No impact on long-term survival of prolonged ICU stay and re-admission for patients undergoing cytoreductive surgery with HIPEC

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Abstract

Background: Cytoreductive surgery (CRS) and Hyperthermic intraperitoneal chemotherapy (HIPEC) are promising new approaches of peritoneal metastases. However these surgical procedures are associated with a high morbidity rate thus intensive care (IC) management following serious complications may be warranted for these patients. The impact of the prolonged IC stay or re-admission on long-term survival remains unknown.

Methods: We retrospectively analysed 122 consecutive HIPEC procedures over a one year period (2010–2011) in a single academic hospital. We analysed complications that would lead to prolonged stay or re-admission into ICU and analysed long term follow-up in patients whether they required intensive care (ICU group) or not (Control group).

Results: ICU group represented 26.2% of the cohort mainly due to septic or haemorrhagic shock. Among them acute kidney injury and respiratory failure were present in 50% and 47% respectively. Cohort overall mortality rate was of 5.7%.

Patients were followed for 4 years and survival analysis was performed adjusting for main confounding factors in a Cox survival model. Survival was not different between groups, with a median survival of 38 months [32; 44] vs. 33 months [26; 39] in the ICU group and Control group respectively.

Conclusion: Prolonged stay or re-admission into ICU does not seem to statistically impact long term prognosis of patients undergoing CRS with HIPEC.

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Keywords: HIPEC; Cytoreductive surgery; Intensive care unit; Prognosis; Long term outcome

Take home message

Despite high morbidity, patients undergoing cytoreductive surgery with HIPEC should be admitted to the ICU if any serious complication occurs, as it does not seems to statistically impact long term prognosis after ICU discharge.

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Introduction

Peritoneal dissemination of metastatic cancer, usually known as carcinomatosis affects 30%−40% of cancer patients.[1] Carcinomatosis can also be secondary to primitive peritoneal tumours such as mesothelioma.[1] Natural history invariably leads to a fatal evolution with a median survival of 6 months.[2−4] Among proposed treatments, Hyperthermic intraperitoneal chemotherapy (HIPEC) was first described in the early 80's by Dr Spratt.[5] More recently, HIPEC procedures associated with cytoreductive surgery has increased. This approach is the only curative option today and a growing number of evidence supports its use in selected patients with ovarian, colorectal or even gastric metastatic disease, thus this strategy is now a serious option in patients with peritoneal metastases (PM). A recent large study by Glehen and co-workers involving more than 500 patients demonstrated that a strategy involving HIPEC for peritoneal metastases improves long term survival.[3] Cytoreductive surgery associated with HIPEC, aims to remove as much cancerous growth as possible with large resections of bowels, liver peritoneum or diaphragm.

These improvements in survival have been possible at the cost of extended surgical procedures, as described previously. Thus, there is an increased demand for intensive care support in these patients. Considering the rate of post-operative morbidity and mortality, 25% and 5% respectively,[3,6] Consequences of an intensive care unit (ICU) management in case of life threatening complications remains a hot topic in cancer patients. Indeed as a consequence of ICU management, multiple organ support may be often necessary, and this may lead to severe burden and prolonged frailty. Thus, one should question the cost of ICU management of patients undergoing CRS with HIPEC. Cancer is the second most common reason for ICU refusal.[7] Many question recently arisen in the ICU medical community regarding prognosis of cancer patients admitted to the ICU (even in the postoperative course). Many papers and a recent meta-analysis tried to question benefit of ICU management and to identify groups of patients who will benefit from ICU admission, without impaired long term prognosis due to ICU care.[8] Indeed, no data are available concerning the impact of ICU on patients undergoing CRS with HIPEC's long term survival and therefore the question "Does patients undergoing CRS with HIPEC benefit from ICU?" may be raised with regards to the acceptability of the long term prognosis of patients undergoing CRS with HIPEC. In this exhaustive retrospective monocentric study, we tried to compare long term survival of a cohort of patients undergoing CRS with HIPEC who required intensive care (ICU group) or not (Control group).

Materials and methods

We enrolled a consecutive cohort of 122 patients between 2010 and 2011. Patients underwent cytoreductive surgery and HIPEC in a single skilled academic centre. A database was built with the information available in the case files of each patient and was anonymised. Primary endpoint was long term survival. For each patient, we reported the following criteria involved in the study design: ICU re-admission (ICU group) or not (Control group), death in the ICU if applicable, dead or alive on December 31st 2014. In the study, demographic information and past history of the patient were recorded by consulting the preoperative evaluation form. These included physiological data, ASA (American society of anaesthesiology) score, comorbidities (hypertension, arrhythmia, past history of myocardial infarction or stroke, diabetes, cardiac, vascular or respiratory insufficiency, and chronic pulmonary disease) reported in the Charlson's index. We also reported neoplastic data such as origin and histology of peritoneal metastases, its extent assessed during surgery with Sugarbaker's peritoneal cancer index (PCI), neoadjuvant chemotherapy and the presence of liver metastasis were also retrieved.

