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Morbidity and Mortality of Patients with Ovarian Cancer After Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy Hyperthermic Intraperitoneal Chemotherapy

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Abstract

Background: Epithelial ovarian cancer (EOC) remains the leading cause of death due to gynecological malignancy, largely because of the large percentage of advanced stage disease (FIGO stage >II) at initial diagnosis. Although the survival benefit of complete surgical cytoreduction is well established, more than half of patients experience recurrent disease. The addition of hyperthermic intraperitoneal chemotherapy (HIPEC) is a promising treatment option targeting peritoneal carcinomatosis. Associated morbidity remains a significant issue hindering widespread technique's implementation. Our aim is to evaluate the morbidity and mortality of HIPEC and CRS. Patients-Methods: Patients presenting to our department with EOC from 01/2005 to 12/2020 were included in the study. All patients were operated by the same surgical team with curative intent. Patients' demographics, perioperative and follow-up data were collected and analyzed. Results: A total of 284 patients with EOC were subjected to cytoreductive surgery with HIPEC administration during the study period. Mean age was 57.2 and average PCI (peritoneal cancer index) 12.9. Length of hospital stay was 13.6 days and operation time averaged 360 minutes. Overall 30-day mortality rate was 2.1% (6/284). Significant complications were encountered in 65 patients (22.9%). ASA score, blood loss and PCI score significantly predicted postoperative complications. Age, administration of NACT and the need for extensive lymph node dissection did not correlate with perioperative outcomes. Conclusions: The addition of HIPEC to cytoreductive surgery show promising results regarding efficacy feasibility with acceptable peri-operative morbidity and mortality when performed in high volume centers by specialized personnel.

Keywords: Morbidity; Mortality; Ovarian cancer; Cytoreductive surgery; HIPEC

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1. Introduction

Epithelial ovarian cancer (EOC) remains the leading cause of death due to gynecological malignancy worldwide with as many as 13.000 deaths annually in the US [1]. This is largely attributable to the advanced disease stage at the time of diagnosis due to lack of disease specific symptoms in its early course [1, 2]. Approximately 70% of patients present with advanced disease (FIGO stage >II) at initial diagnosis and require extensive therapeutic interventions including extensive cytoreduction (CRS), systemic chemotherapy, and targeted therapies in order to achieve favorable outcomes [3]. The mainstay of treatment consists of complete cytoreduction followed by systemic platinum-based chemotherapy, with the adjunct of targeted therapy [4-6]. The survival benefit of complete cytoreduction is well established as the most significant favorable prognostic factor [5, 6]. Despite the wide availability and implementation of this treatment plan, even with the most modern technology, more than half of advanced stage EOC patients will face a recurrence within the first 2-3 years of treatment [2].

CRS in combination with intraperitoneal hyperthermic chemotherapy (HIPEC) is an aggressive treatment option targeting peritoneal carcinomatosis. The purpose of surgical tumor resection is to achieve cytoreduction with no macroscopically visible disease, while the purpose of the administration of HIPEC is the eradication of the microscopic residual tumor. HIPEC was improvised in the decade of 80s as a mean to eradicate cancer cells deposits after cytoreductive surgery while avoiding the adverse effects of systemic chemotherapy [7]. Since its introduction, it has been implemented in the treatment of peritoneal malignancy of various origins with acceptable morbidity and mortality. The treatment success rates are variable and depend on the histologic subtype of the primary neoplasm and associated toxicity on an already fragile patient group. Although, there is significant discrepancy regarding the technique (open, closed, or semi-closed), regimen of choice and dosage among the experts in the field, the main goal remains the uptake of maximum drug concentration within cancer cells, while avoiding systemic drug toxicity. The main argument about its utilization is the associated morbidity. The rate of morbidity of cytoreductive surgery alone for ovarian cancer as an extensive and time-consuming surgical operation varies from 17.1% to 31.5% [8, 9]. The integration of intraperitoneal chemotherapy to cytoreduction is expected to contribute to excessive morbidity because of the additional complications a, which are associated with chemotherapy (hematologic toxicity, renal toxicity and adverse effects on wound healing). The incidence of mortality after cytoreduction alone for ovarian cancer varies from 1.3% to 4.1% [9]. Data originating from specialized surgical centers demonstrate safety and efficacy of the technique when performed in high volume centers by specialized personnel.

