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Extreme cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in treatment of peritoneal metastasis

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ABSTRACT

Objective: It was aimed to define the oncologic concept of "extremeness" in cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) to determine morbidity-mortality results and final oncologic outcomes.

Material and Methods: Prospectively recorded data of 666 patients with peritoneal metastases who had undergone CRS/HIPEC between 2007 and 2020 were analyzed. Patients were divided into two groups as extreme (n= 371) and non-extreme (n= 295). Extreme CRS was defined as resection of ≥5 major organs or creation of ≥2 bowel anastomoses or peritoneal carcinomatosis index (PCI)≥ 15 or re-cytoreductive surgery.

Results: More CC-1 or CC-2 cytoreduction (p< .001), increased mortality and morbidity (p< .001), prolonged operative time (p< .001), increased intra-operative erythrocyte suspension (p< .001), albumin (p< .001), fresh frozen plasma (FFP) (p< .001), and post-operative erythrocyte suspension (p< .001) usage were found in the extreme CRS/HIPEC group. Operative time, CC-1 or CC-2 cytoreduction, presence of ostomy, development of infection, and use of intra-operative albumin and FFP were found to be independent prognostic factors in Cox regression analysis. Three and five-year survival rates were significantly lower in the extreme CRS/HIPEC group (p< .001).

Conclusion: High-volume peritoneal metastatic disease can be completely resected with extreme cytoreduction in carefully selected patients responsive to chemotherapy. Since the significant morbi-mortality related to the treatment of peritoneal metastasis is a real concern, it should be considered in experienced complex cancer centers that provides relatively better oncological outcomes compared to conventional treatments.

Keywords: Cytoreductive surgery, hyperthermic intraperitoneal chemotherapy, peritoneal metastasis

INTRODUCTION

Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is an effective treatment modality in peritoneal metastasis of various solid organ cancers such as colon-rectum, appendix, peritoneal mesothelioma, stomach and ovaries. In selected patients, this aggressive abdomino-pelvic oncologic approach can now be undertaken with decreasing morbi-mortality results and is associated with better survival outcome (1-6). The aim of CRS is to achieve a complete cytoreduction, in which all the visible tumor foci are removed. Only then, regional chemotherapy, HIPEC, can be applied for the eradication of microscopic disease. It has been shown in many studies that a complete cytoreduction is significantly associated with prolonged disease-free and overall survival, and is considered the most important prognostic/predictive factor (2,7). However, to reach a complete cytoreduction is a highly difficult and compelling task in a high-risk cancer patient usually treated with prior surgery and/or chemo-(radio)therapy regimens. It is associated with the center's experience of patient selection, peritoneal cancer index, the extent andntype of tumor burden, and intraoperative multidisciplinary contribution. It is often achieved through complex surgical care that requires very demanded oncologic skillsets of multivisceral organ resection and reconstructive procedures for total tumor resection and gastrointestinal continuity. All of these maximum efforts can end up with increased morbidity, prolonged hospital stay and readmission(s), exhaustion of hospital resources, and the delay of postoperative adjuvant chemotherapy.

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Very recently, many authors have described a subgroup of patients who require complex multiple peritoneal and visceral resections and multiple bowel anastomoses as "extensive" or "aggressive" or "extreme" CRS/HIPEC procedures (8-11). By bringing the cytoreductive surgery concept too far than the so-called "standard" cytoreductive ones, the researchers have reported favourable oncological outcomes with comparative perioperative morbi-mortality.

The aim of this study was to define the oncological concept of "extremeness" in CRS/HIPEC and to interrelate the extreme cytoreduction with the overall complications and final oncologic outcomes.

MATERIAL and METHODS

All procedures performed in this study were in accordance with the ethics standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethics standards. The study was approved by local ethics committee. All patients gave their written consent both for surgery and participating in the study.

