

Factors Affecting Early Morbidity and Mortality in Patients with Complete Cytoreduction for Peritoneal Carcinomatosis

Peritoneal Karsinomatoz için Komplet Sitoreduksiyon Yapılan Hastalarda Erken Morbidite ve Mortaliteyi Etkileyen Faktörler

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Abstract

Objective	Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy practice is the combined treatment modality used in selected patients for the treatment of peritoneal carcinomatosis. In our study, we investigated the development of early complications and the factors affecting the early stages of complications in patients who underwent cytoreductive surgery and hyperthermic intraperitoneal chemotherapy due to peritoneal metastases of tumors of different origin.
Materials and Methods	Medical records of 76 patients who operated in our hospital for peritoneal metastases between 2014 and 2019 evaluated retrospectively. Only 61 patients who underwent complete cytoreduction (CC/0) included in the study.
Results	Peritoneal Cancer Index and operation time found to be independent risk factors for major complication development. In terms of major complication development, operation time and Peritoneal Cancer Index cutoff value found to be 7 hours and 10 respectively.
Conclusion	We have demonstrated in our study that the fact that the PCI is higher than ten and operation time lasts more than 7 hours is the reason that increases major complications and mortality in patients undergoing CC/0. All efforts should be made to perform CC/0 resection, but more care should be taken in patients having a PCI over 10 and when extending the operation time over 7 hours. In these patients, postoperative complications increase peri-operative mortality and lead to early recurrence and short survival.
Keywords	complete cytoreduction; hyperthermic intraperitoneal chemotherapy; peritoneal carcinomatosis

Öz

Amaç	Sitoreduktif cerrahi ve hipertermik intraperitoneal kemoterapi uygulaması, peritoneal karsinomatoz tedavisinde seçilmiş hastalarda kullanılan kombine tedavi yöntemidir. Çalışmamızda orijini farklı tümörlerin peritoneal metastazlarına bağlı olarak sitoreduktif cerrahi ve hipertermik intraperitoneal kemoterapi uygulanan hastalarda erken komplikasyonların gelişimini ve komplikasyonların erken evrelerini etkileyen faktörleri araştırdık.
Gereç ve Yöntem	Hastanemizde 2014-2019 yılları arasında periton metastazı nedeniyle ameliyat edilen 76 hastanın tıbbi kayıtları retrospektif olarak değerlendirildi. Çalışmaya sadece tam sitoreduksiyon (CC/0) uygulanan 61 hasta dahil edildi.
Bulgular	Periton Kanser İndeksi (PKİ) ve operasyon süresinin majör komplikasyon gelişimi için bağımsız risk faktörleri olduğu bulundu. Majör komplikasyon gelişimi açısından ameliyat süresi eşik değeri 7 saat ve Periton Kanser İndeksi eşik değeri 10 olarak bulundu.
Sonuç	Çalışmamızda, CC/0 uygulanan hastalarda PKİ'nin ondan fazla olması ve ameliyat süresinin 7 saatten fazla sürmesinin majör komplikasyonları ve mortaliteyi arttıran neden olduğunu gösterdik. CC/0 rezeksiyonu yapmak için her türlü çaba gösterilmelidir, ancak PKİ'si 10'un üzerinde olan hastalarda ve operasyon süresini 7 saatin üzerine uzatırken daha fazla özen gösterilmelidir. Bu hastalarda postoperatif komplikasyonlar perioperatif mortaliteyi artırarak erken rekürrens ve kısa sağkalma neden olabilir.
Anahtar Kelimeler	komplet sitoreduksiyon; hipertermik intraperitoneal kemoterapi; peritoneal karsinomatoz.

