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ORIGINAL ARTICLE

Prognostic factors and outcomes of cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy in patients with advanced ovarian cancer – A single tertiary institution experience

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Summary

Purpose: *Ovarian cancer (OC) ranks fifth in mortality among females cancer patients. Cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) have radically changed the treatment of OC. The aim of this study was to evaluate overall survival (OS) and disease-free survival (DFS) in our patient population after the application of combined CRS and HIPEC treatment.*

Methods: *The study included patients who met defined inclusion and exclusion criteria and had undergone CRS of peritoneal carcinomatosis from 2006 to 2011. Tumor extension was intraoperatively calculated using peritoneal cancer index (PCI). After CRS had been performed, selected patients underwent closed HIPEC. Assessment of successful surgery was estimated with the completeness of cytoreduction score.*

Results: *The study involved 31 patients. The median DFS was 19 months. The DFS for 1 and 2-year period were 69.2 and 35.2%, respectively. The mean OS was 51 months. The 1-, 2- and 5-year OS was 85.4, 63.3 and 56.3%, respectively. PCI ranged from 1 to 24 and the majority (77.4%) of the patients had PCI score below 13.*

The most frequent carcinomatosis was observed in the omentum (80.6%), followed by adnexae (61.3%), uterus (58.1%), colon (58.1%). spleen (25.8%), diaphragm (25.8%), small intestine (19.4%), bursa omentalis 19.4, liver (9.7%), and pancreas (3.2%).

Conclusion: *The results of the current study are in concordance with the literature which clearly favors combined the CRS and HIPEC treatment. The reported data suggest that this method could be successfully applied in our region and outline the necessity of future multicentric studies that will involve major regional hospitals.*

Key words: *cytoreductive surgery, HIPEC, ovarian cancer, peritoneal carcinomatosis*

Introduction

Globally, OC represents one of the main causes of death among women. It ranks fifth in mortality among all malignancies in females and in addition it is a leading cause of death from gynecological malignancies [1]. Unfortunately, in the past few decades, patients who were diagnosed with peritoneal carcinomatosis from OC were considered inoperable and were therefore treated only with palliative surgery and systemic chemotherapy. Thus, those patients had very low survival rates and only 20-25% of them could achieve long term survival [2].

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Considering the fact that almost 40% of patients suffered from locally disseminated OC, efforts were made toward improvement of technology and biological understanding of the disease. Hence, CRS with HIPEC radically changed the way of treatment [4,5]. Furthermore, today such surgical protocols with combined approach represent standard treatment in cases of pseudomyxoma, mesothelioma as well as in selected cases of colorectal carcinomatosis [6-8]. The first randomized study in patients who suffered from recurrent epithelial OC was published in 2015 and showed survival benefit after combined treatment with HIPEC and CRS [3]. Since ovarian peritoneal carcinomatosis is considerably sensitive to cytotoxic treatment, the high efficiency of combined CRS and HIPEC was confirmed in three major studies [9-11].

Unfortunately, the application of such treatment is still underrepresented in some regional medical centers [12].

The aim of this study was to evaluate OS and DFS in our population and to highlight factors that could influence survival the most. Furthermore, this study could trigger potential future regional multicentric studies with the same purpose and methodology.

Methods

The current study was conducted at the Institute of Oncology and Radiology of Serbia (IORS). The data derived from medical records was used for further patient selection upon defined criteria. The inclusion criteria encompassed previously confirmed diagnosis of OC with peritoneal carcinomatosis, either primary or recurrent (the confirmation was provided from radiological or histopathological reports), patient age between 18 and 80 years, and good general condition with adequate baseline ECOG performance status (PS 0,1). The exclusion criteria involved the presence of unstable cardiac and neurological diseases, and distant metastases (lung, bone and central nervous system). However, an exception was made for patients with synchronous operable liver metastases who were included in the study as well.

Therefore, the sample was composed of patients who met previously defined criteria and had undergone CRS of peritoneal carcinomatosis at the IORS from 2006 to 2011.