This was a retrospective analysis of prospectively collected data on 666 patients with peritoneal metastasis (PM) who underwent CRS and HIPEC at our Peritoneal Surface Malignancy Center from 2007 to 2020. Patients had peritoneal metastases from various types of malignant tumors. The exclusion criteria were:

1. The presence of unresectable extra-abdominal distant metastasis
2. Extensive portal peduncle or small bowel involvement
3. Retroperitoneal bulky or plaque-type tumor invasion
4. Invasion of major vessels or bilateral ureters
5. Circumscribed pelvic side wall involvement
6. Low performance status; nutritonally-frail, and medically unfit patients
7. Refusal to sign the informed consent form (non-compliant to compos mentis)

The patients were divided into two groups as extreme and non-extreme CRS. Extreme CRS was defined as resection of ≥5 major organs or creation of ≥2 bowel anastomoses or peritoneal carcinomatosis index (PCI)≥ 15 or re-CRS. Major organs were considered as any of the following: colon, rectum, small bowel, spleen, pancreas, stomach, gallbladder, diaphragma (full thickness resection), liver (paranchymal resection> one segment), uterus/ovaries, and urinary bladder/ureter/kidney. Omentum, peritoneum, and Glisson capsule resection were not included. Patients having extreme CRS/HIPEC were compared with the non-extreme group in terms of perioperative morbidity, mortality, and the final oncologic outcomes.

Preoperative Assessment

The eligibility of the patient for CRS and HIPEC was evaluated in the multidisciplinary tumor board. The assessment for preoperative staging was initially performed with thoraco-abdominal-pelvic computed tomography and supplemented with MRI and/or positron emission tomography. Co-morbidities were assessed by Charlson co-morbidity index (12). Patients' co-morbidities, the ECOG performance and nutritional status were all managed individually and the prehabilitation program was entegrated according to the risk stratification. In patients who received neoadjuvant chemotherapy, the surgical procedure was planned to perform at least four weeks after the last dose of chemotherapy.

Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

All patients had mechanical bowel preparation and venous thromboembolism prophylaxis. Intravenous 1.5 g cefuroxime axetil and 500 mg metronidazole were administered 30 min before surgery and repeated in q8hr.

The main purpose of CRS, as Sugarbaker PH et al. have previously described, is to achieve the resection of all macroscopic visible tumor nodules in the abdomino-pelvic region (13) (Figure 1). The extent of the peritoneal cancerous involvement and the burden of the peritoneal disease were calculated by PCI (14). After the completion of the surgical procedures, completeness of the cytoreduction was measured, according to "completeness of cytoreduction" score (No residual tumor, CC-0; residual tumor ≤2.5 mm, CC-1 and residual tumor> 2.5 mm, CC-2) (15).

HIPEC perfusion was performed with closed technique and cytotoxic chemotherapy with a peritoneal dialysis solution at 42.5°C for 30 mns (Oxaliplatin) or 90 mns (Mitomycin and Cisplatin). The regimen of chemotherapeutic agent(s) to be used during HIPEC was decided by experienced medical oncologists according to the clinicopathologic and medical features of the patient and the disease. All anastomoses were performed before HIPEC.

Early Postoperative Care and Follow-Up

Common Terminology Criteria for Adverse Events was used to record postoperative morbidity and HIPEC toxicity (16). Death within 30 days after surgery and hospital mortality were recorded as mortality.

Statistical Analysis

Statistical analysis was performed using SPSS 22.0. Categorical variables were compared among the groups using Pearson $\chi 2$ test. Continuous variables were compared by independent samples t-test. Continuous variables were expressed as means and ranges, and categorical variables as frequencies and percentages.