INTRODUCTION

Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is the combined treatment modality used in selected patients for the treatment of peritoneal carcinomatosis (PC). The purpose of cytoreductive surgery is the surgical resection of all visible tumor tissues and intra-operative HIPEC to destroy microscopic tumor cells.¹

The response to systemic chemotherapy is limited in the treatment of the gastrointestinal system tumors and ovarian tumors with peritoneal metastases. In peritoneal cancers, the peritoneal blood barrier prevents chemotherapeutic drugs from reaching the cancer tissue. Hence, patients with peritoneal metastases have lower survival rates than patients with non-peritoneal metastases.^{2,3} Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS / HIPEC), as described by Sugarbaker since the 1990s, provides long life and cure opportunities in selected patients with peritoneal metastases.^{4,5} Today, this treatment is successfully used in the treatment modality of colo-rectal, appendix, ovarian, mesothelioma, and gastric cancers.⁶⁻⁹

The purpose of CRS and HIPEC treatment is to remove the tumors in the intra-abdominal organs and peritoneum (Complete cytoreduction) and then to give heated chemotherapy into the abdomen.^{4,9,10} In this treatment, multiple organ resections may be required due to the involvement of the organs with the tumor. Performing such aggressive surgery brings complications, hence the rate of mortality and morbidity increases.^{1,5,11,12} For morbidity and mortality, different rates have been reported in the literature, while mortality reported between 0-18%, morbidity reported between 30-70%. Mortality and morbidity rates are decreasing with experience and reported respectively as 1.5 - 4.1% and 24-33.4%.¹³⁻¹⁵

Factors that increase postoperative morbidity and mortality are factors such as elevated peritoneal cancer index

(PCI), long operation times, excessive blood loss, patients' age, and performance status, pre-operative sarcopenia, the width of peritonectomy, number of resected organs.^{5,13,16} The experience and learning curve of the center are significant factors for realizing CC/0 resection with low morbidity and mortality rate. Cytoreductive surgery and HIPEC can be performed with lower morbidity and mortality in the high-volume centers.^{13,17}

In our study, we investigated the development of early complications and the factors affecting the early stages of complications in patients who underwent Cytoreductive Surgery and HIPEC due to peritoneal metastases of different tumors.

MATERIALS and METHODS

This study was performed retrospectively by collecting data with the approval of our hospital Ethics Committee on 31/03/2021. The ethical number of this study is E1-21-1684.

Medical records of 76 patients who operated in our hospital for peritoneal metastases between 2014 and 2019 evaluated retrospectively. Sixty-one patients, to whom CC/0 performed removing all visible tumors, were included in the study. Patients that did not undergo CC/0 surgery excluded from the study. In terms of the primary tumors of the patients, 17 patients suffered from colorectal, 14 from gastric, 12 from ovarian tumors, 14 from pseudomyxoma peritonei, one from mesothelioma, and three from small bowel tumors. Patients were prepared for the operation by evaluating CT, MR, colonoscopy, endoscopy, blood tests, and performance status in pre-operative staging.

ECOG (Eastern Cooperative Oncology Group Score) used in the pre-operative evaluation of the patients. Patients with ECOG score over three did not operated due to comorbid diseases. No extra-abdominal metastases detected during the pre-operative examination of the patients. The nutritional status of the patients assessed according to

NRS 2002 and sufficient nutritional support provided to the patients in need.

CRS + HIPEC practice

All operations were performed in the same center and by the same experienced surgical team. In all operations, midline incision between the xiphoid process and pubic tubercle used. PCI was determined as described by Sugarbaker by making an entire abdominal exploration.^{18,19} Patients who were not suitable for surgery or palliative procedures excluded from the study. All other patients operated CC / 0 until there is no visible tumor left, and HIPEC applied to all of these patients after CRS. According to the spread of the surgical tumor, 5-zone peritonectomy and multiple organ resections performed as described by Sugarbaker.^{1,4,19} In all operations, total operation time, blood replacements, organ and peritoneal resections performed, urine flows were recorded. When it ensured that no visible tumor remained, the abdomen washed with 5 liters of heated SF. For HIPEC, two inflow and two outflows drain placed in the abdomen, and the abdomen of the patient temporarily closed for the closed system HIPEC. HIPEC applied to all patients at a temperature of 42-42,5 degrees in Oxaliplatin 350 mg/m² in a 5% dextrose solution for 30 to 60 minutes. A dose of 15 mg/m² Mitomycin is applied in the intraperitoneal to 15 patients for 60 minutes. After the HIPEC application, the abdomen rewashed with 5 liters of heated SF, and all anastomoses performed after this phase.