Although HIPEC has not been incorporated yet in the guidelines for upfront surgical treatment of EOC, CRS+HIPEC is gaining popularity among peritoneal surface malignancy specialists. CRS+HIPEC is currently proposed as a treatment option for optimally debulked recurrent ovarian cancer according to the latest guidelines [10].

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The purpose of the study is the presentation of the morbidity and in-hospital mortality in women with stage II-IV ovarian cancer that were treated with extensive cytoreductive surgery in combination with HIPEC and identify the possible prognostic variables.

2. Method

The files of the patients with epithelial ovarian cancer treated from 2005 until 2020 were retrieved. The database was prospectively maintained. Women who underwent CRS and HIPEC were included. Women who underwent only CRS, or open-close surgery, or those who underwent minor surgery as stoma reconstruction were excluded. The outcomes of interest were overall morbidity and in-hospital mortality. The secondary objective was to determine the predictive value of multiple variables on the primary endpoints. The patients' age, the performance status, the ASA class, the tumor volume, the extent of previous surgery (PSS), the extent and distribution of peritoneal malignancy (PCI), the completeness of cytoreduction (CC-score), the number of peritonectomy procedures, the number of anastomoses, the units of transfused blood during surgery, the units of transfused fresh frozen plasma (FFP) during surgery, and the duration of surgery were all recorded in detail. Details from previous surgery made possible the assessment of PSS (prior surgery score) [11]. The anesthesiologist recorded the patients' ASA class by assessing the medical history and performing typical physical examination. The patients were also assessed for their performance status using the Karnofsky performance scale. All patients were operated by the same surgical team consisting of peritoneal surface malignancy specialists after consultation by a specialist MDT. Written consent was obtained from all patients for data collection. The Ethical Committee of the Hospital approved the data collection and the publication of the results (decision number=89/30.01.2024). Complications were stratified according to Dindo- Clavien classification system [12].

2.1. Surgery

All patients underwent mechanical bowel preparation the day before surgery. Prior to tracheal intubation the anesthesiologist positioned an epidural catheter with the patient sitting on the operating bed. One central line, one peripheral venous line, one transcutaneous arterial line, a Foley catheter, and a gastrointestinal tube were always placed before the surgical incision. Piperacillin with tazobactam and metronidazole were administered just before the initiation of surgery and continued for 5 days. Antithrombotic stockings and low molecular heparin derivatives were given from the 1st postoperative day until the 20th postoperative day. The antibiotic treatment was modified in case of infection according to cultures. Post-splenectomy vaccination was always administered in case of splenectomy.

A mid-line incision from the xiphoid process to the symphysis pubis gave access to the abdominal cavity. The xiphoid process was frequently removed if bilateral subdiaphragmatic procedure was considered. A Thompson self-retaining retractor was always used during cytoreduction. After complete lysis of the adhesions the tumor volume and the extent of the peritoneal dissemination was estimated by using the peritoneal cancer index (PCI). After the completion of surgery one drain was placed under the right hemidiaphragm, one in the

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subhepatic space, two drains were placed in the pelvis and another one under the left hemidiaphragm. A thoracostomy tube was always placed in the pleural cavity to avoid pleural effusion if a subdiaphragmatic peritonectomy procedure had been performed. The tube was maintained for 5 days at least. The epidural catheter was maintained for 2-4 days. The gastrointestinal tube was removed when intestinal peristalsis returned and the anastomoses were considered safe. The central line was maintained for 7-10 days and was routinely changed after the 10^{th} postoperative day. All patients were transferred for at least 24 hours in the ICU and were extubated as soon as their temperature returned to normal. Patients with implantations that were found with a maximal diameter < 0.5 cm were considered as having small volume tumor, while those with nodules of a maximal diameter >0.5 cm or confluent of any size were considered as having large volume tumor [11]. After the completion of surgery the peritonectomy procedures were recorded and the completeness of cytoreduction was assessed [11]. The peritonectomy procedures have been described in detail elsewhere [13,14]. HIPEC was possible with Coliseum technique for 90 min after the resection of the macroscopically visible tumor and all the anastomoses were performed after the completion of HIPEC. Cis-platin (50mg/m2) with doxorubicin (15mg/m2) were used for HIPEC while Ifosphamide (1300mg/m2) were infused IV concomitantly with 3 doses of mesna (260mg/m2) every 4 hours. The Sun-Chip device (Gamida, Paris, France) was used for the administration of HIPEC.