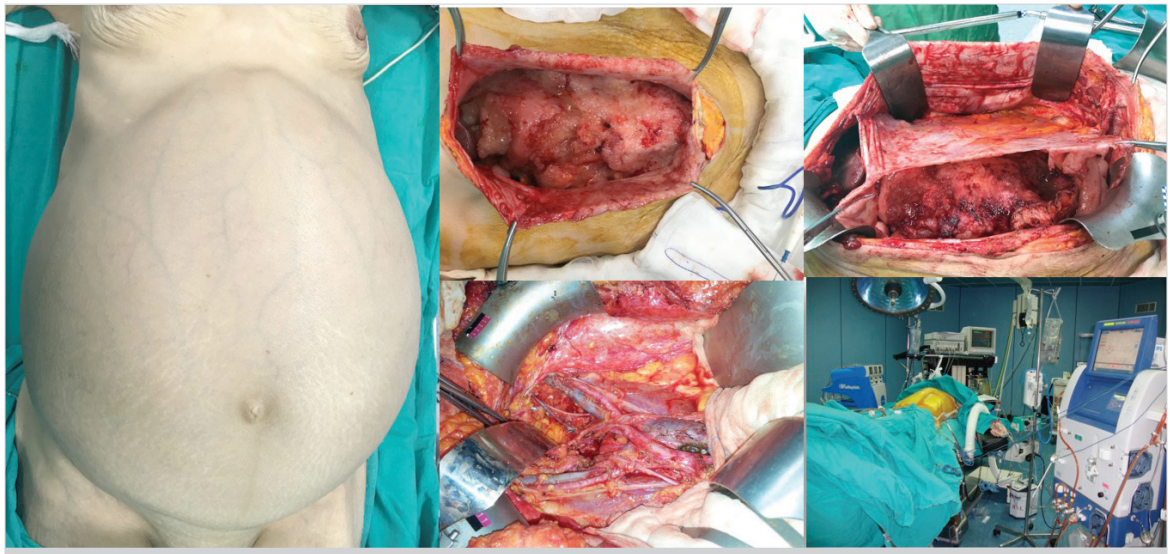


Figure 1. The technique of CRS and application of HIPEC.

Survival rates were calculated using Kaplan-Meier method and were compared with the long-rank test. Multivariate analysis to identify predictors of survival was performed by constructing stepwise Cox proportional hazard models incorporating variables selected on the basis of results of univariate analysis. p values< 0.05 were defined as statistically significant.

RESULTS

There were 666 consecutive cytoreduced and HIPEC-treated patients between 2007 and 2020. Mean age (54.2 ± 12.97 years vs 54.9 ± 21.6 years) and sex distributions (71.4% female vs 76.6% female) were similar in both groups. Median follow-up was 22 (range, 1-135) months. Overall survival in all patients was 35 months (range, 31-40 months). Primary tumors were ovarian in 280 (42.0%), colorectal in 214 (32.1%), appendix in 74 (11.1%), peritoneal mesothelioma in 37 (5.6%), gastric in 26 (3.9%) and unconventional indication in 19 (2.9%) patients. There were 371 (55.7%) patients in the extreme group and 295 (44.3%) patients in the non-extreme group. In the extreme group, PCI was ≥15 in 61.7% (n= 229), patients undergoing ≥5 major organ resections was 50.1% (186), 20.5% (n= 76) of the patients had ≥2 anastomosis, and 13.5% (n= 50) had repeated CRS procedures. In the overall group, 43.4% (n= 289) of the patients had no anastomosis, 45.2% (n= 301) had one anastomosis and 11.4% (n= 76) had ≥2 anastomosis (Table 1).

While the rate of ovarian cancer was equal in both groups, colorectal cancers were more common in the non-extreme group, in contrast to appendix, mesothelioma, and gastric cancers, which were prevelant in the extreme group (p= .007). The presence of co-morbidity was 41.0% (n= 152) in the extreme group and 44.7% (n= 132) in the non-extreme group (p= .328). The patients who received neoadjuvant chemotherapy were 62% (n= 230) in the extreme group and 64.7% (n= 191) in the non-extreme group (p= .465). Patients with metachronous disease were more in the non-extreme group (57.8%) whereas

Table 1. Clinical parameters determining the extreme CRS group

	Extreme % (n= 371)	**Non-extreme % (n= 295)**	**Overall % (n= 666)**
PCI			
≥15	61.7 (229)	0	34.4 (229)
<15	38.3 (142)	100 (295)	65.6 (437)
Number of resected organs			
≥5	50.1 (186)	0	27.9 (186)
<5	49.9 (185)	100 (295)	72.1 (480)
Number of anatomosis			
≥2	20.5 (76)	0	11.4 (76)
<2	79.5 (295)	100 (295)	89.6 (590)
Re-CRS (+)	13.5 (50)	0	7.5 (50)

those with synchronous disease were more in the extreme group (56.2%) (p= .001) (Table 2).