Postoperative period and data analysis

The patients were transferred to the intensive care unit after the operation and followed up. Patients recorded in terms of gastrointestinal, hematological, urinary, respiratory, and neurological complications, and they daily observed. Complication developments were examined retrospectively for the first 30 days. Complication grading performed according to National Cancer Institute Common Terminology Criteria for Adverse Events version (NCICTCAE) 3.0.20 The patients analyzed in three categories; patients

without postoperative complications, patients with minor complications, and patients with major complications. In terms of major complications, endoscopic or CT/USG guided interventions evaluated as grade 3, re-operative interventions were evaluated as grade 4 while the operative death evaluated as grade 5 (20). Complications divided into three groups according to their grades.

- Group: 0, without complications,
- Group: grade 1,2, patients with minor complications,
- Group: grade 3, 4, 5, patients with major complications,

Patients classified according to the development of complications compared in terms of age, gender, primary or recurrence of tumor, ECOG, pre-operative albumin levels, PCI, operation times, organ resection number, number of peritonectomy, pre-operative CEA and CA19-9 values. We evaluated peritonectomy, on five regions as anterolateral, left diaphragmatic, right diaphragmatic, pelvic and hepatoduodenal.

Statistical analysis

We used SPSS software, version 17 (SPSS Inc., Chicago, IL, USA) in this study for statistical analysis. Descriptive data were expressed as mean or median (range). Categorical variables were described using frequency distributions. Independent sample t-test was used to detect differences in the means of continuous variables and the Chi-square test was used in cases with categorical variables. A p-value < 0.05 was considered significant.

RESULTS

Only 61 patients who underwent CC / 0 cytoreduction included in the study. Primary tumor localization areas displayed in table 1.

Primary malignancy area	n (total number of patients)
Over Ca	12 (19.7%)
Colon Ca	17 (27.9%)
PMP	14 (23%)
Gastric Ca	14 (23%)
Other (small intestine, mesothelioma)	4 (6.5%)

The demographic characteristics of the patients are as given in Table-2. Complications and frequency of the complications are as presented in Table 3.

Characteristics of Patients	Total (61 patients)
Female/Male	37 (60.7%) / 24 (39.3%)
Mean Age	54.4 ± 1.19
Median PCI (min-max)	7 (0-30)
Primary / Recurrence	18 (29.5%) / 43 (70.5%)
Mean Pre-operative albumin level	4.25 ± 0.48
ECOG	
ECOG 0	8 (13.1%)
ECOG 1	37 (60.7)
ECOG 2	16 (26.2)
Mean CEA	10.97 ± 2.90
Mean CA19-9	53.11 ± 1.18
Median Operation Time	7 (2-15)
Median number of organs resected	2 (0-6)
Mean number of peritonectomy	2 (0-5)
Complication	
Present	36 (59%)
Absent	25 (41%)
Length of hospital stay after the operation	20.13 ± 1.78

All complications	35 (57.4%)
Pneumonia	4 (11.42%)
Enterocutaneous fistula	5 (14.28%)
Pancreatic fistula	1 (2.85%)
Reoperation due to anastomosis leak and bleeding	3 (8.57%)
Intra-abdominal collection, abscess	9 (25.71%)
Wound infection	8 (22.85%)
Diarrhea	3 (8.57%)
Atelectasis, pleural effusion	3 (8.57%)
Evisceration	3 (8.57%)
Gastrocnemius compartment syndrome	1 (2.85%)
Neurological	2 (5.71%)
Hematological	1 (2.85%)

When the complications of the patients are categorized separately, Grade 1-2 complications observed in 16 patients, Grade 3-4 complications observed in 18 patients, and Grade 5 complications observed in 3 patients, and the data shown in the histogram in Figure 1.

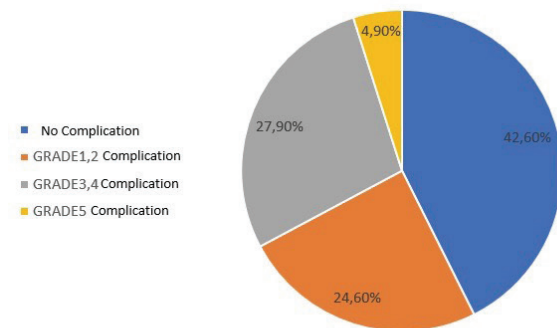


Figure 1: The distribution of complications by grade.

When examined by univariate analysis for the postoperative minor and major complications, it was found that age, gender, primary surgery or recurrence of tumor, number of organ resections, number of peritonectomy areas, CEA and CA19-9 parameters were not related in terms of complications.

