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La moitié des décès après chirurgie de cytoréduction et chimiothérapie hyperthermique intrapéritonéale pourraient être évités : Analyse nationale française des causes profondes de mortalité sur 5562 patients

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Abréviations

En Français	
Abréviation	*Signification*
CCR	Chirurgie de cytoréduction
CHIP	Chimiothérapie hyperthermie intrapéritonéale
CP	Carcinose péritonéale
MM	Morbidité majeure
MPO	Mortalité post-opératoire
RMM	Réunion de morbidité et mortalité

En Anglais	
Abbreviation	*Signification*
ASA	American Society of Anesthesiologists
CC	Completeness of cytoreduction
CRS	Cytoreductive surgery
ECOG	Eastern Cooperative Oncology Group
FTR	Failure-to-rescue
HIPEC	Hyperthermic intraperitoneal chemotherapy
NASA	National Aeronautics and Space Administration
PCI	Peritoneal cancer index
PS	Performance status
PSM	Peritoneal surface malignancies
RCA	Root-Cause Analysis
RCCF	Root cause contributing factor

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Résumé

Introduction : La chirurgie de cytoréduction (CCR) associée à la chimiothérapie hyperthermique intrapéritonéale (CHIP) est une stratégie thérapeutique efficace des tumeurs malignes péritonéales mais qui peut entraîner une mortalité postopératoire significative. L'analyse des causes profondes de mortalité (Root-Cause Analysis, RCA) est une méthode rétrospective permettant d'analyser les événements intercurrents.

Matériels et méthodes : L'ensemble des patients de 22 centres français, opérés par CCR+CHIP entre janvier 2009 et décembre 2018, décédés à l'hôpital en post-opératoire ont été inclus. Les données péri-opératoires de 101 patients ont été collectées de manière conjointe par un chirurgien sénior de chaque centre et un unique chirurgien junior. Trois experts indépendants ont analysé chacun des dossiers afin de définir les décès comme évitable (Prev. group) ou non (Non-Prev. group). Les décès évitables étaient classés sur un diagramme « cause-effet ».

Résultats : Sur les 5562 procédures, 101 patients sont décédés en intra-hospitalier (1,8%). Parmi eux, 54 patients (53%) ont été classés dans le groupe évitable et 47 (47%) dans le groupe non évitable. Vingt-six patients étaient âgés de 70 ans et plus, 22% avaient un ASA score de 3. Un score OMS 1-2 était plus fréquent dans le groupe évitable. L'étiologie de la carcinose était colorectale dans 68% des cas. Le score PCI moyen était plus élevé dans le groupe évitable (16 [9-22.8] vs 11 [5-17], p=0.023), la cytoréduction était incomplète (CC1-2) dans 29% et 24% des cas, respectivement. Les causes de décès évitables étaient classées comme telles : (i) pré-opératoire pour mauvaise indication (59%), (ii) per-opératoire (30%) et (iii) post-opératoire (31%). Des causes multiples étaient objectivées dans 20% des décès.

Conclusion : La moitié des décès après CCR+CHIP pourraient être évités par une sélection pré- et per-opératoire drastique des indications en accord avec les recommandations ainsi qu'une meilleure gestion des complications post-opératoires.

Introduction

La chirurgie de cytoréduction (CCR), qui combine des péritonectomies à des résections d'organes et ayant pour but la résection macroscopique complète de la carcinose péritonéale (CP) (1), améliore le pronostic des patients, lorsqu'elle est associée à une chimiothérapie hyperthermique intrapéritonéale (CHIP) (2-8). Néanmoins, la CCR+CHIP est associée à une morbidité et une mortalité post-opératoires (MPO) significatives (9-10) pouvant compromettre les résultats à long terme (11-12). Récemment, une étude nationale menée sur 10 ans et s'intéressant aux pratiques françaises, a rapporté une mortalité post-opératoire après CCR+CHIP à 90 jours de 2,6%, stable et contrôlée dans le temps (13). Les facteurs prédictifs d'une MPO accrue comprenaient un âge >70 ans, un indice de comorbidité d'Elixhauser ≥8, la survenue d'une morbidité majeure (MM) selon la classification de Clavien-Dindo (14), et le fait d'être opéré dans un centre dit à faible volume, c'est-à-dire réalisant moins de 45 procédures/an. Malgré des procédures chirurgicales plus longues et une morbidité majeure augmentée, les centres à haut volume étaient associés à des taux de *failure-to-rescue* (défini comme le décès des patients ayant au moins une complication majeure dans les 90 jours suivant l'intervention chirurgicale, FTR) plus faibles (3,1 % contre 6,3 %), ce qui souligne la nécessité de centraliser les patients dans des centres à haut volume afin d'améliorer les résultats à court terme. D'autres pays ont rapporté des résultats similaires (15-17) et des efforts significatifs ont été faits pour mieux sélectionner les patients éligibles à ces procédures et standardiser les pratiques péri-opératoires (18).

Dans une volonté constante d'améliorer les prises en charge péri-opératoires, les revues de morbidité et de mortalité (RMM) sont exigées par la Haute Autorité de Santé française. Le but étant d'analyser rétrospectivement les cas ayant présenté des

complications majeures ou un décès, et ainsi de mettre en place et suivre l'effet de nouvelles pratiques avec pour objectif l'amélioration de la qualité des soins et de la sécurité des patients. Basée sur l'analyse d'événements intercurrents, l'analyse des causes profondes ou *Root-Cause Analysis (RCA*) ; initialement mise au point par la *National Aeronautics and Space Administration (NASA)* américaine, a également été utilisée pour l'étude des causes de mortalité en chirurgies pancréatiques (19) et hépatiques (20). Ces études ont révélé une gestion per-opératoire inadéquate (12 % et 33 % respectivement) et des erreurs techniques (21 % et 24 % respectivement).
L'objectif de notre étude est de réaliser l'analyse des causes profondes de la mortalité (RCA) d'une cohorte multicentrique nationale française de patients décédés en intra-hospitalier dans les suites d'une chirurgie combinant CCR et CHIP, afin de mieux comprendre les causes de la mortalité post-opératoire.

Matériels et méthodes

1. Study population

The BIG-RENAPE multicenter registry was set up in 2015 and represented a collaborative effort of main peritoneal surface malignancies (PSM) French centers to prospectively collect data (21). Participant centers were asked to provide data including preoperative, intraoperative, and postoperative variables for each in-hospital deceased patient. Data were collected from 5562 patients with PSM who underwent cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) from January 1, 2009, to December 31, 2018.

2. The Root-Cause Analysis

Original medical records for every patient included in the study were analyzed in each center by a local senior surgeon specialized in CRS+HIPEC jointly with a single surgical fellow (Constance Houlzé-Laroye). Perioperative data were subdivided into 3 categories:

- Preoperative data included patients' medical and surgical history, American Society of Anesthesiologists (ASA) scores, performance status (PS), comorbidities, and neoadjuvant treatments.

- Intraoperative data included the date and type of surgical procedure performed (with mean Sugarbaker's peritoneal cancer index – PCI (22)), completeness of cytoreduction score (CC0-3 (23)), number of resected organs, digestive anastomosis, type of HIPEC regimen, blood loss, any incidents and their impact on the surgical procedure and the operating time.

- Postoperative data included the type of major morbidity (Grade III-IV) according to Clavien-Dindo classification (24), the number of reoperations, and the cause of death.

After review of data consistency and accuracy on a case-by-case basis in each center, a synopsis was performed and anonymously presented to independent CRS+HIPEC senior surgeons qualified as experts. These experts were chosen among high-volume centers performing more than 30-45 CRS+HIPEC per year, and were divided into 3 groups of 3 experts each. After evaluating the collected data from each patient, the expert panel identified the cause of death and classified it in preventable (PREV group) or not-preventable category (NON-PREV group).

Death was defined as preventable when a root cause contributing factor (RCCF) known to increase the risk of death, was identified (25). After identification, RCCFs

were classified within one of the three following categories: pre-, intra- and postoperative patients management, leading to a cause-and-effect diagram.

Inadequate management was defined in accordance with cancer management (26) and patient and perioperative care guidelines (27,28), as well as the recommendations from the French 10-years national practice (13). For colorectal, small bowel or gastric cancer, guidelines on disease extension (PCI) and quality of surgery (CC score) are well defined i.e.: CC0 score and PCI≤24 for colorectal (5,29) or small bowel cancer and <12 for gastric cancer (30).

Inadequate intraoperative management was consistently associated with more extensive and longer procedures, incomplete tumor resection, and unexpected technical incident and complications. Inadequate postoperative management was defined as delayed diagnosis or treatment of complications.

3. Statistical Analysis

Results were expressed as medians with first and third quartiles or proportions and percentages. Groups were compared using Wilcoxon and Chi-2 tests as appropriate. All P-values were determined by bilateral tests, and a P-value <0.05 was considered statistically significant. Analyses were performed by R statistical software (http://www.Rproject.org). A cause-and-effect diagram is shown in Fig. 1.

Résultats

1. Characteristics of patients and surgical procedures performed

A total of 5562 combined CRS+HIPEC procedures were performed between 2009 and 2018 in the 22 participating medical institutions. Among them, 101 patients (1.8%) died during their hospitalization, from which 54 deaths (53%) were classified by the

expert panel as preventable (PREV group). The patient male-to-female ratio was 1:1 with a median age of 64 years old (55 to 70) and an ASA score of 3 in 25.3%. Eastern Cooperative Oncology Group (ECOG) performance status of 1 or 2 (versus 0) was higher in PREV group with 57.9% vs. 22.6% in the NON-PREV group ($p<0.01$). Comorbidities included cardiovascular disease (43.6%), pulmonary disease (17.8%), diabetes mellitus (13.9%), psychiatric disease (9.9%), and obesity (8.9%) and were comparable between the two groups ($P>0.05$). The PSM arose from colorectal cancer (42.6%), primary peritoneal diseases [pseudomyxoma peritonei (24.8%), mesothelioma peritoneal (5.9%), peritoneal serous carcinoma (2.0%)], gastric cancer (12.9%), epithelial ovarian carcinoma (7.9%) or other origins (4.0%). Preoperative chemotherapy was administered in 76.3%, including 26.7% combined with Bevacizumab. Populations and surgeries characteristics are summarized in Table 1.