All specimens were histologically examined. The histologic type of the tumor, the degree of differentiation, the depth of invasion, and the infiltrated lymph nodes were recorded in detail.

2.2. Statistical analysis

Statistical analysis was possible using SPSS (Statistical Package for Social Sciences, version 17). All recorded variables were correlated with morbidity and mortality. Continuous variables were analyzed by using Student's t-test. Fisher's exact test was used to analyze categorical variables. Logistic regression analysis was used in a multivariate analysis to determine the prognostic variables for morbidity and hospital mortality. The backward elimination method was used to determine which clinical variables best predicted the presence of morbidity and in-hospital mortality. A p value < 0.05 was considered statistically significant.

3. Results

From 2005 until 2020, 284 patients with stage II-IV EOC underwent CRS with the intent of potential cure. The 266 patients underwent CRS plus HIPEC because complete or optimal cytoreduction was achieved (CC-0 and CC-1). Incomplete cytoreduction (CC-2 or CC-3) was performed in 18 patients who did not receive HIPEC (Table 1). The mean age of the patients was 57.24±11.3 (16-83) years. The mean PCI was 12.9±8.6 (0-35). The mean hospital stay was 13.6±8 (0-62) days. The mean operative time was 6±1 hours (2-10). The mean number of gastrointestinal tract resection lines and anastomoses was 3±1 (0-6) and 1±1 (0-3) respectively. The mean estimated blood loss was 265±250 (0-3000) ml. The mean number of transfused blood units 0±1 (0-10) and the mean number of FFP (fresh frozen plasma) units was 4±3 (0-12). The patients' general characteristics are listed in Table 1. All patients received adjuvant

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chemotherapy. The histologic subtype was high grade serous in 96.5% (274 patients) and endometrioid in 3.5 % (10 patients).

Morbidity was recorded in 102 patients (35.9%). The severity of complications is listed in Table 2. The type of complications is listed in Table 3. As shown in Table 4 the performance status, the ASA class, the tumor volume, the CC-score, the age, the lymph node resection, the extent of peritoneal dissemination, the estimated blood loss, the transfused blood units, the transfused FFP units, the number of the resection lines, and the number of the anastomoses were all related to morbidity ($p<0.05$). Multivariate analysis showed that the independent variables of morbidity were the ASA class, the extent of peritoneal dissemination (PCI), and the estimated blood loss (Table 4).

As shown in Table 2 the in-hospital mortality rate was 2.1% (6 patients). One patient died after manifesting cerebrovascular accident, another one because of acute renal failure, a third patient died of sepsis following intra-abdominal abscess adequately drained, a fourth patient died of disseminated peritonitis of unknown source, a fifth patient died of uncontrollable disseminated intravascular coagulation, and a sixth patient died of acute liver failure.

Univariate analysis of in-hospital mortality showed that the estimated blood loss, the transfused blood units, and the transfused fresh frozen plasma units were significantly related to mortality ($p<0.05$). Multivariate analysis showed that the single independent variable of mortality was the estimated blood loss (Table 5).

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Table 1. Patients' general characteristics.

Variable	No	%
Performance status		
90-100%	253	89.1
70-80%	28	9.9
50-60%	3	1.1
ASA stage		
I	238	83.8
II	44	15.5
III	2	0.7
PSS		
PSS-0	101	35.6
PSS-1	44	15.5
PSS-2	97	34.2
PSS-3	42	14.8
Tumor volume		
Large volume	254	89.4
Small volume	30	10.6
CC-score		
CC-0	180	63.4
CC-1	86	30.3
CC-2	12	4.2
CC-3	6	2.1
Azge		
<65	221	77.8
>65	63	22.2
NACT	68	23.9
PCI		
0-13	151	53.2
14-20	71	25
21-39	62	21.8

Table 2. Clavien-Dindo classification.