PCI ($p < 0,001$) and operation time ($p < 0,001$) found to be independent risk factors for major complication development. In terms of major complication development, operation time and PCI cutoff value found to be 7 hours (Figure 2) and 10 (Figure 3), respectively.

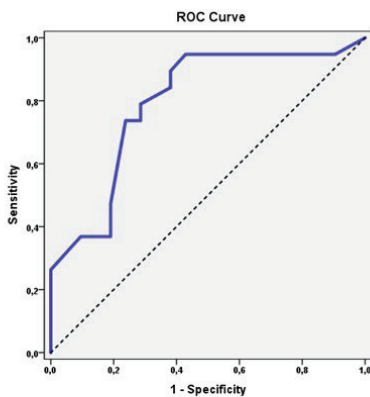


Figure 2: ROC curve for PCI levels compared to groups with no complications and three or more complications.

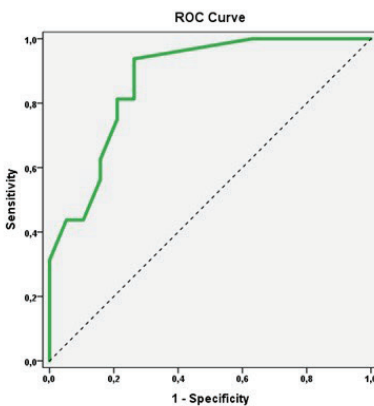


Figure 3: ROC curve for operation times according to groups with no complications and three or more complications.

DISCUSSION

Cytoreductive surgery (CRS) and intraperitoneal hyperthermic intraperitoneal chemotherapy (HIPEC) was described as a surgical procedure by Sugarbaker in 1995 after the publication of its first use in 1980 to treat pseudomyxoma peritonei (PMP). In the last two decades, it occupied an essential place in the treatment of peritoneal metastases caused by colon, PMP and ovarian carcinoma and provi-

ded a chance of treatment.^{4,18,21-23} Many studies have revealed that resection removing all the visible tumors is the most significant prognostic factor for prolonged survival in patients with peritoneal metastases.^{1,17,24,25}

We investigated in our study the factors affecting morbidity and mortality rate after CC / 0 resection and HIPEC surgery in patients with peritoneal carcinomatosis. Literature published in recent years implies that CRS and HIPEC operation, which is mainly performed for colon, ovarian cancer, and PMP, can be used for gastric, neuroendocrine tumors, and some rare sarcomatous malignancies.^{8,21}

Very different morbidity and mortality rates reported after an aggressive treatment as CRS and HIPEC. While low mortality rates reported in experienced centers as 2.8 - 4%, the literature revealed this rate as high as 12-18%.^{11,13,18,26} Similarly, different rates, such as 30-70% and 12-66% for overall morbidity and major morbidity, are presented in the literature.^{11,20,26,27}

We found in our study the total morbidity and mortality rates as 57.4% and 4.9%, respectively. Additionally, we discovered the complication rate exceeding grade 3 to be 32.8%. It is possible to explain the most critical reason for major complications and high mortality with the performance of CC / 0 resection in all patients. We ascertained in our study the two main factors affecting the development of complications of grade 3 and above as PCI and operation time.

Considering the literature, several studies on cytoreduction and HIPEC treatment assessed under the heading of complete cytoreduction; hence, patients who underwent CC / 0 and CC / 1 were evaluated together.^{22,28,29} Survival and morbidity of this group were investigated. The results obtained were the common results of these two categories (CC / 0 and CC / 1).^{5,12,21,30} Hence, the correlation between the average PCI and operation and the average operation time is incorrect. In our study, we investigated the

factors affecting morbidity and mortality in patients who underwent CC / 0 resection exclusively for peritoneal metastases and HIPEC surgery added to their treatment. The operations of CC/O take a long time, and the risk of complication increases since the procedure continues until there is no visible tumor. The diaphragm, pelvic region, vena cava, and portal triad are essential areas, and it takes a long time to apply the dissection. Tumor resection by peeling the liver Glisson capsule is another factor that prolongs time and increases morbidity. Slow and careful surgical dissections may be required to clear these areas from the tumor completely. Thus, the risk of complications increases when trying not to leave visible tumors. We discovered in our study that operation time longer than 7 hours and PCI index above 10 are independent factors that increase the risk of occurrence of the major complications. In our research, we have ascertained that the two most frequent postoperative complications are respectively the intraabdominal abscess and entero-cutaneous fistula. We found the major complication that caused mortality as an anastomosis leak.