Patients in the PREV group had more extensive complications with higher mean PCI (16 (9 to 21.5) vs. 11 (5 to 19), $p=0.053$) and higher mean number of affected regions (8 (4 to 12) vs. 6 (2.5 to 9), $p=0.064$) compared with NON-PREV group. In addition, the PREV group had more extensive surgeries with a trend of higher mean number of resected organs (3 (3 to 4) vs. 3 (2 to 4), $p=0.096$), higher mean number of digestive anastomosis (1 (1 to 2) vs. 1 (1 to 1), $p=0.029$), and intra-operative transfusion (48.6% vs. 17.9%, $p=0.010$).

When investigating surgical reports, 3 important data were evaluated: the extent of the disease (PCI), the quality of the surgical resection (CC-score), and the duration of surgical procedures were occasionally missing. Combining the three criteria, the PREV group had more missing data compared with NON-PREV group (74.1% vs 42.6%, $p<0.01$).

TABLE 1. Characteristics of pre- and intraoperative variables.

	No. (%)			
Demographics characteristics	Total (n=101)	PREV group (n=54)	NON-PREV group (n=47)	p-value
Sex: Male / Female	55 (54.5) / 46 (45.5)	33 (61.1) /21 (38.9)	22 (46.8) / 25 (53.2)	0.15
Age				
Median, yrs	64 (55 to 70)	64 (54 to 70)	64 (56.5 to 69)	1
70 and more	18 (17.8)	13 (24.1)	5 (10.6)	0.078
ASA score §				
1	11 (13.9)	4 (9.3)	7 (19.4)	0.31
2	48 (60.8)	26 (60.5)	22 (61.1)	
3	20 (25.3)	13 (30.2)	7 (19.4)	
ECOG Performance Status §				
0	40 (58)	16 (42.1)	24 (77.4)	0.0085
1	21 (30.4)	17 (44.7)	4 (12.9)	
2	8 (11.6)	5 (13.2)	3 (9.7)	
Comorbidities				
Vascular disease	44 (43.6)	27 (50)	17 (36.2)	0.16
Pulmonary	18 (17.8)	11 (20.4)	7 (14.9)	0.47
Psychiatric disease	14 (13.9)	7 (13)	7 (14.9)	0.78
Diabetes	14 (13.9)	8 (14.8)	6 (12.8)	0.77
Obesity	9 (8.9)	5 (9.3)	4 (8.5)	0.9
Etiology of peritoneal disease				
Colorectal cancer	43 (42.6)	17 (31.5)	26 (55.3)	0.067
Pseudomyxoma peritonei	25 (24.8)	15 (27.8)	10 (21.3)	
Gastric cancer	13 (12.9)	7 (13)	6 (12.8)	
Ovarian cancer	8 (7.9)	6 (11.1)	2 (4.3)	
Peritoneal mesothelioma	6 (5.9)	5 (9.3)	1 (2.1)	
Peritoneal serous carcinoma	2 (2)	0 (0)	2 (4.3)	
Others	4 (4.0)	4 (7.4)	0 (0)	
Neoadjuvant chemotherapy §				
Yes	74 (76.3)	40 (75.5)	34 (77.3)	0.84
Including Bevacizumab	27 (26.7)	12 (22.2)	15 (31.9)	0.27
No	23 (23.7)	13 (24.5)	10 (22.7)	0.84
PCI				
Mean (SD)	13 (6.5 to 20)	16 (9 to 21.5)	11 (5 to 19)	0.053
Unknown status	10	8	2	
Regions affected (/13) (Mean, SD)	7 (3 to 12)	8 (4 to 12)	6 (2.5 to 9)	0.064
CC score				
0	66 (73.3)	34 (70.8)	32 (76.2)	0.26
1	21 (23.3)	11 (22.9)	10 (23.8)	
2	3 (3.3)	3 (6.2)	0 (0)	
Unknown status	11	6	5	
HIPEC used				
Monochemotherapy	72 (71.3)	37 (68.5)	35 (74.5)	0.51
Drug combination	20 (19.8)	11 (20.4)	9 (19.1)	0.88
Oxaliplatin ± Irinotecan	48 (47.5)	22 (40.7)	26 (55.3)	0.14
MMC ± CDDP	44 (43.6)	26 (48.1)	18 (38.3)	0.32
Others	9 (8.9)	6 (11.1)	3 (6.4)	0.41
Resected organs: Mean (SD)	3 (2.5 to 4)	3 (3 to 4)	3 (2 to 4)	0.096
Digestive anastomosis: Mean (SD)	1 (1 to 2)	1 (1 to 2)	1 (1 to 1)	0.029
Operative time (min)				
Mean (SD)	540 (495 to 600)	570 (510 to 600)	540 (490 to 600)	0.36
Unknown status	53 (52.5)	37 (68.5)	16 (34)	<0.001
Intra-operative transfusion				
Yes	23 (35.4)	18 (48.6)	5 (17.9)	0.01
No	42 (64.6)	19 (51.4)	23 (82.1)	
Unknown status (PCI, CC score, operative time)	60 (59.4)	40 (74.1)	20 (42.6)	0.0013

Abbreviations: ASA, American Society of Anesthesiologists; PCI, Peritoneal Cancer Index; CC, complete cytoreduction; HIPEC, hyperthermic intraperitoneal chemotherapy; MMC, mitomycin; CDDP, cisplatin ECOG Performance status, Eastern Cooperative Oncology Group Performance Status, SD, standard deviation. § Percentages are given according to No. of patients per line after exclusion of patients with potential missing data.

2. Compliance with guidelines

The evaluation of guidelines compliance was challenging due to the heterogeneity of PSM presentation and etiology. We investigated 59 patients with colorectal, small bowel or gastric cancer for which guidelines on disease extension (PCI) and quality of surgery (CC score) are well defined. Nine-teen CRS+HIPEC (32.2%) from various PSM origins [100% of small bowel (n=3), 38% for gastric cancer (n=5) and 28% of colorectal cancer (n=12)] did not follow the guidelines.

3. Post-operative complications before death

All patients experienced complications before death, including 75 of abdominal (74.3%) and 82 extra-abdominal complications (81.2%). The 3 major types of abdominal complications were comparable between the PREV and NON-PREV groups, including anastomotic leak (50% and 42.6%, respectively, p=0.58), abdominal hemorrhage (35.2% and 42.6%, respectively, p=0.58) and intra-abdominal collections (7.5% and 4.3%, respectively, p=0.84). Of all patients, a total of 70 (69.3%) had to be reoperated due to a complication, including 37 patients (36.6%) with repeated and frequent reoperations in the PREV group (42.6% vs 29.8%, p=.03). Post-operative complications characteristics are summarized in Table 2.

TABLE 2. Characteristics of post-operative complications

	No. (%)			
	Total (n=101)	PREV group (n=54)	NON-PREV group (n=47)	p-value
Abdominal post-operative complications	75 (74.3)	42 (77.8)	33 (70.2)	0.53
Anastomotic leak	47 (46.5)	27 (50)	20 (42.6)	0.58
Abdominal hemorrhage	39 (38.6)	19 (35.2)	20 (42.6)	0.58
Intra-abdominal collections	6 (5.9)	4 (7.4)	2 (4.3)	0.84
Other:	30 (29.7)	20 (37)	10 (21.3)	0.13
Pancreatic fistula	9 (8.9)	9 (16.7)	0 (0)	
Urological complications	9 (8.9)	6 (11.1)	3 (6.4)	
Digestive ischemia	6 (5.9)	2 (3.7)	4 (8.5)	
Post-operative ileus	4 (4)	1 (1.9)	3 (6.4)	
Liver failure	2 (2)	1 (1.9)	1 (2.1)	
Biliary fistula	2 (2)	2 (3.7)	0 (0)	
Evisceration	1 (.99)	1 (1.9)	0 (0)	
Extra-abdominal post-operative complications	82 (81.2)	41 (75.9)	41 (87.2)	0.23
Acute renal failure	43 (42.6)	22 (40.7)	21 (44.7)	0.84
Cardiovascular complications	31 (30.7)	16 (29.6)	15 (31.9)	0.97
Thrombophlebitis	8 (7.9)	4 (7.4)	4 (8.5)	
Acute Heart failure	8 (7.9)	4 (7.4)	4 (8.5)	
Arrhythmia	7 (6.9)	5 (9.3)	2 (4.3)	
Myocardial infarction	6 (5.9)	1 (1.9)	5 (10.6)	
Others	2 (2)	2 (3.7)	0 (0)	
Pulmonary complications	32 (31.7)	15 (27.8)	17 (36.2)	0.49
Acute pulmonary distress	11 (11)	7 (13)	4 (8.5)	
Inhalation	7 (6.9)	2 (3.7)	5 (10.6)	
Pneumonia	10 (10.9)	4 (7.4)	6 (12.8)	
Pleural effusion	5 (5)	3 (5.6)	2 (4.3)	
Pneumothorax	2 (2)	0 (0)	2 (4.3)	
Hematologic complications	16 (15.8)	8 (14.8)	8 (17)	0.98
Neurologic complications	9 (8.9)	6 (11.1)	3 (6.4)	0.65
Stroke	8 (7.9)	6 (11.1)	2 (4.3)	
Encephalopathy	1 (.99)	0 (0)	1 (2.1)	
Reoperation	70 (69.3)	36 (66.6)	34 (72.3)	0.69
Once	33 (32.7)	12 (22.2)	21 (44.7)	0.03
Twice and more	37 (36.6)	23 (42.6)	14 (29.8)	

4. Description of cause and timing of death

The cause of death was identified by the expert panel in 97% (n=98) of cases: abdominal causes in 61.4% including digestive sepsis (44.6%), tumor progression (9.9%), abdominal hemorrhage (6.9%) and extra-abdominal in 35.6% with pulmonary (14.9%), neurological (6.9%) and cardiovascular complications (5.9%). The causes of death are summarized in Table 3. No difference was found in the cause of death between the two groups except for the pulmonary complication that were more frequent in the NON-PREV group (25.5% vs 5.6%, p=0.005) compared with the PREV group. The mean delay of death (all causes combined) was 34 days (11 to 63) and 36 days (16.5 to 61.8) for abdominal causes with a trend of later death in PREV group

[(36.5 (19.2-68.8) vs. 23 (9.5-61.5), p=0.16) and (39 (23-69.2) vs 22.5 (8-57.8), p=0.034)].

