ORIGINAL ARTICLE

Respiratory Complications in the Immediate Postoperative Period after Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy Nowadays: An Observational Study

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Abstract

Background and objectives: Several respiratory complications have been described after cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC).

Materials and methods: Patients admitted to intensive care unit (ICU) after CRS and HIPEC during 10 years.

Data recorded were: Demographic characteristics; severity of illness; complete blood sample; chest radiographs; type of cancer and extension; HIPEC drug and temperature; ICU and hospital stay; and mortality.

Results: Of the 124 patients included, 67 patients (54.0%) presented respiratory complications: 56 (83.6%) acute respiratory failure, 25 (37.3%) pleural effusion, 13 (19.4%) atelectasis, and 3 (4.5%) other; only 1 (3.0%) developed pneumonia. They had higher severity scores at ICU admission. 1 patient required initiation of invasive mechanical ventilation during ICU admission due to pneumonia, and 1 patient needed placement of a pleural chest tube due to symptomatic pleural effusion.

Only the need for a high fluid balance during surgery was correlated to the development of respiratory complications on multivariate analysis.

Median ICU stay was 5 (4.0–5.0) days. ICU mortality was 0.8.0%.

Conclusion: In our study, 54% of patients treated with CRS and HIPEC developed respiratory complications during the postoperative period. However, the majority of these complications were not severe and did not significantly impact mortality rates or hospital stays.

Keywords: Cytoreductive surgery, Hyperthermic intraperitoneal chemotherapy, Peritoneal carcinomatosis, Prognosis, Respiratory complications.

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Highlights

- Respiratory complications after cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) include acute respiratory failure (83.6%) and pleural effusion (37.3%).
- They appeared in 54% of the patients, although they were not related to an increase in hospital mortality or stay.
- They are related to the need for increased water balance during surgery.

Introduction

In some patients with metastatic cancer at the peritoneal level, treatment with CRS and HIPEC has been shown to improve prognosis, as it has been associated with reduced tumor recurrence at the peritoneal level and improved survival. It consists of a first phase of CRS, aimed at resecting as much of the visible tumor as possible, followed by a second phase of HIPEC, in which the peritoneal cavity is perfused with the chemotherapeutic agent heated to an intraperitoneal temperature of 41–42°C in order to kill any remaining cancer cells.[1–3]

Respiratory complications described after CRS and HIPEC include pleural effusion, respiratory distress, respiratory insufficiency, pneumothorax, atelectasis, chemotherapy-induced pulmonary toxicity, and pulmonary embolism.[3–8]

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Early studies showed a high morbidity and mortality, with an incidence of respiratory complications ranging from 3.2 to 69%.[3,6,7,9–11] Currently, due to the improvement of knowledge that has led to the strict selection of patients, technical improvements, and better postoperative management, complications have been significantly reduced across all types of cancer[4,12] except when considering only ovarian cancer.[13]

In view of the latest published data, we decided to carry out an observational study aimed, as a primary objective, at describing the

Table 1: Baseline characteristics of patients

Demographic	*All patients (n = 124)*	*Patients with respiratory complications (n = 67)*	*Patients without respiratory complications (n = 57)*	*p-value*
Male gender (*n* and %)	61 (49.2%)	31 (46.3%)	30 (52.6%)	0.480
Age, years (mean ± S.D.)	59.3 ± 10.5	59.3 ± 10.3	59.4 ± 10.9	0.951
Charlson score (median and IR)	6.0 (6.0–6.0)	6.0 (6.0–6.0)	6.0 (6.0–6.0)	0.222
Previous illness (*n* and %)				
Pulmonary disease	10 (8.1%)	6 (9.0%)	4 (7.0%)	0.752
Heart disease	3 (2.4%)	1 (1.5%)	2 (3.5%)	0.594
Arrhythmia	1 (0.8%)	1 (1.5%)	0 (0.0%)	1.000
Kidney disease	1 (0.8%)	0 (0.0%)	1 (1.8%)	0.460
Diabetes mellitus	17 (13.7%)	10 (14.9%)	7 (12.3%)	0.670
Hypertension	52 (41.9%)	29 (43.3%)	23 (40.4%)	0.742
Type of cancer (*n* and %)				0.283
Digestive cancer	104 (83.9%)	54 (80.6%)	50 (87.7%)	–
Ovarian cancer	20 (16.1%)	13 (19.4%)	7 (12.3%)	–

IR, interquartile range; *n*, number; S.D., standard deviation

current incidence in the immediate postoperative period during an intensive care unit (ICU) stay of respiratory complications after CRS and HIPEC. Also, the factors associated with its development and the associated mortality.