	No	%
Grade I	30	10.6
Grade II	7	2.5
Grade IIIa	15	5.3
Grade IIIb	42	
Grade IVa	2	
Grade V	6	2.1

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Table 3. Complications.

	No	%
Respiratory tract infection	13	4.6
Cardiac arrhythmia	5	1.8
Liver failure	2	0.7
Postoperative hemorrhage	6	2.1
Anastomotic leak	12	4.2
Wound infection-dehiscence	11	3.9
ARDS	3	1.1
Sepsis of unknown source	2	0.7
Peritonitis	5	1.8
Intra-abdominal abscess	6	2.1
Peripancreatitis	1	0.4
Small bowel penetration	4	1.4
Enterocutaneous fistula	6	2.1
Urine infection	4	1.4
SMV thrombosis	1	0.4
Neurogenic bladder	1	0.4
CVL infection	1	0.4
Pulmonary embolism	3	1.1
Pleural effusion	3	1.1
Hematologic toxicity	3	1.1
DVT	4	1.1
Pneumothorax	1	0.4
Urine leak	2	0.7
DIC	1	0.4
Ileus	2	0.7

Explanations: ARDS=adult respiratory distress syndrome, SMV=superior mesenteric vein, CVL= central venous line, DVT=deep venous thrombosis, DIC=disseminated intravascular coagulation.

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Table 4. analysis of morbidity.

Univariate analysis		**Multivariate analysis**		
Factor	**p value**	**p value**	HR	95% CI
Performance status	0.008			
ASA class	0.006	0.041	4.171	1.028-3.916
PSS	0.879			
Tumor volume	0.014			
CC-score	<0.001			
Lymph node resection	<0.001			
Age	0.021			
NACT	0.199			
PCI	<0.001	<0.001	21.038	1.597-3.21
DS	0.106			
BL	<0.001	0.006	7.7	1.173-2.522
BU	<0.001			
FFP	<0.001			
NA	<0.001			
NRL	0.001			

Explanations: PSS=prior surgery score, NACT-neo-adjuvant chemotherapy, PCI=peritoneal cancer index, DS=duration of surgery, BL= estimated blood loss, BU=transfused blood units, FFP=transfused fresh frozen plasma units, NA=number of anastomoses, NRL=number of resection lines.

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Table 5. analysis of in-hospital mortality.

Univariate analysis		**Multivariate analysis**		
Variable	**p value**	**p value**	HR	95% CI
Performance status	0.829			
ASA class	0.976			
PSS	0.999			
Tumor volume	0.509			
CC-score	0.718			
Lymph node resection	0.795			
Age	0.601			
NACT	0.558			
PCI	0.608			
DS	0.898			
BL	0.017	0.014	6.032	0.101-0.773
BU	0.042			
FFP	0.041			
NA	0.738			
NRL	0.662			

Explanations: PSS=prior surgery score, NACT=neo-adjuvant chemotherapy, DS=duration of surgery, BL=estimated blood loss, BU=transfused blood units, FFP=transfused FFP units, NA=number of anastomoses, NRL=number of resection lines.

4. Discussion

The first cytoreductive surgical operation for the treatment of ovarian cancer was performed by J. Meigs in 1934 [15]. Since then, soon became evident that the survival of patients with ovarian cancer was absolutely related to the residual tumor load. In 1998, Eisenkop et al. showed in a prospective study that complete cytoreduction was feasible and improved survival in women with ovarian cancer [16]. In 2002, Bristow et al. in a meta-analysis showed that cytoreductive surgery without macroscopically residual tumor was the most significant prognostic factor for long survival [4]. This was emphasized in review articles or was reproduced continuously in every other study [17, 18]. The achievement of complete cytoreduction requires extensive surgical manipulations. In 1995 Sugarbaker showed that standard peritonectomy procedures are required to eradicate the peritoneal seedings from the parietal peritoneum [13]. This complex surgery is usually followed by multi-visceral resection for the achievement of complete cytoreduction. All the above surgical manipulations comprise extensive and time-consuming surgery which is expected to be associated by high morbidity and mortality rates. Subsequent studies highlight the significance of upper abdominal peritonectomy, as the strongest predictive factor towards completion of complete cytoreduction [19]. The integration of HIPEC in cytoreductive surgery is expected to increase even more the morbidity rate by adding the possible hematologic adverse effects of chemotherapeutic agents.