Operative time was longer in the extreme group [mean 369.84 min; SD (±116.04) vs 304.02 min; SD (±114.81) (p< 0.001)]. The rate of achieving CC-0 cytoreduction was higher in the non-extreme group (62.5%, 228 patients vs 90.1%, 237 patients) (p= .000). More intra-operative erythrocyte suspension (52.8% vs 27.5%) (p= .000), albumin (27.8% vs 6.2%) (p= .000), fresh frozen plasma (FFP) (41.6% vs 21.6%) (p= .000), and post-operative erythrocyte suspension (23.2% vs 11.5%) (p= .000) were used in the extreme group. Increased post-operative morbidity (p< 0.001), higher HIPEC toxicity (p= .001) and increased infection (p< 0.001) rates were detected in the extreme group (Table 3).

The associated variables such as metachronous/synchronous disease, neoadjuvant chemotherapy, completeness of cytoreduction, operative time, ostomy creation, the use of intraoperative blood products, morbidity, HIPEC toxicity, and infection were modelled into Cox proportional analysis to determine independent prognostic factors of survival. It was determined that the prolonged operative time, CC-1 or CC-2 cytoreduction status, the presence of an ostomy, the development of an infection, and the increased use of intraoperative albumin and/or FFP were independent prognostic factors. (Table 4).

Median survival was 27 months (range, 23-30) in extreme group whereas 53 months (range, 42-64) in the non-extreme group. Three and five-year K-M survival rates were significantly lower in the extreme CRS/HIPEC group (48.8% and 31.9% vs 61% and 44.5%; p< .001) (Figure 2).

There was no morbidity in 74.1% (n= 221) of the patients in the non-extreme group and in 59.8% (n= 222) of the patients in the extreme group. Overall complication rate was higher in the extreme group (124 patients; 33.4%) than in non-extreme group (70 patients; 23.7%) (p< .001). Severe complications (C-D grade III-IV) occurred in 51 (13.7%) and 38 (12.9%) patients in both arms, respectively. In our cohort, there were 89 (21.8%) patients with major complications, and 26 (29.2%) of them were re-operated for anastomotic leak (n= 13), enterocutaneous fistula (n= 2), evisceration (n= 8), mesh infection (n= 1), intra-abdominal bleeding (n= 1), and cerebro-vascular occlusion (n= 1). The complications such as intra-abdominal abscess, gastrointestinal bleeding, intra-abdominal hematoma, and pleural effusion developed in 13 patients, and these were treated with percutaneous and endoscopic interventions without any need for repeat operation. All of these patients were succesfully rescued with timely diagnosis and proper management (none 'failure-to-rescue'). Peri-operative mortality was also higher in the extreme group compared to the non-extreme group (6.7%, 25 patients vs 1.4%, four patients) (p< .001). Nine (31.3%) of 29 patients were re-explored for anastomotic leakage, but could not be rescued despite all efforts.

Table 2. Demographic and clinical characteristics of the patients

	Extreme % (n= 371)	**Non-extreme % (n= 295)**	**General % (n= 666)**	**p***
Sex				
Male	28.6 (106)	23.4 (69)	26.3 (175)	.131
Female	71.4 (265)	76.6 (226)	73.7 (491)	
Age (year, mean ± SD)	54.2 ± 12.97	54.9 ± 21.6		.620
Origin of tumors				
Ovarian	41.2 (153)	43.1 (127)	42 (280)	
Colorectal	29.1 (108)	35.9 (106)	32.1 (214)	
Appendiceal	12.7 (47)	9.2 (27)	11.1 (74)	
P. Mesothelioma	7.3 (27)	3.4 (10)	5.6 (37)	**.007**
Gastric	5.7 (21)	1.7 (5)	3.9 (26)	
Primary PM	1.9 (7)	3.1 (9)	2.4(16)	
Others	2.2 (8)	3.7 (11)	2.9 (19)	
Smoking (+)	22.4 (83)	17.2 (50)	20.2 (133)	.099
Presence of co-morbidites	41.0 (152)	44.7 (132)	42.6(284)	.328
Synchronous/metachronous				
Synchronous	56.2 (205)	42.2 (111)	50.3 (316)	**.001**
Metachronous	43.8 (160)	57.8 (152)	49.7 (312)	
Neoadjuvant chemo (+)	62.0 (230)	64.7 (191)	63.2 (421)	.465

