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ORIGINAL ARTICLE

Intensive care unit hospitalization after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

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Summary

Purpose: *Peritoneal metastasis (PM) is nowadays treated with the complex procedure of cytoreductive surgery and hyperthermic intra-peritoneal chemotherapy (CRS+HIPEC). Given the fact that the procedure presents high morbidity and mortality rates, admitting patients to the Intensive Care Unit (ICU) seems inevitable. In our study, we have tried to determine the factors that indicate when admission in the ICU is necessary.*

Methods: *We retrospectively analyzed 230 patients (140 females, 90 males) with PM, who were operated on from November 2005 until October 2015, and underwent CRS+HIPEC. The patients were divided into two groups, based on whether they were extubated after the operation or not, thus being admitted to the ICU. We also distinguished a group of patients who, after the initial extubation, had to be re-intubated and transferred to the ICU. We assessed morbidity and mortality rates for each of the aforementioned groups, along with the complications developed in each case (thoracic, gastrointestinal, renal).*

Results: *We found that morbidity and mortality rates in both examined groups were approximately similar; the course changed when a complication occurred, and this increased mortality, especially if the onset of the symptoms was delayed. Also, these rates were much worse for the group that had to be re-intubated and transferred to the ICU.*

Conclusions: *On the whole, we conclude that the decision of immediate admission to the ICU post-operatively is hard, as it depends on multiple factors; therefore, the use of an easy predictive method is not realistic and a more individualized and patient-to-patient approach is preferable.*

Key words: *cytoreductive surgery, extubation, HIPEC, intensive care unit, morbidity and mortality, peritoneal metastasis*

Introduction

The management of PM has proven to be a challenge for both medical and surgical oncologists.

In the past, the presence of diffuse implants in the peritoneal cavity denoted terminal stage disease; however current therapeutic approaches are in a position to improve patient outcome.

If left untreated, the medial overall survival with PM ranges between 3 to 6 months [1-3].

In order to treat patients with PM, surgical oncologists have developed procedures involving cytoreductive surgery (CRS) and continuous hyperthermic intra-peritoneal chemotherapy (HIPEC) with high-dose chemotherapy [4].

This procedure, that involves the delivery of locoregional high-dose chemotherapy, can improve the disease locally and minimize the systemic toxicity, providing promising results in the

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Table 1. Patient and procedure characteristics (N=230)

Characteristics	*N (%)*
Age, years, median (range)	56.3 (25-81)
Gender	
Female	140/230 (60)
Male	90/230 (40)
Previous surgery	210/230 (91)
Previous systemic chemotherapy	178/230 (77.4)
Operating time, hrs, median (range)	7 (4-11)
PCI, median (range)	15.8 (2-39)
<20	160/230 (69.5)
>20	70/230 (30.5)

PCI: peritoneal cancer index

Table 2. Primary tumors

Primary tumor	*N (%)*
Ovary	66 (28.7)
Colorectal	58 (25.2)
Pseudomyxoma peritonei	44 (19.1)
Mesothelioma	20 (8.7)
Stomach	15 (6.5)
Endometrium	12 (5.2)
Sarcomas	7 (3.0)
Others	8 (3.5)
Total	230 (100)

survival of patients with PM [5].

CRS and HIPEC are considered to be a complex procedure that requires extensive resection, including peritonectomies, and in a number of cases visceral resections, intraoperative hyperthermic chemotherapy and, therefore, prolonged operative time (7-12 hrs).

Moreover, CRS and HIPEC have been associated with high morbidity (25-45%) and mortality (1.5-5%) rates [6,7]; consequently, many patients need to be admitted to the ICU for stabilization and prompt detection and resolution of complications.

The aim of this study was to determine whether postoperative management after CRS and HIPEC requires ICU admission and to define the cases in which this is necessary.

Methods

We retrospectively analyzed the data from 230 patients with PM (140 females and 90 males, Table 1), who were operated on from November 2005 until October 2015, undergoing CRS and HIPEC. The patients were analyzed as two different groups; those who were immediately extubated after the operation and returned to the ward, and those who were transferred directly from the operating theatre to the ICU. A separate group that was examined, was that of patients that were extubated and not admitted to the ICU, though, during their postoperative course, due to various reasons described below, were in need for reintubation and admission to the ICU.

The parameters that were evaluated were the following:

Tumor histology, age, gender, date of admission and length of stay in the ICU, presence of complications (bleeding), time and management of complications and the peritoneal cancer index (PCI).

Tumor location is presented in Table 2.

All patients underwent exploratory laparotomy, cytoreduction and HIPEC. Briefly, the aim of cytoreduction is to render the patients grossly free of disease.

The procedure involves the insertion of 4 large-core catheters through the abdominal wall; 2 of them are placed in the left and right hypochondriac region serving as influx, and the other 2 in the pelvis, serving as efflux of the perfused solution.

In order to achieve and monitor the temperature of the solution, 4 probes are placed in parallel fashion with the 4 catheters.