Materials and Methods

We included all consecutive patients who received treatment with CRS and HIPEC and were admitted to our ICU directly from the operating theater, from January 1, 2013 to December 31, 2023, and who agreed to participate in our study (demonstrated by signed informed consent). The only exclusion criterion applied in this study was that the patient declined the offer to participate in this study.

The Institutional Ethics and Clinical Trials Committee of University Hospital Príncipe de Asturias approved this unfunded study.

Variables collected from patient were: Demographic characteristics, severity of disease (measured with the following scales: APACHE II[14] at ICU admission and SOFA score[15] performed on a daily basis), complete blood test (including arterial blood gases) were performed at admission and daily during the ICU (the worst value was collected in the case of having several analytical data in one day), chest radiographs at ICU admission and within the first 96 hours, need of mechanical ventilation and vasoactive support, transfusion of blood products, type of cancer, Peritoneal Carcinomatosis Index (PCI),[1] HIPEC drug and temperature, dates of admission to and discharge from ICU, date of discharge from hospital and status at discharge from ICU and from hospital (alive or dead).

Patients in the ICU were managed according to established protocols, which included oxygen therapy, early mobilization, and incentivized spirometry. Provided that they have no contraindication for it, all patients received venous thromboembolism prophylaxis with enoxaparin.

Qualitative variables are described as percentages and compared using the Chi-square test. Quantitative variables with normal distribution according to the Kolmogorov–Smirnov test are expressed as means ± standard deviation (S.D.) and compared using the Student's *t* test; otherwise, if variables did not meet that criterion, they are described as medians and interquartile ranges and compared using the Mann–Whitney test.

The level of statistical significance was set to a $p = <0.05$, using bilateral contrast, and results were expressed with a 95% confidence interval.

Results

We included in the study 124 patients, since, although 125 were admitted to our ICU after CRS and HIPEC during the study period, 1 did not wish to participate in the study.

Of these patients, 50.8% were women with a mean age of 59.3 ± 10.5 years. Among them, 104 (83.9%) patients had a diagnosis of digestive cancer with a median PCI[1] of 5.0 (1.7–10.2) (Table 1).

Sixty-seven patients (54.0%) developed some type of respiratory complications: 56 patients (83.6%) had respiratory failure, 25 (37.3%) had pleural effusion, 13 patients (19.4%) had atelectasis, and 3 patients (4.5%) had other complications; only 2 patients (3.0%) developed pneumonia.

There were no differences at baseline characteristics between patients who developed respiratory complications and those who did not (Table 1). During surgery, patients who developed respiratory complications received a higher positive fluid balance compared to those who did not develop respiratory complications: 4885.2 ± 1562.2 mL vs 4547.2 ± 1182.4 mL, respectively, $p = 0.000$ (Table 2).

At ICU admission, only 6 patients (4.8%) were under mechanical ventilation without differences depending on whether they developed respiratory complications or not (Table 3). Among these patients, all except 1 who died within the initial 48 h of admission due to massive pulmonary embolism were successfully extubated in the first 24 h of admission.

Among the patients who developed respiratory complications, only one patient (1.5%) required initiation of invasive mechanical ventilation during ICU admission due to pneumonia, and 1 patient needed placement of a pleural chest tube due to symptomatic parapneumonic pleural effusion; the rest were treated conservatively with conventional oxygen therapy and antibiotics, respiratory physiotherapy, and/or diuretics.