P. Mesothelioma: Peritoneal mesothelioma.
*Pearson $\chi 2$ test and independent samples t-test.

Table 3. Surgical characteristics and outcomes

	Extreme (n= 371), n (%)	Non-extreme (n= 295), n (%)	p*
Operative time (min, mean ± SD)	369.84 SD (±116.04)	304.02 SD (±114.81)	**<0.001**
Complete cytoreduction			
CC-0	62.5 (228)	90.1 (237)	**.000**
CC-1-2	37.5 (137)	9.9 (26)	
Ostomy (+)	45.4 (167)	13.4 (39)	**.000**
Intraoperative RBCs	52.8 (195)	27.5 (80)	**.000**
Intraoperative albumin	27.8 (102)	6.2 (18)	**.000**
Intraoperative FFP	41.6 (152)	21.6 (57)	**.000**
Post-operative RBCs	23.2 (85)	11.5 (33)	**.000**
ICU (+)	62.4 (231)	37.6 (110)	**.001**
Morbidite			
Grade I-II	19.7 (73)	10.8 (32)	
Grade III-IV	13.7 (51)	12.9 (38)	**<0.001**
Grade V	6.7 (25)	1.4 (4)	
HIPEC toxicity	12.7 (47)	5.4 (16)	**.001**
Infection	28.9 (107)	12.8 (37)	**<0.001**

RBC: Red blood cell, FFP: Fresh frozen plasma, ICU: Intensive care unit.
*Pearson $\chi 2$ test and independent samples t-test.

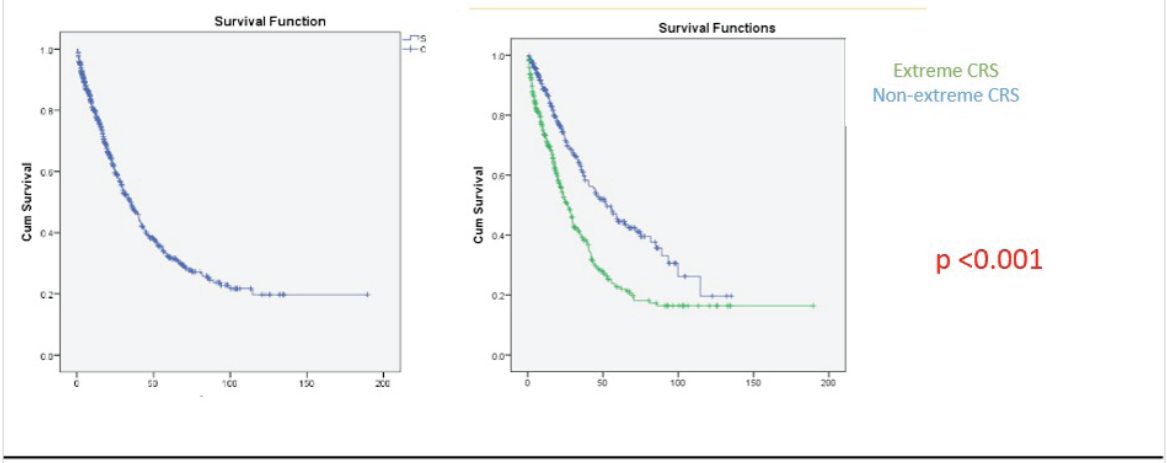
Table 4. Multivariate analysis

	HR	95% CI	p*
Synchronous/metachronous	1.492	1.028-2.166	.035
Operative time (min)	1.003	1.001-1.005	.000
CC-0/CC-1/-2	4.024	2.440-6.638	.000
Ostomy (+)	2.920	1.879-4.539	.000
Infection	1.867	1.149-3.032	.012
Intraoperative albumin	3.916	2.201-6.968	.000
Intraoperative FFP	1.725	1.138-2.614	.010

FFP: Fresh frozen plasma.
*Stepwise Cox proportional hazard models.