Intraoperative surgical data were recorded: the number of peritonectomies and resected organs, diaphragmatic and liver metastasis resection, completeness of cancer resection (CCR), surgery and HIPEC duration.[9]

Management of patients undergoing CRS with HIPEC in our institution follows a standard procedure. After surgery, all patients are admitted in a postoperative intensive care unit (PICU) for 24 h. After a period lasting generally 16−18 h, patients are transferred to a step down unit (SDU) where they stay until they can be discharged to the surgical ward and then go back home or to a rehabilitation facility.

PICU data recorded included some basic Laboratory data, mechanical ventilation duration, haemodynamic parameters with fluid management and electrolytes therapy, vasopressors requirement and blood transfusion. Other postoperative data included surgical drains volume, immediate complications and outcome at day 1.

Classification of patients in ICU and non ICU group is of major importance for the understanding of the study. Numerous reasons may lead a patient to the ICU, we considered that an ICU patients undergoing CRS with HIPEC was 1) a patient that could not be discharged to the SDU at day 1 for any medical reason (bed unavailability in the SDU was not considered as an ICU criteria) or 2) a patient who was readmitted to the ICU after discharge to the SDU or the ward, for any medical reason. These two groups are separately analysed.

Statistical analysis

Overall survival was defined between the hospital discharge and death from any cause or the last observation.

Continuous variables were reported as mean ± standard deviation or median and interquartile range as appropriate. Categorical variables were reported as numbers and

percentages. Continuous variables were compared using the Mann−Whitney test, and categorical variables were compared using the Chi-square test or the Fisher exact test according to applicability. Survival curves were obtained using the Kaplan−Meier method and compared with the log-rank test.

Confounding factors were selected as previously known factors reported by Glehen and Coll.[10] These main variables were then introduced in univariate Cox models. The proportional rate assumption was checked and tested using Schoenfeld residuals. Survival was estimated and plotted according to the patients ICU group. A model was fitted introducing ICU group the main confounding factors adjusted. Multivariate analysis was performed with a Cox proportional hazard model. The results are presented as relative rates with confidence intervals at 95%.

Analyses were performed with SPSS statistical software for Windows (SPSS, v20, IBM, NY USA) and the R software (software 3.0.2, 2012). (Ref: R Development Core Team R: A Language Environment for Statistical Computing Vienna, Austria ISBN 3-900051-07-0. URL: http://www.R2013-project.org).

Results

In the study were included 122 consecutive patients who underwent cytoreductive surgery with HIPEC. Among them, 90 did not present any severe complications (Control group) while 32 (26.2%) needed re-admission in the intensive care unit (ICU group). Characteristics of patients are described in Tables 1A and 1B. We found no statistical differences between the ICU and the Control groups concerning patients' general characteristics (age, sex, BMI, Charlson index, ASA, origin of cancer). Concerning the general carcinologic characteristics, carcinomatosis extension was significantly higher in ICU group vs. Control group, with a mean PCI score of 16.12 ± 9.08 vs. 11.03 ± 8.46 (p = 0.006), during the peroperative period, we found no statistical difference, expected for the need of diaphragmatic resection, which was more often required in the ICU group (75% vs 49% - p = 0.013).

Patients with primitive peritoneum cancer received less adjuvant chemotherapy (31.6% vs 70.6% for colon tumour and 82.4% for ovarian cancers).

Completeness of surgery did not differ between groups in a univariate analysis. After cytoreduction, 83% of control patients were classified CCR-0, 15% were classified CCR-1 and 2% were classified CCR-2 compared with 72% of patients classified CCR-0, 28% classified CCR-1 and none classified CCR-2 in the ICU group. The total duration of the combined procedure did not differ significantly between the 2 groups with 464 ± 77 min in the Control group and 504 ± 73 min in the ICU group. We therefore found no statistical difference in the duration of the HIPEC procedure. Moreover we found no significant difference in the chemotherapies used for HIPEC.

Table 1
A: General characteristics of patients. B: General carcinologic characteristics of patients.