Patients who developed respiratory complications had higher SOFA[15] and APACHE II[14] scores at ICU admission [1.0 (1.0–3.0) vs 1.0 (0.0–2.0) ($p = 0.000$)] and 9.7 ± 3.9 vs 8.0 ± 3.9 ($p = 0.020$),

Table 2: Intraoperative period

Variables	*All patients (n = 124)*	*Patients with respiratory complications (n = 67)*	*Patients without respiratory complications (n = 57)*	*p-value*
Peritoneal Carcinomatosis Index (median and IR)	5.0 (1.7–10.2)	6.0 (2.0–12.7)	5.0 (1.0–10.0)	0.305
Intraperitoneal chemotherapy (*n* and %)*				
Mitomycin C	88 (77.2%)	45 (71.4%)	43 (84.3%)	0.103
Cisplatin	53 (42.7%)	33 (49.3%)	20 (35.1%)	0.112
Doxirubicin	19 (30.6%)	12 (29.3%)	7 (33.3%)	0.742
Adriamycin	1 (1.6%)	1 (2.4%)	0 (0.0%)	1.000
Oxaliplatin	16 (22.5%)	9 (20.5%)	7 (25.9%)	0.592
Fluorouracil	9 (14.3%)	8 (19.0%)	1 (4.8%)	0.251
Temperature (median and IR)	43.0 (42.0–43.0)	43.0 (43.0–43.0)	43.0 (41.0–43.0)	0.091
Fluid balance during surgery (mean ± S.D.)	4327.7 ± 1556.1	4885.2 ± 1562.2	4547.2 ± 1182.4	**0.000**
Length of surgery (median and IR)	9.5 (8.0–11.0)	9.0 (8.0–10.2)	10.0 (8.0–11.0)	0.575
Transfusion of blood products during surgery (*n* and %)	18 (14.5%)	11 (16.4%)	7 (12.3%)	0.515

IR, interquartile range; *n*, number; S.D., standard deviation. *Patients received more than 1 chemotherapy drug. Bold values indicate the variables with statistically significant *p*-values

Table 3: Intensive care unit admission

Variables	*All patients (n = 124)*	*Patients with respiratory complications (n = 67)*	*Patients without respiratory complications (n = 57)*	*p-value*
Mechanical ventilation at ICU admission	6 (4.8%)	5 (7.5%)	1 (1.8%)	0.217
Vasoactive support at ICU admission	9 (7.3%)	7 (10.4%)	2 (3.5%)	0.177
APACHE II (mean ± S.D.)	8.9 ± 4.0	9.7 ± 3.9	8.0 ± 3.9	**0.020**
SOFA at ICU admission (median and IR)	1.0 (1.0–2.0)	1.0 (1.0–3.0)	1.0 (0.0-2.0)	**0.000**
Vasoactive support during ICU admission (*n* and %)	16 (13.0%)	11 (16.4%)	5 (8.9%)	0.285
Worse SOFA (median and IR)	2.0 (1.0–3.0)	2.0 (1.0–4.0)	1.0 (0.0–2.0)	**0.000**
Transfusion of blood products during ICU stay (*n* and %)	20 (16.1%)	17 (25.4%)	3 (5.3%)	**0.003**

ICU, intensive care unit; IR, interquartile range; *n*, number; S.D., standard deviation. *Patients received more than 1 chemotherapy drug. Bold values indicate the variables with statistically significant *p*-values

Table 4: Outcomes

Outcomes	*All patients (n = 124)*	*Patients with respiratory complications (n = 67)*	*Patients without respiratory complications (n = 57)*	*p-value*
ICU stay (median and IR)	5.0 (4.0–5.0)	5.0 (4.0–5.0)	4.0 (3.0–5.0)	0.238
Hospital stay (median and IR)	10.0 (8.0–13.0)	10.0 (8.0–13.0)	10.0 (8.5–13.0)	0.990
ICU mortality (*n* and %)	1 (0.8%)	1 (1.5%)	0 (0.0%)	1.000
Hospital mortality (*n* and %)	1 (0.8%)	1 (1.5%)	0 (0.0%)	1.000

ICU, intensive care unit; IR, interquartile range; *n*, number

respectively). Also, they reached a higher SOFA[15] score during ICU admission [2.0 (1.0–4.0) vs 1.0 (0.0–2.0), $p = 0.000$], and more patients required transfusion of blood products [17 (25.4%) vs 3 (5.3%), $p = 0.003$] (Table 3).

Median ICU and hospital stay were 5 (4.0–5.0) days and 10.0 (8.0–13.0) days, respectively. Only 1 patient (0.8%) of those included in the study died due to massive pulmonary embolism during the ICU stay. We found no statistically significant differences in either ICU or in-hospital length of stay or survival among patients who developed respiratory complications or not (Table 4).