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Cytoreductive surgery alone is associated with 33% morbidity rate although severe morbidity does not seem to exceed 11% [17]. The morbidity and mortality rates are dependent on the extent of the surgical procedure which is directly related to the extent of the peritoneal dissemination [21]. There are many other factors that influence the development of complications. The advanced age, the performance status, the low albumin level, the presence of ascites, and the stage IV disease have significant risk of developing postoperative complications, while peritonectomy procedures, splenectomy, and colon resection have been identified as significant predictors for complications [9, 21]. The data about the development of postoperative complications in regard to primary or interval cytoreduction are conflicting. Other studies support that the rate of complication is higher in primary cytoreduction compared to complications on interval cytoreduction [22] and others support that there is no difference in postoperative complications between primary and interval cytoreduction [23]. Systematic abdomino-pelvic lymph node resection has been found to increase a) the operating time, b) the transfusion rate by 12%, and c) the incidence of lymph-cysts and lower limb lymphedema [9].

The integration of HIPEC in the treatment of ovarian cancer showed that the rate of morbidity was increased and varied from 65.6% to 71.4%. However, the rate of severe morbidity (Grade III and IV) varied from 23.9% to 65.6%, and the rate of in-hospital mortality from 0-4.3% [24, 25]. Macri et al, showed in a multi-center Italian retrospective study that although the extent of peritoneal dissemination, the number of blood transfusions, the completeness of cytoreduction, and the number of anastomoses were related to morbidity, only the number of blood transfusions and the extent of peritoneal dissemination were predictors of severe morbidity [25]. In general, CRS alone or in combination with HIPEC is a treatment option performed for peritoneal malignancy of any primary that is associated with morbidity and mortality that is similar to major gastrointestinal surgical procedure such as Whipple's procedure [26, 27]. The unacceptable high morbidity and mortality rate that has been reported in the past appears to reflect the inexperience of the center or improper patient selection [28, 29]. These short-term outcomes have led to the decision that cytoreductive surgery can be safely performed if the learning curve has been achieved [30- 32]. The required number of surgical operations is at least 110 and according to others is 140-150 cytoreductions [30, 31, 33].

Cytoreductive surgery for ovarian cancer is similar to cytoreduction performed for any other primary tumor. It has been shown that the prognostic indicators of severe morbidity are extensive previous surgery, smoking history, poor performance status, and extensive cytoreduction [34]. One of the first publications has shown that the duration of surgery, the number of peritonectomy procedures, and the number of the suture lines have been related to morbidity [35]. Enterocutaneous fistulas and anastomotic leaks have been recorded as the most frequent complications. Extensive lysis of the adhesions result to seromuscular tears of the small bowel which later develop enterocutaneous fistulas. In addition, fistulas very frequently develop after bowel obstruction, and prior intraperitoneal chemotherapy or radiotherapy [36]. It has been established that HIPEC has an adverse effect on wound healing, thus the development of fistulas is more probable [35]. Resections of pancreas or rectum, as well as multiple anastomoses have

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been identified to be related to morbidity, while advanced age and re-operation are related to mortality [34].

A recently published single-centre study, investigating morbidity and in-hospital mortality in interval cytoreductive surgery and HIPEC for advanced stage ovarian cancer (III/IV) demonstrated an overall complication rate of 58.1 % and no in-hospital mortality in a total of 31 patients [37]. However, significant complications (Grade 3 and 4) were only observed in 6.5 %. We did include a larger number of patients, including both upfront, interval and secondary/tertiary debulking. Differences in the sample size and patient selection constitute difficult the direct comparison with our study.