After the 4 catheters and 4 probes are secured in the abdominal cavity, the perfusion of approximately 4 litres of warmed to 42.5 ^{o}C solution is initiated, at a rate of 1.5lt/min. This may be performed either with the open (coliseum) or the closed abdomen technique, whilst the perfusate agent varies, according to previously described protocols [8-10].

General anesthesia is administered to all patients by anesthesiologists familiar with the procedure and the institutional practice, using standard monitoring. In the absence of contraindications, insertion of an epidural catheter, prior to induction of anesthesia, is often decided.

Results

Our results are more thoroughly presented in the respective Figures and Tables.

More specifically, the patients' course of treatment, hospitalization in the ICU, extubation time, complications etc., are all presented in Figure 1.

First, since the ability to extubate the patient plays a rather significant role in whether hospitalization in the ICU is necessary or not, we present our immediate extubation criteria in Table 3, the patient still being in the recovery room.

Also, the majority of the patients (71.7%) who were immediately admitted to the ICU postoperatively, were extubated within the first 3 days. The

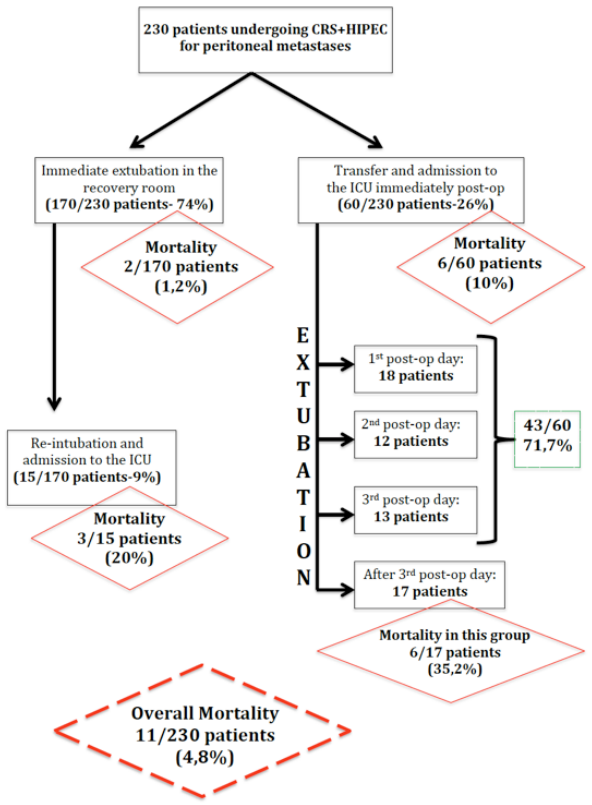

Figure 1. Numbers and percents of patients extubated immediately or transferred to ICU. Days of post-op extubation and mortality in each group.

Table 3. Immediate extubation criteria after CRS+HIPEC

Criteria	
Duration of procedure	≤ 8 hrs
Duration of HIPEC	≤ 60 min
Systolic BP at the end of the operation	> 100mmHg
$PaCO_2$	≤ 40
PaO_2	≥ 70
HCO_3 deficit	≤ 4mEq/L
Diuresis	>80ml/hr
Heart rate	< 100/min
PCI	<15

BP: blood pressure, PCI: peritoneal cancer index

remaining 17 patients presented more complications, worse course and higher mortality (35.2%).

As we mentioned before, when examining non-ICU-admitted patients, a group of 15 patients stood out, as there was a need for re-intubation and admission to the ICU, due to acute respiratory distress syndrome (ARDS), sepsis or re-operation. In this group, the mortality rate appeared to be significantly higher, when compared to both the patients initially admitted in the ICU and the ones who were not (Table 4).

Postoperative complications are shown in more detail in Table 4. It has to be noted at this point that complications and mortality rate differed, but not significantly, when ICU- admitted patients were compared to non-ICU- admitted ones (combined data from Figure 1 and Table 4).

In particular, from thoracic complications, ARDS stood out, with high percentages in all 3 examined groups, followed by atelectasis and pneumonia, which were the second and third most common thoracic complications, respectively.

Finally, the most common gastrointestinal complication proved to be the digestive fistulas, whereas acute renal failure was observed at low rates in the two initial groups, but reached much higher percentages for patients that were re-intubated and admitted to the ICU.

Discussion

Peritoneal metastases come as a result of a multi-step process of locoregional cancer spread [11-13].

In detail, tumor cells must first gain access to the peritoneal cavity, spread intra-abdominally via the peritoneal fluid and get attached to the mesothelial surface; then, invasion of the peritoneal surface ensures the necessary vascularization.

Despite the major breakthroughs in the management of this disease, in order to reduce morbidity and mortality, CRS and HIPEC demand a specialized and experienced team, adequate hardware and technology, along with other facilities [14].

In our study, as shown in the Tables, morbidity and mortality reached 44.2% and 4.7%, respectively.