TABLE 3. Characteristics of postoperative death

	No. (%)			
	Total (n=101)	PREV group (n=54)	NON-PREV group (n=47)	p-value
Cause of death				
Abdominal	62 (61.4)	36 (66.7)	26 (55.3)	0.24
Digestive sepsis	45 (44.6)	25 (46.3)	20 (42.6)	0.86
Tumor progression	10 (9.9)	7 (13)	3 (6.4)	0.27
Abdominal hemorrhage	7 (6.9)	4 (7.4)	3 (6.4)	0.84
Extra-abdominal	36 (35.6)	17 (31.5)	19 (40.4)	0.35
Pulmonary complications	15 (14.9)	3 (5.6)	12 (25.5)	0.0049
Neurologic complications	7 (6.9)	5 (9.3)	2 (4.3)	0.32
Sepsis	7 (6.9)	5 (9.3)	2 (4.3)	0.55
Cardiovascular complications	6 (5.9)	4 (7.4)	2 (4.3)	0.28
Hematologic complications	1 (1.0)	0 (0)	1 (2.1)	0.48
Unknown status	3 (3)	1 (1.9)	2 (4.3)	0.90
Delay of death (d) (Mean, SD)	34 [11 to 63]	36.5 [19.2-68.8]	23 [9.5-61.5]	0.16

Abbreviations: SD, standard deviation.
§ Percentages are given according to No. of patients per line after exclusion of patients with potential missing data.

5. Analysis of contributing factor and root cause in the preventable death group

Among all patients in the PREV group, preoperative management was found to be inadequate in 32 patients (59.3%) due to inappropriate indication (n=31) or preoperative work-up (n=1). The indication was judged inadequate for patients (n=22) or disease (n=9) related causes. Patients related causes were ASA score of 3 (n=13), ECOG Performance status of 2 (n=3), age (75±4.2 years; n=9), comorbidities with 3 severe cardiovascular disease, 2 cirrhosis, 5 severe lung disease (2 chronic obstructive pulmonary disease, 2 pleural mesothelioma, one recent pulmonary embolism) and major surgical background with multiple anterior CRS (n=3) or thoracic CRS for pleural mesothelioma (n=1). Disease related causes were too extensive carcinomatosis in gastric cancer (PCI=20.5±7.2; n=4) and mucinous colon cancer

(PCI=39; n=1), 2 days-delayed HIPEC after hemorrhagic or emergency CRS (n=3) and no neoadjuvant chemotherapy in gastric carcinomatosis (n=1).

Inadequate intraoperative management was identified in 16 patients (29.6%). Seven patients received inadequate procedure with too extended and unplanned (n=5) or hemorrhagic (n=2) procedures. In six cases, a technical error related to digestive leak or sepsis was found. In three patients, an untrained anesthetic team was responsible for poor hemodynamic management with 2 cardiac arrests during surgery and one early anastomosis leak.

Inadequate postoperative management was found in 17 patients (31.5%) with suboptimal treatment of complications in 8 patients (14.8%), delayed treatment in 6 patients (11.1%), and delayed diagnostic in 3 patients (5.6%).

Pre-, intra- and postoperative contributing factors and RCA are described in a cause-and-effect diagram (Figure 1) and patients characteristics (Table 4).

FIGURE 1. Cause-and-effect diagram: Each branch of the fishbone represents pre- (n=32), intra- (n=16), and postoperative (n=17) management procedures (categories). Multifactorial cause of death were found in 11 patients (20%). Each of these categories has subcategories for which the cause is preventable (root causes).

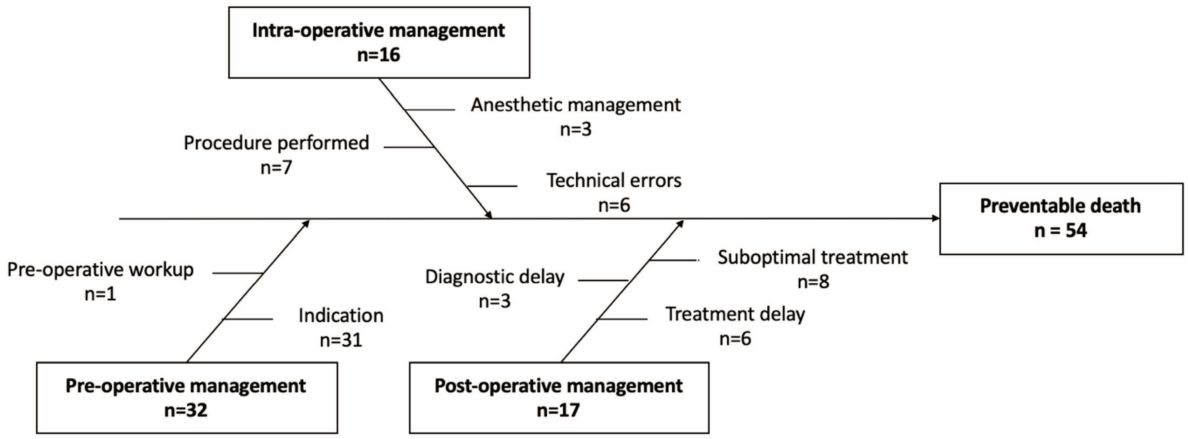

TABLE 4. Characteristics of root cause contributing factors (RCCF) in the 54 patients of PREV-group.

PREOPERATIVE MANAGEMENT	**32 (59.3%)**
Inadequate indication	**31 (57.4%)**
Related to patient characteristics	*22 (40.7%)*
ASA 3	13 (24.1%)
ECOG Performance Status of 2	3 (5.6%)
Age	9 (16.7%)
Major comorbidities	10 (18.5%)
Major history of surgery	4 (7.4%)
Related to disease characteristics	*9 (16.7%)*
Too extensive PCI score	5 (9.3%)
Delayed HIPEC 48h after CRS	3 (5.6%)
No chemotherapy before CRS for gastric cancer	1 (1.9%)
Inadequate preoperative work-up	**1 (1.9%)**
INTRAOPERATIVE MANAGEMENT	**16 (29.6%)**
Inadequate procedure performed	**7 (13%)**
Unplanned too extensive surgery	*5 (9.3%)*
P1: 70yrs, ASA3, peritoneal mesothelioma, diaphragmatic resection, extended small bowel and colonic resection, ileosigmoid anastomosis	
P2: 79yrs, ASA2, colorectal cancer, PCI=17, CC1	
P3: 71yrs, gastric cancer, PCI=12, major surgery (gastrectomy, pelvectomy, bilateral diaphragmatic resection, small bowel resection x2)	
P4: 69yrs, thrombocytopenia, colorectal cancer, discovery of a metastatic aortic ganglion, iliac vein wound, ganglion hemorrhage	
P5: 54yrs, small bowel carcinoma, hemodynamic instability with acute renal failure, CC1 resection, CDDP regimen for HIPEC	
Hemorrhagic surgery	*2 (3.7%)*
P1: 65yrs, colorectal cancer, oxaliplatin regimen for HIPEC despite uncontrolled pelvic bleeding (6 RBC transfusion)	
P2: 62yrs, peritoneal mesothelioma,hemorrhagic CRS with hemodynamic instability(2RBC transfusion),oxaliplatin+irinotecan regimen for HIPEC	
Technical errors	**6 (11.1%)**
P1: Incorrectly positioned HIPEC drain causing a stomach leak	
P2-5: No ileostomy performed (CRA with intraoperative leak n=2, vascular comorbidities n=1, low CRA n=1)	
P6: Textiloma	
Inadequate anesthetic management	**3 (5.6%)**
P1-3: Untrained anesthesiologist, hemodynamic instability with inadequate management (intraoperative acute heart failure n=2, postoperative acute renal failure with extra-renal depuration n=1)	
POSTOPERATIVE MANAGEMENT	**17 (31.5%)**
Diagnostic delay	**3 (5.6%)**
P1-3: Clinical and biological alteration: CT scan performed after 3, 5, 6 days respectively	
Treatment delay	**6 (11.1%)**
P1-3: Abdominal hemorrhage: reoperated after 2, 4, 5 days respectively	
P4-6: Anastomotic leak: reoperated after 2, 11, 15 days respectively	
Suboptimal treatment	**8 (14.8%)**
P1: Persistent sepsis with abdominal collection: drainage after 56 days	
P2: Abdominal hemorrhage initially monitored, reoperated after 7 days	
P3: Abdominal hemorrhage initially monitored, reoperated after 9 days and complicated by an anastomotic leak	
P4: Urinary sepsis with inappropriate antibiotic	
P5: CRA leak with no prior ileostomy, reoperation with ileostomy performed, persistent sepsis: Hartmann procedure performed, persistent sepsis without reoperation	
P6: CRA leak monitored	
P7: CRA leak monitored, leading to abdominal hemorrhage	
P8: Abdominal hemorrhage treated by arterial embolization leading to a right colon necrosis undiagnosed	
Unique root cause contributing factor	**43 (79.6%)**
Multiple Root cause contributing factors	**11 (20.4%)**

Abbreviations: ASA, American Society of Anesthesiologists; CC, complete cytoreduction; CDDP, cisplatin; CRA, colorectal anastomosis, CRS, Cytoreductive Surgery; ECOG Performance Status, Eastern Cooperative Oncology Group Performance Status; HIPEC, hyperthermic intraperitoneal chemotherapy; P, patient; PCI, Peritoneal Cancer Index; RBC, red blood cell; yrs, years

Discussion

La chirurgie de cytoréduction associée à la CHIP est une procédure complexe qui nécessite une équipe de chirurgiens et d'anesthésistes formée et expérimentée (31). Un investissement majeur des équipes la pratiquant est nécessaire au vu de la durée opératoire, de la complexité et de la variabilité technique de chaque procédure, ainsi que de par le coût économique lié à la machine de CHIP. Ceci pourrait expliquer, en partie, la mortalité postopératoire relativement faible qui est rapportée au niveau national en France (MPO à 90 jours de 2,6% (13)) ou en Allemagne (MPO intra-hospitalière de 3,4% (17)) comparée à d'autres chirurgies digestives oncologiques (MPO à 90 jours de 5,1% (24)). Ces grandes études nationales à partir de bases de données administratives donnent une vision large des procédures chirurgicales et permettent d'identifier des facteurs prédictifs de mortalité post-opératoire. Au-delà de cet aspect, un autre angle de réflexion est développé dans l'approche par RCA, prévoyant, sur une base individuelle, l'analyse de chaque patient décédé (25) afin d'identifier les facteurs contributifs au décès.