DISCUSSION

Although CRS/HIPEC has significant but acceptable perioperative morbidity and non-negligible mortality rates, it is the only potential oncologic management strategy with curative intent in peritoneal surface oncology centers with specific experience and expertise with multidisciplinary tumor board (1-7,17). In time, compelling evidence has emerged revealing the relatively low morbi-mortality and better oncological results with this triplet oncologic therapy. However, if we accept the establishment of complete cytoreduction as one further oncologic step over the standart conventional organ-based surgery to clear out the whole tumor burden, there even appears to be a wide spectrum of peritoneal metastatic disease that raise concerns about how far we can carry these aggressive approaches. The limit of the extensiveness/aggressiveness is still not very well-defined, and the current data is scarce. Thus, the authors aimed to evaluate the effect of extreme cytoreduction and HIPEC on post-operative morbi-mortality and final oncologic outcomes in a large group of patients at a dedicated center. Extreme CRS was defined by parameters including PCI over 15, five or more organ resections, two or more anastomoses, and repetitive cytoreductive surgeries. Procedures meeting at least one of these four parameters were determined as extreme CRS. Of 666 patients, 295 were included in the extreme CRS group. In the extreme CRS group, less CC-0 cytoreduction, more ostomy creations, and more intraoperative and postoperative blood



Overall survival	Extreme(%)	Non-extreme(%)	All pts(%)
24 mos	52.2	73.8	61.4
36 mos	39.7	61.0	48.8
60 mos	22.7	44.5	31.9

Figure 2. Overall survival in full-spectrum of the patients and in extreme and non-extreme CRS groups.

product consumption were observed. These patients experienced a higher incidence of postoperative complications, infections, HIPEC toxicity, and perioperative mortality. Additionally, the overall survival of patients with extreme CRS was inferior to that of patients with non-extreme CRS.

The limit on the extensiveness of cytoreduction to achieve the best reliable results in the management of peritoneal metastasis is still a matter of ongoing debate. Some centers determined PCI as a limiting factor and accepted PCI> 20 as not to operate (18,19). It is insistantly proven that the higher PCI score is a powerful predictor of complications and overall survival. However, high PCI score is not always possible to determine the extensiveness of the cytoreduction and the number of multivisceral organs to be removed. The difficult anatomical localization and the inherent biological aggresiveness of the tumor usually play a more important role and a small tumor with aggressive biological behavior in a low-volume disease may loco-regionally spread to multiple nearby organ(s)/structure(s). Some centers, including ours, with the guidance of John Birkmeyer's centralization effect in complex cancer care, use the experience they have developed in time to predict whether he/she can perform a complete cytoreduction or bail out surgical intervention as a threshold (20). As it is proven to be utmost important prognostic factor in the classical oncologic R0 resection, the complete cytoreduction can be the potential curative treatment only. In our opinion, this treatment modality should not be taken away from the patient even in the presence of high volume disease.

Delving into the literature, there are very few studies examining the limit on the extensiveness of CRS/HIPEC. Franko et al. have included 65 patients with CRC-PC (colorectal cancer-peritoneal carcinomatosis) who were treated with CRS/HIPEC, having the patients into two groups based on the number of multivisceral organ resections (MVR) (MVR group≥ 2 organs and non-MVR group= one or no organ resection). They have reported that MVR is unrelated to morbi-mortality, and survival. However, it has been shown that performing bowel anastomosis rather than MVR is associated with morbidity (9). Based on the center experience, taking a cut-off value of two or more organ resections for CRS/HIPEC, which often requires multivisceral organ resections, was one of the main problem of the study. In another study from the same center in which 282 patients undergoing CRS/HIPEC due to appendiceal carcinomatosis have been included, the patients have been divided into two groups as the extensive CRS group (n= 60) and the comparison group (n= 222). The extensive CRS group has been defined as patients who underwent> 3 organ resections or> 2 anastomoses. Besides, in patients with ≥5 organ resections and ≥3 anastomoses, they have defined a subgroup of patients thorough the extensive group and evaluated them separately as the extreme group (n= 10), and the term "extreme CRS" has been used for the first time in the related literature. They have elegantly repor-