	ICU (n = 32)	Control (n = 90)	p	Total (n = 122)
Age (years) (mean ± SD)	59 ± 8	55 ± 9	0.148	56 ± 9
Male sex (n (%))	16 (50%)	28 (31%)	0.937	44 (36%)
BMI (mean ± SD)	24 ± 4	24 ± 3	0.837	24 ± 3
ASA score (median [IQR25;75])	2 [1;2]	2 [1;2]	0.882	2 [1;2]
Charlson's index (median)	10 [9;11]	9.5 [9;10]	**0.019**	10 [9;10]

	ICU (n = 32)	Control (n = 90)	p	Total (n = 122)
PCI score (mean ± SD)	16.12 ± 9.08	11.03 ± 8.46	**0.006**	12.42 ± 8.89
Colorectal peritoneal metastasis − n (%)	18 (56%)	49 (55%)	0.589	67 (55%)
Neoadjuvant CT − n (%)	24 (75%)	63 (70%)	0.833	87 (71%)
Cytoreductive status				
CCR-0	23 (71.9%)	74 (83.1%)	0.279	97 (80.2%)
CCR-1	9 (28.1%)	13 (14.6%)		22 (18.2%)
CCR-2	0 (0.0%)	2 (2.2%)		2 (1.7%)
Surgery duration − min (mean ± SD)	464 ± 77	504 ± 73	0.053	475 ± 77
Diaphragmatic resection − n (%)	24 (75%)	44 (49%)	**0.013**	68 (55%)

BMI = Body mass index; ASA = American score of anaesthesiology. PCI = peritoneal carcinosis index; CT = Chemotherapy; CCR = completeness of cytoreduction.

During the PICU stay, patients in the ICU group received vasopressors more often than those in the Control group (25% vs 3.3% - p = 0.001).

When patients were admitted to the ICU, their mean arterial blood pressure was 77 ± 17.9 mmHg. Mean heart rate was 106 ± 19.6 beats per minute. Vasopressors were required for 34% of them and 41% of them were mechanically ventilated. Median stay in the ICU was 8.5 [3.75−15.75] days.

The main reasons for ICU transfer were divided in 5 categories: Septic shock 28.1%, haemorrhagic shock 21.9%, haemodynamic instability or arrhythmia 15.6%, acute respiratory failure 6.2% and prolonged post-operative acidosis 6.2%. Patients often suffered multiple organ failures (more than 2). We noticed almost 50% of renal failure and 47% of respiratory distress associated with other organ failures.

Concerning readmission sources, 44% of patients were admitted immediately after the initial 24 h stay in PICU, whereas 56% were admitted after PICU discharge. 52% of them were admitted from the operating theatre, from the surgical ward and 18% from SDU. Mean delay for re-admission was 22 ± 29 days, in the part of ICU group admitted later after PICU discharge. Concerning long term follow-up median was 3.6 [2.0; 4.3] years, with a minimum follow-up of 5 days and a maximum of 5 years.

Among the ICU group, 9 patients died in ICU (28.1%). No statistically significant difference was found between

patients admitted in the ICU immediately after PICU stay and those admitted later after ICU stay. This later group was significantly most frequently associated with septic shock (p = 0.012) and reoperation (p = 0.014).

Long term survival analysis was performed using main cofounding factors in a Cox survival model, on patients admitted to the ICU. The selected factors were PCI score (as a continuous variable), completeness of cytoreduction (CCR), tumour type (colorectal, ovarian and peritoneal)[3,10] and no diaphragm resection. We based our long term survival analysis on patients who survived the ICU management, and compared them to Control group. This way we suppressed impact of immediate death during ICU management.

Long term follow-up is plotted on Graph 1a, we found no difference between ICU and Control group, using the log-rank test (p = 0.181).

On a univariate analysis, without adjustment, factors associated with long term mortality are reported on Table 2. On a multivariate Cox analysis model, predictive factors associated with long term mortality are presented in Table 2. ICU admission was not associated with long term survival.

Overall long term survival was not significantly decreased in the ICU group compared to control with an average 5-year survival in the Control group was 87.7% (95% CI: 81.2–94.8) compared to ICU group 69.6% (95% CI: 53.1–91.2) (Graph 1). Median follow-up was 3.8 years in the Control group and 3.5 years in the ICU group. The overall 1-year and 3-year survival was 95.6 (95% CI: 91.4–99.9) and 76.5% (95% CI: 68.2–85.8) in the Control group compared to 78.3 (95% CI: 63.1–97.1) and 65.2 (95% CI: 48.4–87.9) in the ICU group.

Long term follow-up comparing immediate and delayed ICU admission is plotted on Graph 1b, we found no difference between ICU and Control group, using the log-rank test (p = 0.45).