We performed a logistic regression analysis to assess the factors associated with the development of respiratory complications. The increased fluid intake during surgery was associated with the occurrence of respiratory complications (Table 5).

Discussion

We found that the incidence of respiratory complications in the immediate postoperative period in ICU stays was high (up to 54% of patients); fortunately, most of them were not severe (97.6%). We only had 1 patient who required mechanical ventilation due to pneumonia and 1 patient who died from massive pulmonary embolism. Only 1 patient needed the placement of a pleural chest tube due to symptomatic parapneumonic pleural effusion.

Table 5: Factors related to development of respiratory complications

	Odds ratio (95% Confidence interval)	*p-value*
Univariate analysis		
Age, years	0.999 (0.966–1.033)	0.951
Male gender	1.290 (0.636–2.619)	0.480
Charlson score	1.190 (0.946–1.497)	0.138
Diabetes mellitus	1.253 (0.444–3.538)	0.670
Hypertension	1.128 (0.551–2.310)	0.742
Pulmonary disease	1.303 (0.349–4.867)	0.694
Arrhythmia	0.000 (0.000)	1.000
Previous heart disease	0.417 (0.037–4.719)	0.480
Previous kidney disease	0.000 (0.000)	1.000
Cancer of digestive origin	1.720 (0.635–4.656)	0.286
Duration of surgery, hours	0.979 (0.809–1.186)	0.831
Temperature, degrees centigrade	1.368 (0.926–2.022)	0.116
Fluid balance during surgery, mL	1.001 (1.000–1.001)	**0.001**
Transfusion of blood products during surgery	1.403 (0.505–3.897)	0.516
Peritoneal Carcinomatosis Index	1.041 (0.988–1.098)	0.132
Intraperitoneal chemotherapy: Mitomycin C	0.465 (0.183–1.181)	0.107
Intraperitoneal chemotherapy: Cisplatin	1.796 (0.870–3.707)	0.113
APACHE II	1.118 (1.016–1.230)	**0.023**
SOFA at ICU admission	1.006 (0.976–1.037)	0.713
Mechanical ventilation at ICU admission	4.516 (0.512–39.840)	0.175
Vasoactive support at ICU admission	3.208 (0.639–16.107)	0.157
Vasoactive support during ICU admission	2.004 (0.652–6.610)	0.225
Worse SOFA	1.007 (0.976–1.039)	0.654
Transfusion of blood products during ICU stay	6.120 (1.691–22.149)	**0.006**
Multivariate analysis		
Fluid balance during surgery, mL	1.001 (1.000–1.001)	**0.001**

Bold values indicate the variables with statistically significant *p*-values

Different rates of respiratory complications in the postoperative period have been described (3.2–69%),[3,6,7,9–11,16] depending on the duration of the postoperative period, the type of underlying tumor, the criteria for respiratory complications, the respiratory data collected, and the patient inclusion criteria applied in studies.

Kusamura et al.[10] described an incidence of 7.1% of respiratory complications after CRS and HIPEC during long-term follow-up of 209 interventions realized during 1995–2004 due to peritoneal metastasis of several origins, being the second most common complication. They reported pneumonia in 9 patients, pleural effusion in 4, pulmonary embolism in 1 and respiratory failure in 1.

Arakelian et al.[7] reported that among 76 patients included in their study between 2005 and 2006, after CRS and HIPEC and followed until hospital discharge, 69% of them had both atelectasis and pleural effusion, and 15% had radiological signs suggestive of heart failure (enlargement, dilatation, or congestion of pulmonary vessels) on radiographs or computed tomography scans performed at the discretion of the physician based on clinical symptoms. However, only in 16% of them pleural drainage was placed, and none of them required reintubation.

Preti et al.[9] found an incidence of severe respiratory complications (defined as pleural effusion, respiratory distress, and pneumonia, which were not asymptomatic or without mild symptoms according to their own classification) of 10% among the patients with appendiceal and colorectal peritoneal metastasis included in their study realized between 2006 and 2009: pleural effusion in 4.6% of patients, pneumonia in 3.2%, and respiratory distress in 4.2%.