Dans notre étude, 101 patients ont été étudiés sur une période de 10 ans conférant un taux de MPO intra-hospitalier de 1,8%. Nous avons choisi d'étendre notre délai d'inclusion à tous les décès intra-hospitaliers afin d'être en adéquation avec la littérature actuelle (32), de mieux évaluer les complications, et d'identifier les moyens de les minimiser. Les décès des patients étaient répartis de manière égale selon le délai à " avant 30 jours " (46,5%) et " entre 30 et 90 jours " (41,5%). Douze patients (12%) sont décédés après 90 jours. Soulignant la nécessité d'utiliser, au minimum, les données de morbidité à 90 jours dans toutes les études incluant des procédures chirurgicales majeures telles que la CCR+CHIP (29,33).

Dans notre étude, la cause du décès n'a pas pu être identifiée dans seulement 3% des cas, ce qui correspond au taux le plus bas rapporté par RCA sur les taux de mortalité après résection pancréatique (25%) ou hépatique (12%). Ceci peut s'expliquer par notre méthodologie innovante qui consiste à inclure pour la première fois une évaluation combinée des dossiers des patients par le chirurgien senior du centre et un investigateur junior (CHL), suivie d'une seconde revue par un panel d'experts. La relecture par le groupe d'experts visait à évaluer chaque élément de la chaîne d'événements cliniques précédant un décès afin d'en identifier la cause et ainsi de classer le décès comme évitable ou non évitable.

Tous les patients ont présenté une morbidité majeure de grade III-IV avant le décès, avec des complications abdominales liées à la chirurgie (74%) et des complications extra-abdominales (81%), principalement dues à des complications abdominales. Au total, deux tiers des causes de décès identifiées sont d'origine abdominale, principalement des septicémies digestives (45%) ; le tiers restant est extra-abdominal, majoritairement des complications pulmonaires (15%).

Les résultats de notre étude révèlent que plus de la moitié des décès postopératoires après CCR+CHIP sont évitables. Les patients classés dans le groupe PREV étaient plus âgés, avec un score ECOG plus élevé, présentaient une maladie plus étendue avec un score PCI et un nombre de régions envahies plus élevés. Leurs interventions chirurgicales étaient plus étendues avec un nombre plus élevé d'organes réséqués et d'anastomoses digestives, ainsi qu'un taux plus élevé de transfusion sanguine et une durée opératoire plus longue. Ces caractéristiques sont des facteurs de risque connus de MPO, décrits dans toutes les grandes études (13,17) et définissent des critères de sélection opératoire communs à toutes les étiologies de tumeurs malignes du péritoine (2-8).

En outre, nous avons évalué la conformité de sélection des patients par rapport aux recommandations oncologiques en vigueur, les deux facteurs pronostiques majeurs étant le score PCI et les critères de qualité de la résection chirurgicale (CC score). En raison de la complexité de l'indication dans diverses étiologies de tumeur maligne du péritoine comme le cancer de l'ovaire ou des maladies rares, dans lesquelles un score PCI étendu et une résection incomplète CC1 auraient pu être autorisées, nous avons concentré notre analyse sur les cancers invasifs d'origine colorectale, de l'intestin grêle et gastrique pour lesquels les critères sont clairement établis. Pendant la période de notre étude, les recommandations ont évolué : une CCR complète avec résection CC0 était fortement recommandé, mais le seuil du score PCI a diminué avec le temps. Nous avons donc retenu le seuil recommandé au début de notre période d'inclusion, à savoir : <24 pour le cancer colorectal/ intestin grêle (5,29) et <12 pour le cancer gastrique, afin de nous affranchir d'un biais historique (30). En tenant compte de ces critères, les recommandations n'ont pas été suivies dans 30 % des cas. Le seuil du score PCI recommandé est actuellement abaissé à <17-20 pour le cancer colorectal (34) et <7 pour le cancer gastrique (3,35), ainsi - si les directives sont respectées - nous pourrions nous attendre à une diminution drastique de la MPO après CCR+CHIP dans les prochaines années.

En ce qui concerne les facteurs contributifs, notre groupe d'experts a mis en évidence un facteur pré-opératoire dans 60% des cas, un facteur per-opératoire dans 30% des cas et un facteur post-opératoire dans 30% des cas, conduisant à des facteurs multiples de décès évitables dans 20% des cas. Plusieurs mesures peuvent être mises en œuvre afin d'éviter les complications et les décès. Un bilan pré-opératoire complet pour évaluer l'état du patient et l'extension de la maladie est indispensable et doit faire l'objet d'une discussion par un comité d'experts, certifié en matière de tumeurs

malignes du péritoine. Une équipe pluridisciplinaire experte doit inclure des chirurgiens ainsi que des anesthésistes, des oncologues, des radiologues et des pathologistes (31). Les centres experts sont plus enclins à améliorer le traitement des patients atteints d'une maladie grave et à limiter le taux de *failure-to-rescue* (13). Enfin, de par les progrès des traitements médicaux, les résultats des chirurgies étendues et potentiellement mortelles doivent être mis en parallèle avec l'amélioration de la survie grâce à la chimiothérapie (36,37) combinée à des soins de soutien améliorés (38). Par conséquent, toute maladie étendue inattendue lors d'une intervention chirurgicale doit être suivie d'une discussion et d'une révision de l'approche thérapeutique nécessaire afin d'améliorer la qualité des soins et de diminuer les décès évitables.

Notre étude présente certaines limites. Tout d'abord, notre cohorte n'a pas été extraite de la base de données prospective du Programme de Médicalisation des Systèmes d'Information (PMSI). Trente-huit des 46 centres ont répondu favorablement à notre demande de procédure par RCA, permettant de rapporter 101 décès sur 10 ans de CCR+CHIP. Seize centres n'ont enregistré aucun décès au cours de leur expérience. Sur la base de notre étude précédente (13), 98% des décès ont été déclarés par nos centres participants (101 sur les 103 patients récupérés du PMSI), ce qui confère un biais de mémoire réduit. Deuxièmement, l'approche par RCA prend en compte uniquement les patients décédés, et non les patients ayant présenté une morbidité majeure après une CCR+CHIP. Ce point a été approfondi dans notre étude précédente qui met en évidence plusieurs facteurs de risque communs de MPO (13).

Conclusion

Après une analyse par Root-Cause Analysis et une étude au cas par cas des dossiers par un groupe d'experts, il résulte que plus de la moitié des décès après une CCR et une CHIP étaient évitables, principalement par un suivi consciencieux des recommandations et une sélection drastique des indications combinée à une prise de décision per-opératoire adéquate.

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Annexes

1. Annexe 1 : Publication de l'article

ESA PAPER

Half of Postoperative Deaths After Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy Could be Preventable

A French Root Cause Analysis on 5562 Patients

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Objective: To perform a retrospective root-cause analysis of postoperative death after CRS and HIPEC procedures.

Background: The combination of CRS and HIPEC is an effective therapeutic strategy to treat peritoneal surface malignancies, however it is associated with significant postoperative mortality.

Methods: All patients treated with a combination of CRS and HIPEC between January 2009 and December 2018 in 22 French centers and died in the hospital, were retrospectively analyzed. Perioperative data of the 101 patients were collected by a local senior surgeon with a sole junior surgeon. Three independent experts investigated the typical root cause of death and provided conclusions on whether postoperative death was preventable (PREV group) or not (NON-PREV group). A typical root cause of preventable postoperative death was classified on a cause-and-effect diagram.

Results: Of the 5562 CRS+HIPEC procedures performed, 101 in-hospital deaths (1.8%) were identified, of which a total of 18 patients of 70 years old and above and 20 patients with ASA score of 3. Etiology of peritoneal disease was mainly colorectal. A total of 54 patients (53%) were classified in the PREV group and 47 patients (47%) in the NON-PREV group. The results of the study show that in the PREV group, WHO performance status 1-2 was more frequent and the Median Peritoneal Cancer Index was higher compared with those of the NON-PREV group. The cause of death in the PREV group was classified as: (i) preoperatively for debatable indication (59%), (ii) intraoperatively (30%) and (iii) postoperatively in 17 patients (31%). A multifactorial cause of death was found in 11 patients (20%).

Conclusion: More than half of the postoperative deaths after combined CRS and HIPEC may be preventable, mainly by following guidelines regarding preoperative selection of the patients and adequate intraoperative decisions.