Therefore, identification of the involved risk factors that increase these parameters, is of substantial importance. A direct proportional relation may be identified with the following:

a. Tumor histology
b. PCI
c. Degree of cytoreduction
d. The team's learning curve
e. The surgical technique [15-17]

The group with the higher mortality rate

Table 4. Complications in each patient group

Complications	*Initially admitted to ICU (N=60)*		*Initially not admitted to ICU (N=170)*		*Re-intubated and in need of admission to the ICU (N=15)*	
	N	%	*N*	%	*N*	%
Pneumonia	10	16.6	18	10.6	4	26.8
Atelectasis	6	10	36	21.2	6	40
Pleural effusion	8	13.2	9	5.3	5	33
ARDS	14	23.3	5	2.9	12	80
Postop bleeding	4	6.6	9	5.3	1	6.6
Anastomotic leak	3	5	12	7	1	6.6
Pancreatitis	3	5	9	5.3	2	13.4
Enterocutaneous fistula	4	6.6	18	10.6	5	33
Acute renal failure	4	6.6	6	3.5	8	53.4
Catheter sepsis	8	12.8	30	17.6	6	40
Neutropenia	2	3.2	19	11.2	7	46.6
Mortality	6	10	2	1.2	3	18

ARDS: acute respiratory distress syndrome

which could be assumed to have had the worst prognosis, was that of the patients who, after the initial extubation in the recovery room were in need of re-intubation and ICU admission. The main causes for this development were identified to be ARDS, sepsis and reoperation, mainly presented with bleeding, anastomotic leakage, wound dehiscence and intraabdominal sepsis.

Morbidity and mortality related to CRS and HIPEC come as a result of the combined effects of cytoreduction and the physiological repercussion of the intraoperative chemotherapy and hyperthermia [18].

First of all, a large intraabdominal dissection area, combined with peritonectomy and bowel resections, can cause massive fluid loss. In addition, systemic hyperthermia, which is required during HIPEC, can also lead to hemodynamic changes and instability, resulting in moderate blood loss, peripheral vasodilation and massive fluid accumulation [19]. These alterations in the patient's physiological demands and homeostasis may increase the overall morbidity and mortality. Finally, a significant amount of complications may occur due to the toxicity caused by the cytotoxic drugs that are administered during HIPEC [20].

Consequently, many variables have been reported to be related to postoperative complications; therefore, these variables should be evaluated in order to decide whether a patient needs ICU admission or not after a CRS and HIPEC procedure. Specifically, before making this decision, a surgeon who performs CRS and HIPEC should take into account the patient's age, the performance status, the extent of the procedure, whether diaphragmatic peritoneal resections were performed or not, the number of visceral resections, the perioperative blood loss and respective transfusions, the number and type of anastomoses, the dosage of the administered cytotoxic agent, the (prolonged) operating time, the serum lactate dehydrogenase levels and the (large) intraoperative fluid turnover [20-22].

As we have already mentioned, morbidity and mortality rates were different, though not significantly, when comparing ICU hospitalized and non-hospitalized patients. The important differences were observed in the cases involving major postoperative complications, which demanded reintubation, reoperation and ICU hospitalization, a result that has also been confirmed by previous studies [16].

While the prevalence of these complications could be considered similar, when comparing ICU admitted and non- admitted patients, the severity of these complications is much greater if they appear with a delayed onset, which leads to reintubation and admission to the ICU.

Among the complications, acute renal failure occurred in 5% of the total number of patients, with statistically non-significant differences between the ICU hospitalized and non-hospitalized groups. On the contrary, this percentage increased enormously in critically ill patients, who underwent reoperation. One factor that was identified as crucial for the onset of renal failure was the toxicity of the chemotherapeutic agent and the volume demands. Literature suggests that acute

renal failure after CRS and HIPEC ranges from 1.3 to 4.9% [23,24].

Thoracic complications, such as ARDS, pneumonia, atelectasis and pleural effusion, especially after the use of mitomycin or after diaphragmatic peritonectomies, may be observed in all examined groups, and frequently require interventions or may lead to ICU admission. Specifically, the development of ARDS is present in the majority of patients who need to be admitted to the ICU after initial extubation (80%), having been, in most cases, the main reason for reintubation and transfer to the ICU. Therefore, in our study, ARDS is thought to be a significant predictive factor for increased mortality.

Gastrointestinal complications were found at similar levels for both groups, with digestive fistulas being the most common (ranging from 6.6 to 33%), followed by pancreatitis (5-13.4%), anastomotic leakage (5-7%) and postoperative bleeding (5.3-7%). The same trends have been identified from previous studies, but it should be noted here that the prevalence is higher, when comparing the respective data concerning common elective surgery [16,25-27].

Finally, as already mentioned, the later a patient is extubated in the ICU, the worse his recovery is, since patients that are not extubated in the first 3 postoperative days present a high mortality rate of 35.2% (6/17 patients).

In conclusion, we have identified multiple parameters that play a significant role in the patient's postoperative course, which could indicate whether ICU hospitalization is necessary or not. Therefore, we support that a standardized approach, in the form of a scoring system for instance, could not be easily created and applied in order to decide which patients should be admitted to the ICU after CRS and HIPEC. However, we are in need of a more individualized, patient-to-patient approach, also taking the following into account: patient characteristics, PCI, the extent of resections, the intraoperative anesthesiological parameters and the risk factors.

Conflict of interests

The authors declare no confict of interests.

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