Discussion

In this study, we provide piece of evidence that patients undergoing CRS with HIPEC with serious complications who had prolonged stay or were re-admitted into ICU have similar long term survival as patients undergoing CRS with HIPEC who had not. This data provides incentive to admit patients undergoing CRS with HIPEC with serious adverse event following surgery to the ICU and give them full code critical care management since their long term prognosis is not clearly impaired by the ICU and therefore will benefit of ICU care. CRS and HIPEC is high risk surgery with substantial morbidity and mortality.[3] In this study, we found a high morbidity rate (26.2%), with an ICU mortality rate both similar to what was previously described.[11] One major key in the management of HIPEC procedure is the patient background.[6] Peritoneal metastases are usually considered as a terminal disease with a very poor life expectancy.[12,13] Although HIPEC showed promising results from large multicentre trials, it is not routinely recommended as a standard of care.[10,14,15] Performing high risk surgery in patients with peritoneal metastases is obviously associated with a high risk of serious adverse events requiring in-ICU management. Moreover, the presence of cancer is of the most common reason cited by intensivist for refusal of ICU admission.[7] It is known that ICU management is associated with impaired postoperative recovery in patients undergoing CRS with HIPEC.[16] Therefore one can question whether or not patients undergoing CRS with HIPEC with serious adverse effects should benefit of ICU management. Prognosis of cancer patients admitted to the ICU is poor, as previously reported by several authors.[17,18] One study by Timmers and coll. may suggest that patients admitted in the ICU after planned oncological surgery may have better outcome.[19]

After this study, we partly confirm the hypothesis that long term follow-up, over nearly 5 years after hospital discharge, is not statistically significantly impacted by ICU transfer or prolonged ICU in the post-operative course of HIPEC from life threatening complication. We found a median survival similar to recent publications.[6,10] This result is in accordance with some recent findings in management of onco haematological patients. Although ICU care benefit of patients with solid cancers is still debated,

Graph 1. a: Long term survival analysis depending on ICU admission. b: Long term survival analysis depending on type of ICU admission.

Table 2
Cox regression results for univariate and multivariate models.

Variables	Univariate analyses			Multivariate analyses		
	HR	95% CI	p value	HR	95% CI	p value
ICU	1.63	0.79−3.34	0.204	1.74	0.83−3.65	0.14
PCI	1.06	1.02−1.1	0.002	1.08	1.03−1.13	0.001
Adjuvant CT	3.08	1.20−7.88	0.007	7.69	2.26−26.20	0.001
Cytoreduction score = 1	6.26	1.45−27.04	0.051	10.57	1.55−72.32	0.016
Age	1.01	0.99−1.05	0.312			
Diaphragmatic resection	1.84	0.96−3.55	0.062			

ICU = Intensive care unit admission; PCI = peritoneal carcinomatosis index; CT = chemotherapy.

very little is known about long term prognosis.[8] Recent published data on lung cancer patients reports, despite recent encouraging progress, poor prognosis in the most severe cases.[20] Other findings support some benefit in selected patients.[21] Haematological patients present the same ethical questioning and although these patients were commonly deemed to have a poor prognosis (they were often not admitted to ICU for acute condition[22]), selected patients with haematological malignancies requiring ICU clearly benefit from it as demonstrated by Azoulay et al.[23] We provide additional data indicating that a full code strategy as previously described is required for patients undergoing CRS with HIPEC admitted to the ICU as their long term prognosis is not impaired by ICU management, whether it is needed immediately or later after surgery.[24] Of course, one should keep in mind that patients undergoing CRS with HIPEC are very selected as they present few comorbidities, as confirmed by the median ASA score in both groups. Recent studies indicated that elderly patients or those with many comorbidities have a worsen outcome following HIPEC.[25,26] Moreover, in a recent large cohort of one thousand patients, authors reported that CCR score of 2 (no control of the carcinologic disease) is associated with impaired long term survival.[6] In this study, less than 3% of the patients were CCR-2. This work is the first to evaluate the benefits of ICU management for patients undergoing CRS with HIPEC with serious postoperative complications on a large monocentric consecutive cohort. Despite its retrospective origin, one strength of this study is to focus on life threatening complications regardless of its origin. The only inclusion criterion is ICU admission requirement. Previous studies reporting postoperative adverse events only focused on surgical classifications which show some heterogeneity.[27,28] In a recent report, Votanopoulos et al. using the Clavien−Dindo classification found that serious complications were associated with impaired long term survival.[26] Herein our study, we defined ICU requirement as a grade IV or V complication of the Clavien−Dindo classification. Thus it is not possible to compare grade I or II complications with grade IV ones.

We studied the whole cohort of patients during a limited time period to avoid selection bias. Confusion bias was limited by the Cox model analysis with well-known long terms prognosis factors for HIPEC mortality.[3,10]

Conclusion

Cytoreductive surgery combined with HIPEC is today the best curative opportunity for patients suffering from peritoneal metastases. It remains a difficult procedure with high rates of morbidity and mortality. Indeed, 1 patient over 4 is likely to present severe complications leading to ICU prolonged stay or re-admission. This study supports the fact that long term prognosis do not seem to be strongly impaired by ICU management of life threatening postoperative complications.

Conflict of interest

This work had no specific funding, and there are no conflict of interest disclosures from any authors concerning this article.

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