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Keywords: cytoreductive surgery, HIPEC, peritoneal metastasis, peritoneal surface malignancies, postoperative mortality, root cause analysis

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Cytoreductive surgery (CRS) combining peritonectomy and organ resection for complete macroscopic removal of all the peritoneal surface malignancies (PSM)[1] followed by hyperthermic intraperitoneal chemotherapy (HIPEC) was shown to improve patients prognosis.[2–8] CRS+HIPEC is associated with significant post-operative morbidity and mortality[9,10] that hinder long-term outcomes.[11,12] A recent national-based study on a 10-year French surgical practice reported a stable over time 90-day post-operative mortality (POM) of 2.6%.[13] Predictive factors of increased POM included age >70 years, Elixhauser comorbidity index ≥8, occurrence of major morbidity (MM) according to Clavien-Dindo classification,[14] and medical establishments performing less than 45 procedures/year (low-volume centers). Despite more extended surgeries with increased MM, high-volume centers were associated with lower failure-to-rescue rates (3.1% vs 6.3%), highlighting the necessity to centralize patients into high-volume centers to improve short-terms outcomes. Other countries reported similar results[15–17] and significant effort has been made to select patients eligible for the procedures and standardize perioperative clinical pathways.[18]

With a constant willingness to improve postoperative outcomes, morbidity and mortality review are required from the French High Authority for Health to retrospectively analyze cases ending in death or complications to implement and monitor actions improving the quality of patient care and safety. Based on the same approach used to investigate an entire population, root-cause analysis (RCA) was first introduced by the US National Aeronautics and Space Administration on pancreatic[19] and hepatic[20] surgeries, revealing inadequate intraoperative management (12% and 33% respectively) and technical errors (21% and 24% respectively).

The objective of our study is to perform an RCA of a French national multicenter cohort of deceased patients subjected to a combined CRS and HIPEC procedure, to gain new insights on postoperative mortality.

METHODS

Study Population

The BIG-RENAPE multicenter registry was set up in 2015 and represented a collaborative effort of main PSM French centers to prospectively collect data.[21] Participant centers were asked to provide data including preoperative, intraoperative, and postoperative variables for each in-hospital deceased patient. Data were collected from 5562 patients with PSM who underwent CRS+HIPEC from January 1, 2009, to December 31, 2018.

The Root-cause Analysis

Original medical records for every patient included in the study were analyzed in each center by a local senior surgeon specialized in CRS+HIPEC jointly with a single surgical fellow. Perioperative data were subdivided into 3 categories:

- Preoperative data included patients' medical and surgical history, American Society of Anesthesiologists (ASA) scores, performance status, comorbidities, and neoadjuvant treatments.
- Intraoperative data included the date and type of surgical procedure performed (with mean Sugarbaker's peritoneal cancer index – PCI),[22] completeness of cytoreduction score,[23] number of resected organs, digestive anastomosis, type of HIPEC regimen, blood loss, any incidents and their impact on the surgical procedure and the operating time.
- Postoperative data included the type of major morbidity (Grade III-IV) according to Clavien-Dindo classification,[24] the number of reoperations, and the cause of death.

After review of data consistency and accuracy on a case-by-case basis in each center, a synopsis was performed and anonymously presented to independent CRS+HIPEC senior surgeons qualified as experts. These experts were chosen among high-volume centers performing more than 30 to 45 CRS+HIPEC per year, and were divided into 3 groups of 3 experts each. After evaluating the collected data from each patient, the expert panel identified the cause of death and classified it in preventable (PREV group) or not-preventable category (NON-PREV group).

Death was defined as preventable when a root cause contributing factor known to increase the risk of death, was identified.[25] After identification, root cause contributing factors were classified within one of the three following categories: pre-, intra- and post-operative patients management, leading to a cause-and-effect diagram.

Inadequate management was defined in accordance with cancer management[26] and patient and perioperative care guidelines,[27,28] and the recommendations from the French 10-years national practice.[13] For colorectal, small bowel or gastric cancer, guidelines on disease extension (PCI) and quality of surgery (CC score) are well defined i.e.: CC0 score and PCI≤ 24 for colorectal[5,29] or small bowel cancer and <12 for gastric cancer.[30]

Inadequate intraoperative management was consistently associated with more extensive and longer procedures, incomplete tumor resection, and unexpected technical incident and complications. Inadequate postoperative management was defined as delayed diagnosis or treatment of complications.

Statistical Analysis

Results were expressed as medians with first and third quartiles or proportions and percentages. Groups were compared using Wilcoxon and Chi-2 tests as appropriate. All P-values were determined by bilateral tests, and a *P*-value < 0.05 was considered statistically significant. Analyses were performed by *R* statistical software (http://www.Rproject.org). A cause-and-effect diagram is shown in Fig. 1.

RESULTS

Characteristics of Patients and Surgical Procedures Performed

A total of 5562 combined CRS+HIPEC procedures were performed between 2009 and 2018 in the 22 participating medical institutions. Among them, 101 patients (1.8%) died during their hospitalization, from which 54 deaths (53%) were classified by the expert panel as preventable (PREV group). The patient male-to-female ratio was 1:1 with a median age of 64 years old (55 to 70) and an ASA score of 3 in 25.3%. Eastern Cooperative Oncology Group (ECOG) performance status of 1 or 2 (versus 0) was higher in PREV group with 57.9% vs. 22.6% in the NON-PREV group ($P < 0.01$). Comorbidities included cardiovascular disease (43.6%), pulmonary disease (17.8%), diabetes mellitus (13.9%), psychiatric disease (9.9%), and obesity (8.9%) and were comparable between the two groups ($P > 0.05$). The PSM arose from colorectal cancer (42.6%), primary peritoneal diseases [pseudomyxoma peritonei (24.8%), mesothelioma peritoneal (5.9%), peritoneal serous carcinoma (2.0%)], gastric cancer (12.9%), epithelial ovarian carcinoma (7.9%) or other origins (4.0%). Preoperative chemotherapy was administered in 76.3%, including 26.7% combined with

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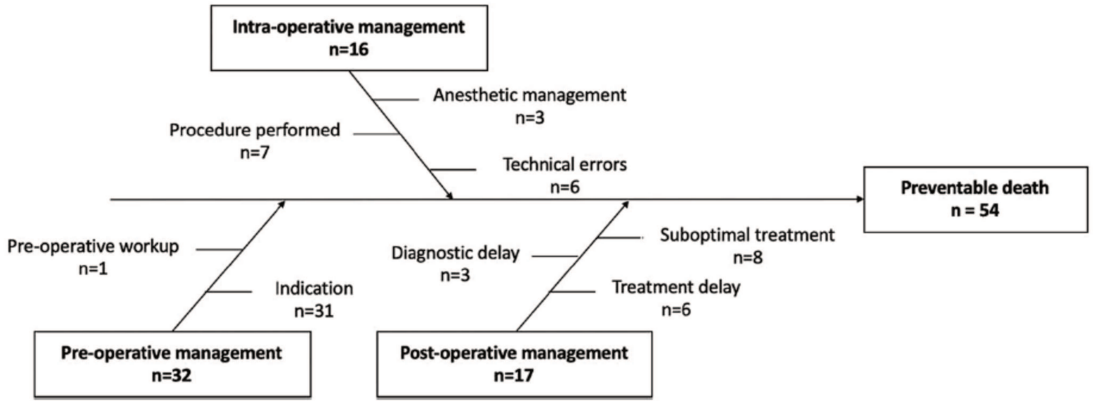

FIGURE 1. Cause-and-effect diagram: Each branch of the fishbone represents pre- (n = 32), intra- (n = 16), and postoperative (n = 17) management procedures (categories). Multifactorial cause of death were found in 11 patients (20%). Each of these categories has subcategories for which the cause is preventable (root causes).

Bevacizumab. Populations and surgeries characteristics are summarized in Supplementary Table 1; http://links.lww.com/SLA/D406.

Patients in the PREV group had more extensive complications with higher mean PCI [16 (9 to 21.5) vs 11 (5 to 19), $P = 0.053$] and higher mean number of affected regions [8 (4 to 12) vs 6 (2.5 to 9), $P = 0.064$] compared with NON-PREV group. In addition, the PREV group had more extensive surgeries with a trend of higher mean number of resected organs [3 (3 to 4) vs 3 (2 to 4), $P = 0.096$], higher mean number of digestive anastomosis [1 (1 to 2) vs 1 (1 to 1), $P = 0.029$], and intraoperative transfusion [48.6% vs 17.9%, $P = 0.010$].

When investigating surgical reports, 3 important data were evaluated: the extent of the disease (PCI), the quality of the surgical resection (CC-score), and the duration of surgical procedures were occasionally missing. Combining the three criteria, the PREV group had more missing data compared with NON-PREV group (74.1% vs 42.6%, $P < 0.01$).

Compliance with Guidelines

The evaluation of guidelines compliance was challenging due to the heterogeneity of PSM presentation and etiology. We investigated 59 patients with colorectal, small bowel or gastric cancer for which guidelines on disease extension (PCI) and quality of surgery (CC score) are well defined. Nine-teen CRS+HIPEC (32.2%) from various PSM origins [100% of small bowel (n = 3), 38% for gastric cancer (n = 5) and 28% of colorectal cancer (n = 12)] did not follow the guidelines.

Post-Operative Complications before Death

All patients experienced complications before death, including 75 of abdominal (74.3%) and 82 extra-abdominal complications (81.2%). The 3 major types of abdominal complications were comparable between the PREV and NON-PREV groups, including anastomotic leak (50% and 42.6%, respectively, $P = 0.58$), abdominal hemorrhage (35.2% and 42.6%, respectively, $P = 0.58$) and intra-abdominal collections (7.5% and 4.3%, respectively, $P = 0.84$). Of all patients, a total of 70 (69.3%) had to be reoperated due to a complication, including 37 patients (36.6%) with repeated and frequent reoperations in the PREV group (42.6% vs 29.8%, $P = .03$). Post-operative complications characteristics are summarized in Table 1.