Well-designated randomized controlled trials are required to define the merits of HIPEC in specific subgroups of patients with ovarian cancer not only in terms of overall and disease-free survival, but also in terms surgical morbidity and mortality. Van Driel et al. conducted a multicenter RCT to evaluate the benefit of HIPEC in patients with Stage III ovarian cancer undergoing interval debulking. The findings confirmed a significant benefit in the HIPEC group in terms of overall and recurrence free survival. With regards to safety, grade 3 and 4 complications were similar between the HIPEC and the control group. Overall, severe complications were estimated at 27% for patients receiving HIPEC. Our results are consistent with a slightly lower complication rate in the HIPEC group (22.9% vs 27%). Inclusion of patients with less advanced disease (Stage II) and different regime for HIPEC could explain the slight differences observed [38].

Lim et al conducted a randomized trial recruiting patient with Stage III and IV ovarian cancer that underwent optimal primary or interval debulking. The intervention group which received HIPEC had increased progression-free and overall survival, but the difference did not reach statistical significance. By subgroup analysis in patients undergoing interval debulking, the difference in the primary endpoints reached statistical significance in favor of HIPEC. The same trend was not confirmed in the primary debulking subgroup. The same study investigated associated complications and commented on the higher incidence of overall Grade 3 and 4 complications in the HIPEC groups, which was significant for electrolyte disturbances in the HIPEC group [39].

The potential role of upfront HIPEC for advanced stage ovarian cancer has been previously investigated. Paris et al. conducted a prospective analysis of 40 cases of advanced ovarian cancer that received upfront HIPEC during primary cytoreduction with the addition of bevacizumab [40]. The results demonstrated acceptable progression free survival and morbidity in this group. Associated complications were manageable and there were no delays in subsequent adjuvant chemotherapy administration.

Emerging evidence also suggests that other variables such as the time interval between HIPEC and last systemic chemotherapy warrant consideration in patient selection. Kim et al.

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systematically reviewed and analyzed data from comparative studies and RCTS and concluded that recent systemic chemotherapy exposure within 6 months signifies a considerable benefit of HIPEC [41].

Regarding recurrent disease and the role of HIPEC in secondary debulking surgery, the literature is inconsistent. Few randomized trials attempted to provide some insight to that hypothesis. The initial HORSE study stated that addition of HIPEC to secondary debulking surgery for recurrence in platinum-sensitive tumors (relapse > 6 months after initial platinum-based chemotherapy) carries no additional benefit in regards to the progression-free survival in cases without neoadjuvant chemotherapy [42]. The subsequent larger CHIPOR demonstrated that HIPEC is associated with significant improvement in overall survival in patients experiencing a first relapse > 6months after initial exposure to platinum-based chemotherapy, provided that 6 cycles of platinum-based chemotherapy were administered preoperatively [43]. The above studies give us significant insight and highlight the need of further research to detect significant differences between different subgroups and guide patient selection.

In our study morbidity was not found to be related to interval or primary, secondary or tertiary cytoreduction. Although it was related to many variables, the ASA class, the extent of peritoneal dissemination, and the estimated blood loss were identified as the predictors of morbidity. The most frequent severe complications were the anastomotic failures. The in-hospital mortality was 2.1% (6 patients) and was found to be associated to blood loss during surgery. The blood loss was also identified as the predictor of in-hospital mortality. We have not recorded high incidence of entero-cutaneous fistulas and the hematologic toxicity has been very low. The study includes 284 women with stage II-IV epithelial ovarian cancer treated between 2005 and 2020. During the same period a respectable number of patients with peritoneal malignancy of any other origin underwent treatment with CRS and HIPEC by the same surgical team which means that the learning curve had been already achieved. Nevertheless, 18 women with ovarian cancer comprising 6.3% of the sample underwent incomplete cytoreduction. Although the preoperative work-up demands thorough examination of the patients and proper patient selection, the imaging techniques fail to depict the real extent of the peritoneal malignancy leading to improper patient selection with disappointing results because of unacceptably increased morbidity.

The strength of the study is the large number of the included patients who were treated by the same surgical team. Although the patients were prospectively enrolled the end-points were retrospectively identified which includes selection bias. Other weaknesses of the study are that the patients' nutritional status or significant histopathologic data were not taken into account in the analysis. Inclusion of those additional variables might give valuable data. Our study represents our experience from a single center and incudes patients that underwent either interval debulking or primary, secondary, and even tertiary debulking. Heterogeneity of the patients sample needs to be considered in results interpretation.

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