Cascales et al.[3] reported an incidence of symptomatic respiratory complications of 3.2% (defined as grade II–V of version 4.0 of the National Cancer Institute Common Terminology Criteria for Adverse Events[17] during hospitalization after CRS and HIPEC and until hospital discharge among 247 patients with peritoneal carcinomatosis secondary to ovarian carcinoma, platinum-sensitive recurrences, colorectal cancer, and gastric cancer treated between 2008 and 2017. The complications were mainly pleural effusion requiring pleural drainage tube placement, but none died as a direct result of respiratory complications.

Sand et al.[11] in their study conducted between 2007 and 2017 with follow-up until 25 April 2019, found an incidence of severe respiratory complications (defined as a grade of 3 or more in the Clavien-Dindo classification[18] of 17% among the 417 patients who received CRS and HIPEC for digestive, ovarian, or peritoneum cancer. They report that 60 patients developed pleural effusion or pneumothorax and required pleural drainage, and 25 patients were reintubated or required prolongation of mechanical ventilation/non-invasive ventilation due to the development of pulmonary complications (respiratory failure, pneumothorax…).

Sinukumar et al.[6] reported a 6.8% rate of pulmonary complications among the 378 patients who underwent CRS +/- HIPEC for peritoneal metastasis of different origins between 2013 and 2017, followed until postoperative day 90. Complications included pneumonitis requiring ICU readmission and/or reintubation, acute respiratory distress syndrome, pleural effusion, and hydropneumothorax.

Zhou et al.[16] describe 11.6% of respiratory complications (6 pneumonia and 4 pleural effusion) among the 86 patients who undergo CRS and HIPEC between 2017 and 2019 and follow-up during 30 days after surgery.

As Arakelian,[7] we found a high incidence of respiratory complications (up to 54%) as we collected all respiratory complications regardless of severity. However, our rate of severe complications was lower at 2.4%, possibly due to the decreased morbidity and mortality over time described in literature and related to a better selection of patients, technical improvement, and, possibly in our case, the initial postoperative management in the ICU.

In multivariate analysis, we found that higher fluid therapy received during surgery correlates with the occurrence of respiratory complications. Although Arakelian et al.,[7] did not find a direct correlation between fluid therapy and respiratory complications, they noted that patients requiring thoracocentesis or chest tubes implanted received larger amounts of fluids during surgery. Other factors have been associated with respiratory complications in the studies carried out: diaphragmatic peritonectomy cascales,[3] higher

PCI (although with different cut-off points according to the studies: >14[3] or >24[7], full-thickness diaphragmatic injury,[11] diaphragmatic resection,[11] blood replacement,[9] and ASA classification grade.[7]

Although the only patient who died in this study was due to a respiratory complication, we did not find a statistical association between the development of respiratory complications and ICU or hospital mortality. Few studies focus on morbidity and mortality associated with the development of respiratory complications. As in our study, Sand et al.[11] described that the development of respiratory complications alone did not affect survival rate; however, when combined with other non-respiratory complications, survival rates decreased. On the contrary, Arakelian et al.[7] found that the development of segmental or larger atelectasis increased the length of mechanical ventilation and therefore ICU and hospital stays. Preti et al.[9] reported that the only death in their study was due to respiratory distress followed by severe neutropenia, and Ramos et al.[4] described 3 deaths during hospital stay due to pulmonary complications: oxaliplatin-induced pulmonary toxicity, sepsis with multiorgan failure due to pleural infection, and bronchial aspiration.

This study has several limitations. There was no standardized intraoperative period management. We included an amalgam of patients with different types of cancer and who received different chemotherapy drugs. We did not measure the rate of diaphragmatic peritonectomy or resection. In our protocol, all patients who undergo CRS and HIPEC remain in the ICU for the first 5 postoperative days, which may influence ICU and hospital stay.

Our strength is to be the most recent study center in respiratory complications developed in the first hours or days after CRS and HIPEC, during ICU stay, in Spain.

Conclusion

In conclusion, our findings indicate that 54% of patients treated with CRS and HIPEC developed respiratory complications during the postoperative period. However, the majority of these complications were not severe and did not significantly impact mortality rates or hospital stays.

Ethics Approval

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Hospital Universitario Príncipe de Asturias on June 30, 2014.

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Author Contributions

Conceptualization and Methodology: María-Consuelo Pintado.
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