Description of Cause and Timing of Death

The cause of death was identified by the expert panel in 97% (n = 98) of cases: abdominal causes in 61.4% including digestive sepsis (44.6%), tumor progression (9.9%), abdominal hemorrhage (6.9%) and extra-abdominal in 35.6% with pulmonary (14.9%), neurological (6.9%) and cardiovascular complications (5.9%). The causes of death are summarized in Table 2. No difference was found in the cause of death between the two groups except for the pulmonary complication that were more frequent in the NON-PREV group (25.5% vs 5.6%, $P = 0.005$) compared with the PREV group. The mean delay of death (all causes combined) was 34 days (11 to 63) and 36 days (16.5 to 61.8) for abdominal causes with a trend of later death in PREV group [(36.5 (19.2–68.8) vs 23 (9.5–61.5), $P = 0.16$) and (39 (23–69.2) vs 22.5 (8–57.8), $P = 0.034$)].

Analysis of Contributing Factor and Root Cause in the Preventable Death Group

Among all patients in the PREV group, preoperative management was found to be inadequate in 32 patients (59.3%) due to inappropriate indication (n = 31) or preoperative work-up (n = 1). The indication was judged inadequate for patients (n = 22) or disease (n = 9) related causes. Patients related causes were ASA score of 3 (n = 13), ECOG Performance status of 2 (n = 3), age (75 ± 4.2 years; n = 9), comorbidities with 3 severe cardiovascular diseases, 2 cirrhosis, 5 severe lung disease (2 chronic obstructive pulmonary disease, 2 pleural mesothelioma, one recent pulmonary embolism) and major surgical background with multiple anterior CRS (n = 3) or thoracic CRS for pleural mesothelioma (n = 1). Disease related causes were too extensive carcinomatosis in gastric cancer (PCI = 20.5 ± 7.2; n = 4) and mucinous colon cancer (PCI = 39; n = 1), 2 days-delayed HIPEC after hemorrhagic or emergency CRS (n = 3) and no neo-adjuvant chemotherapy in gastric carcinomatosis (n = 1).

Inadequate intraoperative management was identified in 16 patients (29.6%). Seven patients received inadequate procedure with too extended and unplanned (n = 5) or hemorrhagic (n = 2) procedures. In six cases, a technical error related to digestive leak or sepsis was found. In three patients, an untrained anesthetic team was responsible for poor hemodynamic management with 2 cardiac arrests during surgery and one early anastomosis leak.

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TABLE 1. Characteristics of Postoperative Complications

	No. (%)			
	Total (n = 101)	PREV group (n = 54)	NON-PREV group (n = 47)	*P*-value
Abdominal postoperative complications	75 (74.3)	42 (77.8)	33 (70.2)	0.53
Anastomotic leak	47 (46.5)	27 (50)	20 (42.6)	0.58
Abdominal hemorrhage	39 (38.6)	19 (35.2)	20 (42.6)	0.58
Intra-abdominal collections	6 (5.9)	4 (7.4)	2 (4.3)	0.84
Other:	30 (29.7)	20 (37)	10 (21.3)	0.13
Pancreatic fistula	9 (8.9)	9 (16.7)	0 (0)	
Urological complications	9 (8.9)	6 (11.1)	3 (6.4)	
Digestive ischemia	6 (5.9)	2 (3.7)	4 (8.5)	
Post-operative ileus	4 (4)	1 (1.9)	3 (6.4)	
Liver failure	2 (2)	1 (1.9)	1 (2.1)	
Biliary fistula	2 (2)	2 (3.7)	0 (0)	
Evisceration	1 (.99)	1 (1.9)	0 (0)	
Extra-abdominal post-operative complications	82 (81.2)	41 (75.9)	41 (87.2)	0.23
Acute renal failure	43 (42.6)	22 (40.7)	21 (44.7)	0.84
Cardiovascular complications	31 (30.7)	16 (29.6)	15 (31.9)	0.97
Thrombophlebitis	8 (7.9)	4 (7.4)	4 (8.5)	
Acute Heart failure	8 (7.9)	4 (7.4)	4 (8.5)	
Arrhythmia	7 (6.9)	5 (9.3)	2 (4.3)	
Myocardial infarction	6 (5.9)	1 (1.9)	5 (10.6)	
Others	2 (2)	2 (3.7)	0 (0)	
Pulmonary complications	32 (31.7)	15 (27.8)	17 (36.2)	0.49
Acute pulmonary distress	11 (11)	7 (13)	4 (8.5)	
Inhalation	7 (6.9)	2 (3.7)	5 (10.6)	
Pneumonia	10 (10.9)	4 (7.4)	6 (12.8)	
Pleural effusion	5 (5)	3 (5.6)	2 (4.3)	
Pneumothorax	2 (2)	0 (0)	2 (4.3)	
Hematologic complications	16 (15.8)	8 (14.8)	8 (17)	0.98
Neurologic complications	9 (8.9)	6 (11.1)	3 (6.4)	0.65
Stroke	8 (7.9)	6 (11.1)	2 (4.3)	
Encephalopathy	1 (.99)	0 (0)	1 (2.1)	
Reoperation	70 (69.3)	36 (66.6)	34 (72.3)	0.69
Once	33 (32.7)	12 (22.2)	21 (44.7)	0.03
Twice and more	37 (36.6)	23 (42.6)	14 (29.8)	

Inadequate postoperative management was found in 17 patients (31.5%) with suboptimal treatment of complications in 8 patients (14.8%), delayed treatment in 6 patients (11.1%), and delayed diagnostic in 3 patients (5.6%).

Pre-, intra- and postoperative contributing factors and RCA are described in a cause-and-effect diagram (Figure 1) and patients characteristics (Table 3).

DISCUSSION

CRS+HIPEC is a complex procedure that need a trained and experienced team of surgeons and anesthesiologists.[31] An intense commitment of the surgeons performing this procedure can be inferred from the time-consuming operative act, the technical complexity and variability as well as the economical investment related to the HIPEC machine. This could explain in part the relatively low

TABLE 2. Characteristics of Postoperative Death

	No. (%)			
	Total (n = 101)	PREV group (n = 54)	NON-PREV group (n = 47)	*P*-value
Cause of death				
Abdominal	62 (61.4)	36 (66.7)	26 (55.3)	0.24
Digestive sepsis	45 (44.6)	25 (46.3)	20 (42.6)	0.86
Tumor progression	10 (9.9)	7 (13)	3 (6.4)	0.27
Abdominal hemorrhage	7 (6.9)	4 (7.4)	3 (6.4)	0.84
Extra-abdominal	36 (35.6)	17 (31.5)	19 (40.4)	0.35
Pulmonary complications	15 (14.9)	3 (5.6)	12 (25.5)	0.0049
Neurologic complications	7 (6.9)	5 (9.3)	2 (4.3)	0.32
Sepsis	7 (6.9)	5 (9.3)	2 (4.3)	0.55
Cardiovascular complications	6 (5.9)	4 (7.4)	2 (4.3)	0.28
Hematologic complications	1 (1.0)	0 (0)	1 (2.1)	0.48
Unknown status	3 (3)	1 (1.9)	2 (4.3)	0.90
Delay of death (d) (Mean, SD)	34 [11 to 63]	36.5 [19.2–68.8]	23 [9.5–61.5]	0.16

SD indicates standard deviation.

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TABLE 3. Characteristics of Root Cause Contributing Factors (RCCF) in the 54 Patients of PREV-group

PREOPERATIVE MANAGEMENT	**32 (59.3%)**
Inadequate indication	**31 (57.4%)**
Related to patient characteristics	*22 (40.7%)*
ASA 3	13 (24.1%)
ECOG Performance Status of 2	3 (5.6%)
Age	9 (16.7%)
Major comorbidities	10 (18.5%)
Major history of surgery	4 (7.4%)
Related to disease characteristics	*9 (16.7%)*
Too extensive PCI score	5 (9.3%)
Delayed HIPEC 48h after CRS	3 (5.6%)
No chemotherapy before CRS for gastric cancer	1 (1.9%)
Inadequate preoperative work-up	**1 (1.9%)**
INTRAOPERATIVE MANAGEMENT	**16 (29.6%)**
Inadequate procedure performed	**7 (13%)**
Unplanned too extensive surgery	*5 (9.3%)*
P1: 70 yr, ASA3, peritoneal mesothelioma, diaphragmatic resection, extended small bowel and colonic resection, ileosigmoid anastomosis	
P2: 79 yr, ASA2, colorectal cancer, PCI = 17, CC1	
P3: 71 yr, gastric cancer, PCI = 12, major surgery (gastrectomy, pelvectomy, bilateral diaphragmatic resection, small bowel resection x2)	
P4: 69 yr, thrombocytopenia, colorectal cancer, discovery of a metastatic aortic ganglion, iliac vein wound, ganglion hemorrhage	
P5: 54 yr, small bowel carcinoma, hemodynamic instability with acute renal failure, CC1 resection, CDDP regimen for HIPEC	
Hemorrhagic surgery	*2 (3.7%)*
P1: 65 yr, colorectal cancer, oxaliplatin regimen for HIPEC despite uncontrolled pelvic bleeding (6 RBC transfusion)	
P2: 62 yr, peritoneal mesothelioma, hemorrhagic CRS with hemodynamic instability (2 RBC transfusion), oxaliplatin+ irinotecan regimen for HIPEC	
Technical errors	**6 (11.1%)**
P1: Incorrectly positioned HIPEC drain causing a stomach leak	
P2–5: No ileostomy performed (CRA with intraoperative leak n = 2, vascular comorbidities n = 1, low CRA n = 1)	
P6: Textiloma	
Inadequate anesthetic management	**3 (5.6%)**
P1–3: Untrained anesthesiologist, hemodynamic instability with inadequate management (intraoperative acute heart failure n = 2, postoperative acute renal failure with extra-renal depuration n = 1)	
POSTOPERATIVE MANAGEMENT	**17 (31.5%)**
Diagnostic delay	**3 (5.6%)**
P1–3: Clinical and biological alteration: CT scan performed after 3, 5, 6 days respectively	
Treatment delay	**6 (11.1%)**
P1–3: Abdominal hemorrhage: reoperated after 2, 4, 5 days respectively	
P4–6: Anastomotic leak: reoperated after 2, 11, 15 days respectively	
Suboptimal treatment	**8 (14.8%)**
P1: Persistent sepsis with abdominal collection: drainage after 56 days	
P2: Abdominal hemorrhage initially monitored, reoperated after 7 days	
P3: Abdominal hemorrhage initially monitored, reoperated after 9 days and complicated by an anastomotic leak	
P4: Urinary sepsis with inappropriate antibiotic	
P5: CRA leak with no prior ileostomy, reoperation with ileostomy performed, persistent sepsis: Hartmann procedure performed, persistent sepsis without reoperation	
P6: CRA leak monitored	
P7: CRA leak monitored, leading to abdominal hemorrhage	
P8: Abdominal hemorrhage treated by arterial embolization leading to a right colon necrosis undiagnosed	
Unique root cause contributing factor	**43 (79.6%)**
Multiple root cause contributing factors	**11 (20.4%)**