We determined in our study that the operations performed due to recurrent disease, the number of organ resections, and the number of peritonectomy did not affect postoperative complications. Various studies have shown that the number of resected organs increases postoperative complications.^{16,20,31} We discovered in our research that the average number of organ resections is 2.2 (0-6), and it did not increase the postoperative complication. Peritonectomy includes the anterior parietal, left diaphragm, right diaphragm, and pelvic peritonectomy and omental bursectomy, as defined by Sugarbaker. In our study, we revealed the average number of peritonectomized areas to be 1.8 (0-5). Left diaphragm and anterior peritonectomy performed most frequently. Although the number of peritonectomy has been shown to increase peri-operative morbidity in some series, the effect of the number of peritonectomy on complication development was not identified in our series. Chua et al. showed that left diaphragmatic peritonectomy

increased complication development. Still, in our series, although it was the most common peritonectomy area, no statistically significant effect was observed on the complication development.^{32,33} Although complete cytoreduction performed due to recurrent disease are more susceptible to injuries during dissection, we noticed that in our study, it did not increase the complication development.

In their study, Geert et al. found that postoperative complications were a predisposing factor for the development of early recurrence.³⁴ In the study where factors such as PCI, CC score, blood loss examined, they reported that only the development of Grade 3 \geq postoperative complications was a risk factor for early recurrence, and the survival in these patients was significantly low. In another study evaluating colorectal-induced peritoneal metastases that are cure and non-cure, it published that postoperative complications were less in cured patients and more in non-cured patients.²⁸ Based on the conclusions of these studies, it is reasonable to say that the development of postoperative complications not only affects peri-operative survival but also increases the frequency of early recurrence and decreases survival.

Verwaal et al. reported 48 months of median survival and 45% of 5-year survival in peritoneal metastases of colorectal origin cancers after aggressive cytoreduction in their prospective randomized study.³⁵ In recurrent ovarian cancers, 52 months of median survival reported in platinum-sensitive patients with CRS + HIPEC, and 48 months of median survival was reported with patients-resistant patients.²³ Elias et al. published 62 months of median survival in peritoneal cancers in their retrospective series.³⁶ Studies have revealed that complete cytoreduction (CC / 0) with no visible tumor remains an independent prognostic factor and is one of the most critical determinants of survival.^{1,9,13,24,35}

Berger et al. discovered the increase in mortality and morbidity after extreme CRS / HIPEC in their study.¹¹ In our

series, operation time and PCI found to be significant risk factors in terms of both major complications and minor complications in line with the literature.^{5,13,20,27}

The extended operation period has reported as an independent variable that increases complications in many studies, even if the cutoff point is not provided.^{11,27,37} We found in our research that operation time longer than 7 hours was a significant risk factor for the development of major complications.

In the literature, PCI values pose a risk for complication development given as high values such as 17-30.^{5,17,20,33} Unlike the results of the literature, we found that the value of PCI exceeding 10 was a significant risk factor for major complications. It is possible to explain the most crucial reason for the low level of major complications with the performance of CC / 0 resection in all patients. As in other studies, we think that the examination of CC0 and CC1 resections in the same category may have led to high PCI value. When a complete resection performed, lower PCI may require more extended operations. Complete resection directly affects morbidity and mortality.

CONCLUSION

We have demonstrated in our study that the fact that the PCI is higher than ten and operation time lasts more than 7 hours is the reason that increases major complications and mortality in patients undergoing CC / 0. All efforts should be made to perform CC/0 resection, but more care should be taken in patients having a PCI over 10 and when extending the operation time. In these patients, postoperative complications increase peri-operative mortality and lead to early recurrence and short survival.

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Conflict of interest/Competing interests

The authors declare that they have no conflict of interest.

This study was performed retrospectively by collecting data with the approval of the Hospital Ethics Committee on 31/03/2021. The ethical number of this study is E1-21-1684.

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