-Pabst et al.[29] series, the procedure-related morbidity rate was 43%. The AEs were mostly of low grade, including grade 2 transient kidney injury observed after 8% of interventions. Three patients experienced a severe AE. One of the patients had a grade 3 subcutaneous chemotherapy extravasation at the trocar-entry site, managed medically. The remaining two patients had grade 4 small bowel anastomotic leakage after undergoing incomplete CRS and simultaneous PIPAC, managed surgically. One patient with extensive and bulky tumors died of a typical tumor lysis syndrome after the second PIPAC procedure.[29] These reports echo our two post-PIPAC digestive perforations attributed to tumor shrinkage. Thanks to the international sharing of experience, we currently know that PIPAC should not be performed at the same time as any digestive anastomosis.[41] Similarly, the two complications we observed happened in our early experience and were related to the lack of peritoneal space to guarantee the security of the aerosolization. As a comparison, Le Roy et al.[11] reported severe AEs for four patients (20%), mostly resulting from intraabdominal hemorrhage.

Our study had several limitations. The main limitation was due to the retrospective and non-comparative nature of the analysis, with potential bias in the selection of patients for this strategy. As highlighted earlier, considering the

suggestion from concordant reports that preoperative systemic chemotherapy could be deleterious for patients with resectable DMPM, our center's treatment policy is to perform upfront CRS-HIPEC when possible.[9,16,42]

Another drawback was the impossibility of independently evaluating the efficacy of systemic chemotherapy and PIPAC to convert the disease resectability of these patients. The ongoing prospective randomized MESOTIP trial will help to clarify the results of this neoadjuvant strategy.[12]

In conclusion, the results suggest that multimodal treatments combining surgery, intraperitoneal chemotherapy, and systemic chemotherapy, performed in expert centers, is a promising option for patients with initially non-resectable DMPM.

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