ASA indicates American Society of Anesthesiologists; CC, complete cytoreduction; CDDP, cisplatin; CRA, colorectal anastomosis; CRS, Cytoreductive Surgery; ECOG Performance Status, Eastern Cooperative Oncology Group Performance Status; HIPEC, hyperthermic intraperitoneal chemotherapy; P, patient; PCI, Peritoneal Cancer Index; RBC, red blood cell; yrs, years.

postoperative mortality that are nationally reported in France (90-days POM of 2.6%)[13] or Germany (in-hospital-POM of 3.4%)[17] compared with other oncologic digestive surgeries (90-days POM of 5.1%).[24] Those large nationwide studies from administrative database give a macroscopic vision of surgical procedures and allow to identify predictive factors of POM. Beyond this aspect, another angle of reflection is developed in the RCA approach providing, on an individual basis, the analysis of each deceased patient[25] to identify contributing factors to the death.

In the present analysis, 101 patients were studied on a 10-years period conferring an intra-hospital POM rate of 1.8%. We chose to extend our delay of inclusion to all intra-hospital deaths to be in adequacy with the current literature,[32] to better evaluate the complications, and to identify ways to minimize them. Patients death was equally distributed depending on delay to "before 30 days" (46.5%) and "between 30 and 90 days" (41.5%). Twelve patients (12%) died after 90 days. Highlighting the necessity to use 90-day morbidity data in all studies including major surgical procedures such as CRS+HIPEC.[29,33]

In our study, the cause of death could not be identified in only 3% of the population, which is the lowest rate reported by RCA on mortality rates after pancreatic (25%) or hepatic resection (12%). This might be explained by our innovating methodology that consists in including for the first time a combined evaluation of patients' files

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by the operating senior surgeon and one junior investigator from each center, followed by a second review from an expert panel. The panel's review aimed at evaluating each element of the clinical events chain preceeding a death to identify and classify the cause of death into a preventable or non-preventable death.

All patients experienced major grade III-IV morbidity before death, with either surgical,-related abdominal complications (74%) and extra-abdominal (81%) complications, mostly due to abdominal complications. A total of two third of identified causes of death arise from abdominal causes, mostly from digestive sepsis (45%); the remnant third were extra-abdominal, mainly from pulmonary complications (15%).

The results of our study reveals that more than half of the postoperative deaths following CRS+HIPEC procedures are preventable. Patients classified in the PREV group were older with a higher ECOG score, presenting a more widespread disease with higher PCI and number of invaded regions. Their surgeries were more extensive with higher number of resected organs and digestive anastomosis, higher rate of blood transfusion and operative time. These characteristics are typical risk factor of POM described in all larges studies[13,17] and define a pattern of selection that is common to every etiologies of PSM.[2–8]

Furthermore, we evaluated the compliance with oncological guidelines, the two strongest prognostic factors (PCI), and quality criteria of the PSM surgery (CC score). Due to the complexity of the indication in various PSM etiologies as ovarian cancer or rare diseases, in which extensive PCI and incomplete CC1 resection might have been allowed, we focused our analysis on invasive cancer of colorectal, small bowel and gastric origins. During the time of our study, the standard of care evolved: complete CRS with CC0 resection was a strong recommendation, but the cut-off of PCI decreased over time. We selected the cut-off recommended at the beginning of our period of inclusion i.e.: <24 for colorectal/small bowel cancer[5,29] and <12 for gastric cancer to avoid a historical bias.[30] With these criteria, 30% of the guidelines were not followed for CRS+HIPEC. As the recommended PCI threshold is currently lowered to <17–20 for colorectal cancer[34] and <7 for gastric cancer,[3,35] we might expect in the next few years a drastic decrease of POM after CRS+HIPEC if the guidelines are respected.

Concerning contributing factor, our expert panel found a preoperative factor in 60%, an intraoperative factor in 30% and a postoperative factor in 30% of cases, leading to multiple factors of preventable death in 20% of cases. Several measures can be implemented to avoid complications and death. An extensive preoperative work-up to evaluate the patient's state and disease extension is mandatory and must be reviewed in a tumor and PSM certified board. A multi-disciplinary team with expertise in PSM must include surgeons as well as anesthesiologists, oncologists, radiologists and pathologists.[31] Expert medical centers are more inclined to improve the treatment of patients with severe disease and avoid failure-to-rescue.[13] Lastly, with the progress of medical treatments, results of extensive and possibly deadly surgeries must be balanced with the improvement of survival resulted in chemotherapy[36,37] combined with enhanced supportive care.[38] Therefore, any unexpected extended disease during surgery must be followed by a discussion and revision of the therapeutic approach needed to improve the quality of care and decrease preventable death.

Our study has some limitations. First, our cohort was not extracted from the French National Health Service prospective database (Programme de Médicalisation des Systèmes d'Information). Thirty-eight on the 46 centers responded favorably to our request of RCA process, allowing reporting 101 death on 10 years of CRS+HIPEC. Sixteen centers had no death on their experience of CRS+HIPEC. Based on our previous study,[13] 98% of deaths were reported by our participating centers (101 on the 103 retrieved patients from the Programme de Médicalisation des Systèmes d'Information) conferring a reduced memory bias. Secondly, RCA approach only takes into account deceased patients, and not patients who experienced major morbidity after CRS + HIPEC. This was further explored in our prior study that highlights several common risk factors of POM.[13]

CONCLUSION

After RCA and case-by-case study review by an expert panel, more than half of the death after CRS and HIPEC were preventable, mainly by following guidelines regarding preoperative selection of the patients combined with extension of PSM and adequate intraoperative decisions.

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DISCUSSANTS

André J.L. D'Hoore (Leuven, Belgium)

Thank you for this very interesting dataset. I need to commend you on the huge amount of work that was completed, in order to analyze these data. Your excellent outcomes are due to the fact that you have selected quite important or good centers with the right expertise and that you have a very low mortality rate.

I have the following comments and questions. First, you say that most of the preventable deaths were in the group of patients, for which there was some misjudgment in the amount of tumor. Some of them had a tumor load that was too large when you started to perform the debulking. So, my question is whether newer imaging techniques (MRI-full body) could reduce the number of explorations and inappropriate cytoreductive surgeries in high PCI?

Second, I saw that quite a few patients had anastomotic leak and leak-related morbidity or mortality. Postoperative septic complications are a major risk for death. Are there strict rules to offer patients a diverting stoma to reduce the impact of AL?

Response From Clarisse Eveno (Lille, France)

Thank you, Dr. D'Hoore, for your very interesting comments and questions. Concerning the imaging technique, or the mortality rate of imaging techniques, such as CT scans or MRI, what is very important is the expertise of the radiologist in peritoneal disease. CT scans remain the international standard for pre-operative work-up in peritoneal disease and is more easily interpreted by a surgeon specialized in cytoreductive surgery. Peritoneal MRI is the full-abdomen MRI that needs to be done in expert centers and has promising results when combined with a CT-scan, allowing for improvement in the qualitative evaluation of the PCI score. MRI is also particularly useful in mucinous cancer and pseudomyxoma for the analysis of small lesions that could necessitate an extensive peritonectomy, total liver lobectomy or other organ resection, such as splenectomy. Also, PET-CT is not accurate to predict the resectability of peritoneal disease, but it could be used to diagnose associated extra-peritoneal disease and avoid exploration and inappropriate cytoreductive surgeries.

Finally, preoperative staging laparoscopy is recommended in all gastric cancer, due to the small lesions that are easily missed and when abdominal imaging shows an important tumor burden with a risk of borderline resectability. In our study, among the five patients that were identified with a high PCI beyond the recommended limit of the laparotomy, four patients had no staging laparoscopy, including three gastric cancers and one mucinous cancer of the appendix with pre-chemo laparoscopy, showing a high PCI of 39.

Concerning your second question, which is very accurate for the impact of diverting stoma, there are no particular rules in cytoreductive surgery. In the literature, the post-operative rate of anastomotic leaks in peritoneal disease operated in expert centers is similar to the one following colorectal surgeries (around 5%) and the historic rule of doing a diverting stoma in colorectal anastomosis below the Douglas pouch is often followed, especially when complete peritonectomy of the Douglas pouch is combined with the

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anastomosis. As in colorectal surgery, we adapt the realization of the stoma to the patient's characteristics (age, BMI, etc.) and the surgery's characteristics (operative time and blood loss). However, we also perform a stoma more easily when performing an extensive cytoreductive surgery with multiple digestive resections and anastomosis to decrease the rate of post-operative leak and sepsis. In our study, four patients were classified as having a technical error performed during surgery, without confection of diverting stoma and colorectal anastomosis. Half of them had a positive air leak test; one of them had an ASA score of 3 with a background of diabetes and vascular disease; and the last one had a low colorectal anastomosis. So, if there is a recent trend in colorectal surgery to decrease the use of diverting stoma, surgeons performing cytoreductive surgeries share the same ambition and an international study on the current surgical practice is ongoing.