ted higher median PCI, longer operative time, more blood loss, and longer hospital stay in the extensive CRS group. However, they have noted that extensive CRS, even in extreme CRS setting, is not associated with severe morbidity, 60-day mortality or inferior oncologic outcomes (11). In a retrospective study by Berger et al., 257 patients undergoing 269 procedures with a wide array of tumor origins have been included in the study. Extreme CRS group (n= 50), defined as a resection of ≥5 organs or ≥3 bowel anastomoses, has been compared with patients undergoing less extensive procedures (n= 219). They have found that there was significantly higher major 30-day morbidity and higher 90-day mortality in the extreme CRS/HIPEC group. In a subgroup analysis of colorectal cancer (CRC)-PM treated with extreme CRS/HIPEC, they have demonstrated that median disease-free survival and overall survival were worse and the extreme-CRS/HIPEC independently predicted decreased overall survival in CRC-PM patients (8).

The authors integrated the 're-cytoreduction' as a component of extremeness. After CRS/HIPEC, with the compounded effects of previous major surgery, complications, and HIPEC, reoperative abdomino-pelvic surgery potentially becomes a difficult task than a virgin abdomen is encountered. Access is limited by obliterative adhesions, often with dense scarring, the absence of planes of cleavage, and the distorted anatomical planes. The problem is increased by a history of previous pelvic sepsis or irradiation. Thus, reentry into the abdomen after previous major laparotomy should be an exceptional venture. Re-CRS often requires extensive dissection of scarred multiple adhesions, road-mapping through the ceramicized structures/tissues, and situational awareness for no-point-of return. There are limited studies showing that re-CRS/HIPEC increases long-term oncologic outcomes (three-year survival was ranging from 0% to 66% and median survival was 20 to 56 months) with acceptable morbidity and mortality rates (major morbidity and mortality were 15% to 50% and 0% to 5%, respectively) similar to initial CRS/HIPEC procedure (7,21-24). However, primary cytoreduction, which already contains marathon complex surgical procedures by its inherent nature, gains even more complexity with re-CRS. It is obvious that re-cytoreductive attempts performed in poorly selected cases at a center with a low volume and proficieny will adversely affect mortality and morbidity rates and oncological outcomes.

Morbidity following CRS/HIPEC has been very well-defined. Many high-volume centers have published 12% to 55% major morbidity rates. In most of these studies, the extent of peritoneal disease, duration of surgery, number of resected organs, and number of anastomosis have been found as predictors of morbidity (3,17,25,26). In our study, we proposed the indices of number of resected major organs, the number of anastomosis, and the repeated cytoreduction in addition to PCI for defining the extremeness of the CRS/HIPEC. The cumulative data showed that these oncologic efforts resulted with early postoperative morbidity and mortality and inferior oncologic outcomes.

Three randomized controlled trials have described the benefit of CRS/HIPEC in CRC-PM, reporting significant survival advantage as opposed to the standard therapy, and median survival in large series has ranged from 32 to 47 months with a five-year survival of 20% to 50% (7,27,28). Although this study consisted of mixed tumor origins, median survival was 27 months even in the extreme group where the tumor burden and extended radical attacks were high. In the non-extreme group, median survival was 52.6 months. There is little data on the management of patients with peritoneal metastases with traditional treatment options other than CRS/HIPEC. Verwaal et al. have discovered that median survival for CRC patients randomized to receive systemic chemotherapy (± palliative surgery) was 12.6 months (4). In a separate study, median survival for patients who underwent laparotomy and canceled CRS/HIPEC followed by palliative chemotherapy has been found as 11.2 months (19). Finally, according to a subgroup analysis of two prospective randomized studies, median survival for CRC-PM patients treated with systemic chemotherapy has been concluded as 12.7 months (29). Our study strikingly showed that in the extreme group, being the next oncological level of macroscopic tumor eradication, the final oncological results might be worse than in the non-extreme group, but it is clear that even in the extreme group, CRS/HIPEC is still a reliable curative treatment to prolong survival.