Matthias Turina (Zurich, Switzerland)

Dr. Eveno, thank you very much for your work. I'm just interested in two details, which you did not discuss further. You said that inadequate indications for surgery and technical errors were among the causes of increased mortality. Could you please elaborate on both these topics?

Response From Clarisse Eveno (Lille, France)

With regard to technical errors, these occurred when, sometimes, the colorectal anastomosis had an air leak during the surgery and no stoma was performed. As for inadequate indications, this relates to when you have a higher tumor burden and you still perform the surgery, performing multiple visceral resections when it's not indicated. For example, this could be when you have a gastric peritoneal disease and you still perform a surgery with multiple resections, knowing that you won't increase survival. This made up the majority of wrong indications.

Antonio Pinna (Weston, FL, USA)

Can preoperative laparoscopy improve pre-surgical staging?

Response From Clarisse Eveno (Lille, France)

Thank you, Dr. Pinna, for your question. Yes, laparoscopy may improve pre-surgical staging to avoid unnecessary laparotomy. It is particularly true for gastric cancer because peritoneal disease is often invisible on a CT scan or MRI. In our study, this recommendation was frequently not followed; among patients that were identified with too high PCI, 80% had no pre-operative staging.

Inne Borel-Rinkes (Utrecht, The Netherlands)

Regarding your impressively low failure to rescue. Do you adhere to any specific (aggressive) policy for post-operative imaging and intervention?

Response From Clarisse Eveno (Lille, France)

Thank you, Dr. Borel-Rinkes, for your interesting question. Seventeen patients died because of post-operative management. In most cases, patients presented a clinic and/or biological degradation, which was investigated too late or not at all, leading to death. Our study highlights the necessity to be more proactive in the management of postoperative complications, with the help of imaging and surgery.

Kuno Lehmann (Zurich, Switzerland)

Thank you, Dr. Eveno, for this nice talk. In your opinion, what is the critical/most effective factor that needs changing to avoid postoperative mortality?

Response From Clarisse Eveno (Lille, France)

More than half of postoperative deaths after combined CRS and HIPEC may be preventable, mainly by following guidelines regarding the preoperative selection of the patients and adequate intraoperative decisions. A debatable indication is responsible for more than half of preventable deaths.

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Supplementary Table 1. Characteristics of Pre and Intraoperative Variables

Demographics characteristics	No. (%)			*P*-value
	Total (n = 101)	PREV group (n = 54)	NON-PREV group (n = 47)	
Sex: Male/Female	55 (54.5)/46 (45.5)	33 (61.1)/21 (38.9)	22 (46.8)/25 (53.2)	0.15
Age				
Median, yr	64 (55 to 70)	64 (54 to 70)	64 (56.5 to 69)	1
70 and more	18 (17.8)	13 (24.1)	5 (10.6)	0.078
ASA score*				
1	11 (13.9)	4 (9.3)	7 (19.4)	0.31
2	48 (60.8)	26 (60.5)	22 (61.1)	
3	20 (25.3)	13 (30.2)	7 (19.4)	
ECOG Performance Status*				
0	40 (58)	16 (42.1)	24 (77.4)	0.0085
1	21 (30.4)	17 (44.7)	4 (12.9)	
2	8 (11.6)	5 (13.2)	3 (9.7)	
Comorbidities				
Vascular disease	44 (43.6)	27 (50)	17 (36.2)	0.16
Pulmonary	18 (17.8)	11 (20.4)	7 (14.9)	0.47
Psychiatric disease	14 (13.9)	7 (13)	7 (14.9)	0.78
Diabetes	14 (13.9)	8 (14.8)	6 (12.8)	0.77
Obesity	9 (8.9)	5 (9.3)	4 (8.5)	0.9
Etiology of peritoneal disease				
Colorectal cancer	43 (42.6)	17 (31.5)	26 (55.3)	0.067
Pseudomyxoma peritonei	25 (24.8)	15 (27.8)	10 (21.3)	
Gastric cancer	13 (12.9)	7 (13)	6 (12.8)	
Ovarian cancer	8 (7.9)	6 (11.1)	2 (4.3)	
Peritoneal mesothelioma	6 (5.9)	5 (9.3)	1 (2.1)	
Peritoneal serous carcinoma	2 (2)	0 (0)	2 (4.3)	
Others	4 (4.0)	4 (7.4)	0 (0)	
Neoadjuvant chemotherapy*				
Yes	74 (76.3)	40 (75.5)	34 (77.3)	0.84
Including Bevacizumab	27 (26.7)	12 (22.2)	15 (31.9)	0.27
No	23 (23.7)	13 (24.5)	10 (22.7)	0.84
PCI				
Mean (SD)	13 (6.5 to 20)	16 (9 to 21.5)	11 (5 to 19)	0.053
Unknown status	10	8	2	
Regions affected (/13) (Mean, SD)	7 (3 to 12)	8 (4 to 12)	6 (2.5 to 9)	0.064
CC score				
0	66 (73.3)	34 (70.8)	32 (76.2)	0.26
1	21 (23.3)	11 (22.9)	10 (23.8)	
2	3 (3.3)	3 (6.2)	0 (0)	
Unknown status	11	6	5	
HIPEC used				
Monochemotherapy	72 (71.3)	37 (68.5)	35 (74.5)	0.51
Drug combination	20 (19.8)	11 (20.4)	9 (19.1)	0.88
Oxaliplatin ± Irinotecan	48 (47.5)	22 (40.7)	26 (55.3)	0.14
MMC ± CDDP	44 (43.6)	26 (48.1)	18 (38.3)	0.32
Others	9 (8.9)	6 (11.1)	3 (6.4)	0.41
Resected organs: Mean (SD)	3 (2.5 to 4)	3 (3 to 4)	3 (2 to 4)	0.096
Digestive anastomosis: Mean (SD)	1 (1 to 2)	1 (1 to 2)	1 (1 to 1)	0.029
Operative time (min)				
Mean (SD)	540 (495 to 600)	570 (510 to 600)	540 (490 to 600)	0.36
Unknown status	53 (52.5)	37 (68.5)	16 (34)	<0.001
Intraoperative transfusion				
Yes	23 (35.4)	18 (48.6)	5 (17.9)	0.01
No	42 (64.6)	19 (51.4)	23 (82.1)	
Unknown status (PCI, CC score, operative time)	60 (59.4)	40 (74.1)	20 (42.6)	0.0013

ASA indicates American Society of Anesthesiologists; CC, complete cytoreduction; CDDP, cisplatin ECOG Performance status, Eastern Cooperative Oncology Group Performance Status; HIPEC, hyperthermic intraperitoneal chemotherapy; MMC, mitomycin; PCI, peritoneal cancer index; SD, standard deviation.

*Percentages are given according to No. of patients per line after exclusion of patients with potential missing data.

AUTEURE : Nom : LAROYE - HOULZE **Prénom : CONSTANCE**

Date de soutenance : 06 mai 2022

Titre de la thèse : La moitié des décès après chirurgie de cytoréduction et chimiothérapie hyperthermique intrapéritonéale pourraient être évités : Analyse nationale française des causes profondes de mortalité sur 5562 patients.

Thèse - Médecine - Lille 2022

Cadre de classement : Chirurgie viscérale

DES + spécialité : DES Chirurgie Générale, DESC Chirurgie Viscérale et Digestive

Mots-clés : Chirurgie de cytoréduction, CHIP, Carcinose péritonéale, Root-cause analysis, Mortalité post-opératoire

Introduction : La chirurgie de cytoréduction (CCR) associée à la chimiothérapie hyperthermique intrapéritonéale (CHIP) est une stratégie thérapeutique efficace des tumeurs malignes péritonéales mais qui peut entraîner une mortalité postopératoire significative. L'analyse des causes profondes de mortalité (Root-Cause Analysis) est une méthode rétrospective permettant d'analyser les événements intercurrents.

Matériels et méthodes : L'ensemble des patients de 22 centres français, opérés par CCR+CHIP entre janvier 2009 et décembre 2018, décédés à l'hôpital en post-opératoire ont été inclus. Les données péri-opératoires de 101 patients ont été collectées de manière conjointe par un chirurgien sénior de chaque centre et un unique chirurgien junior. Trois experts indépendants ont analysé chacun des dossiers afin de définir les décès comme évitable (Prev. group) ou non (Non-Prev. group). Les décès évitables étaient classés sur un diagramme « cause-effet ».

Résultats : Sur les 5562 procédures, 101 patients sont décédés en intra-hospitalier (1,8%). Parmi eux, 54 patients (53%) ont été classés dans le groupe évitable et 47 (47%) dans le groupe non évitable. Vingt-six patients étaient âgés de 70 ans et plus, 22% avaient un ASA score de 3. Un score OMS 1-2 était plus fréquent dans le groupe évitable. L'étiologie de la carcinose était colorectale dans 68% des cas. Le score PCI moyen était plus élevé dans le groupe évitable (16 [9-22.8] vs 11 [5-17], p=0.023), la cytoréduction était incomplète (CC1-2) dans 29% et 24% des cas, respectivement. Les causes de décès évitables étaient classées comme telles : (i) pré-opératoire pour mauvaise indication (59%), (ii) per-opératoire (30%) et (iii) post-opératoire (31%). Des causes multiples étaient objectivées dans 20% des décès.

Conclusion : La moitié des décès après CCR+CHIP pourraient être évités par une sélection pré- et per-opératoire drastique des indications en accord avec les recommandations ainsi qu'une meilleure gestion des complications post-opératoires.

Composition du Jury :

Président : Monsieur le Professeur Guillaume PIESSEN

Assesseurs : Monsieur le Professeur Etienne GAYAT, Madame le Docteur Olivia SGARBURA, Madame le Docteur Anne PLOQUIN

Directrice de thèse : Madame le Professeur Clarisse EVENO