The limitations of this study include its retrospective nature with inherent bias. Many patients were regional or extra-regional referrals, who might represent the more advanced spectrum disease with different diagnostic work-ups and surgical interventions. The heterogenous nature of patient population is another drawback of this study. These patients have been treated in a real-world situation in a complex scenario, with various operative techniques differing from intraoperative findings. But this real-world basis also adds an uncontrollable variable to the data set. The data set was also collected over a long time period, which may introduce a degree of inherent bias, given the compounding effect of evolving chemotherapeutic regimens over time. Furthermore, we were unable to reflect the beneficial effects of postoperative chemotherapy that may be confounders to our current survival analysis because the patients who had a complication or had a significant co-morbidities were less likely to receive adjuvant chemotherapy, which may be one of the negative contributions for decreased survival particularly in extreme-group. Despite these limitations, this study represents one of the largest cohorts with prospectively maintained database and durable predictors of short- and long-term outcomes. The results were obtained in

carefully selected patients treated by a multidisciplinary team in a high-volume specialized cancer center. In order to minimize the effects and inaccuracies of a retrospective study, more patients were recruited, more than the number in the previous largest studies (7,11).

CONCLUSION

In conclusion, as the extent of the peritoneal metastatic disease is increased, the extremeness of the radical surgery is gradually increased to achieve complete cytoreduction in carefully selected patients. Not all high-volume peritoneal metastatic patients should be considered unresectable. Extreme cytoreduction can be a potential treatment to achieve complete resection, which the trade-off will be increased morbi-mortality.

Ethics Committee Approval: This study was approved by Dokuz Eylül University Non-Invasive Research Ethics Committee (Decision no: 2022/26-17, Date: 17.08.2022).

Peer-review: Externally peer-reviewed.

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Conflict of Interest: The authors have no conflicts of interest to declare.

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ORİJİNAL ÇALIŞMA-ÖZET
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Peritoneal metastaz tedavisinde ekstrem sitoredüktif cerrahi ve hipertermik intraperitoneal kemoterapi

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ÖZET

Giriş ve Amaç: Morbi-mortalite ve nihai onkolojik sonuçları belirlemek için sitoredüktif cerrahi ve hipertermik intraperitoneal kemoterapi (SRC/HİPEK) tedavisinde onkolojik "ekstrem" kavramını tanımlamayı amaçladık.

Gereç ve Yöntem: 2007 ve 2020 yılları arasında SRC/HİPEK uygulanan peritoneal metastazlı 666 hastanın prospektif olarak kaydedilmiş verileri analiz edildi. Hastalar ekstrem (n= 371) ve ekstrem olmayan (n= 295) olmak üzere iki gruba ayrıldı. Ekstrem sitoredüktif cerrahi, ≥5 majör organ rezeksiyonu veya ≥2 bağırsak anastomozu veya peritoneal karsinomatozis indeksinin (PCI)≥15 olması veya tekrarlayan sitoredüktif cerrahi işlemleri olarak tanımlandı.

Bulgular: Daha fazla CC-1 veya CC-2 sitoredüksiyon (p< ,001), artmış mortalite ve morbidite (p< ,001), uzamış ameliyat süresi (p< ,001), ameliyat sırasında artan eritrosit süspansiyonu (p< ,001), albümin (p< ,001), taze donmuş plazma (TDP) (p< ,001) ve ameliyat sonrası eritrosit süspansiyonu (p< ,001) kullanımı ekstrem SRC/HİPEK grubunda bulundu. Cox regresyon analizinde ameliyat süresi, CC-1 veya CC-2 sitoredüksiyon, ostomi varlığı, enfeksiyon gelişimi ve intraoperatif albümin ve TDP kullanımı bağımsız prognostik faktörler olarak bulundu. Üç ve beş yıllık sağkalım oranları ekstrem SRC/HİPEK grubunda anlamlı olarak daha düşüktü (p< ,001).

Sonuç: Yüksek hacimli peritoneal metastatik hastalık, kemoterapiye yanıt veren özenle seçilmiş hastalarda ekstrem sitoredüksiyon ile tamamen rezeke edilebilir. Peritoneal metastaz tedavisinde korkulan morbidite ve mortalite sonuçları göz önüne alındığında, konvansiyonel tedavilere göre nispeten daha iyi onkolojik sonuçlar sağlayan ekstrem SRC deneyimli kanser merkezlerinde yapılmalıdır.

Anahtar Kelimeler: Sitoredüktif cerrahi, hipertermik intraperitoneal kemoterapi, peritoneal metastaz

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