All patients were treated with the same surgical protocol previously described by Sugarbaker [13]. Tumor extension was intraoperatively calculated using the PCI (Figure 1) [14]. PCI score was used as an intraoperative assessment tool to help deciding whether to perform CRS or just palliative surgery.

Subsequently, after the CRS had been performed, all patients underwent closed HIPEC during 45-90 min. The closed HIPEC method uses 2000-3500ml of isotonic saline solution with dissolved cisplatin (50mg/m^2), heated at 41 °C and applied through abdominal drain tubes using perfusion systems (Belmont hyperthermia pump, Belmont Instrument Corporation, Billerica, Massachusetts, USA).

The assessment of the successfulness of surgery was estimated with the completeness of cytoreduction score (CC) defined by Sugarbaker [15]. According to the author, the first stage (CC-0) corresponded to absence of macroscopic residual disease, while the second stage (CC-1) involved evidence of residual tumor nodules with diameter less than 0.25cm, the third stage (CC-2) encompassed the presence of residual tumor nodules measuring from 0.25 to 2.5cm and finally the fourth stage (CC-3) referred to cases with residual nodules larger than 2.5cm.

Overall, postoperatively most of the patients received adjuvant chemotherapy.

The study database was comprised of data derived from medical records, which enclosed all the intraoperative data such as type of surgery, completeness of CRS, PCI, duration of HIPEC procedure, as well as solution temperature, etc. Furthermore, the database also included the follow-up data which were recorded through telephone interviews and encompassed the date of the most recent oncological follow-up, recurrence status and the vital status (alive with disease, alive without disease, dead, lost to follow-up).

Statistics

The study results are presented in Tables and Figures, in the form of absolute and relative numbers through frequencies, percentages, mean, standard deviation (SD), median and range. In order to identify factors which influence patient DFS and OS, statistical analyses involved evaluation of patient characteristics (age, number of patients older than 55 years of age, ECOG PS, presence of preoperative symptoms), primary disease characteristics (presence of mucinous component in primary tumor, primary tumor positive lymph nodes), peritoneal carcinomatosis characteristics (presence of metachronous carcinomatosis, synchronous carcinomatosis, time from primary disease to metachronous carcinomatosis, PCI score frequency, organ involvement by carcinomatosis), and treatment characteristics (number of patients who received blood transfusion, volume of blood transfusion, volume of auto transfusion, duration of HIPEC, CC score frequency, number of hospitalization days, presence of postoperative complications, further chemotherapy, number of cycles of applied chemotherapy). During the analyses, the relation between the aforementioned variables and patient DFS as well as OS was tested by univariate Cox regression method. The Kaplan-Meier product-limit method was applied for

Table 1. Patient, primary disease characteristics and Cox regression analysis

Characteristics		*Cox regression analysis*	
	N (%)	*Deceased HR (95% CI)*	*Progressed HR (95% CI)*
Patient characteristics			
Age (years)			
Mean±SD	54.4±11.9	1.027 (0.967-1.091)*	1.004 (0.958-1.052)
Age > 55 years			
Mean±SD	17±54.8	2.329 (0.600-9.039)*	1.507 (0.533-4.263)
ECOG PS			
0	8 (61.5)		
1	2 (15.4)	1.937 (0.408-9.187)	1.697 (0.583-4.937)
2	3 (23.1)		
Preoperative symptoms			
No	10 (32.3)		
Yes	17 (54.8)	1.336 (0.332-5.372)	-
Missing data	4 (12.9)		
Primary disease characteristics			
Mucinous tumor component			
No	27 (87.1)		
Yes	4 (12.9)	0.039 (0.001-80.071)	0.031 (0.001-6.129)
Primary tumor positive lymph nodes			
No	9 (29.0)		
Yes	1 (3.2)		-
Missing data	21 (67.7)		

*statistically significant (p<0.05)

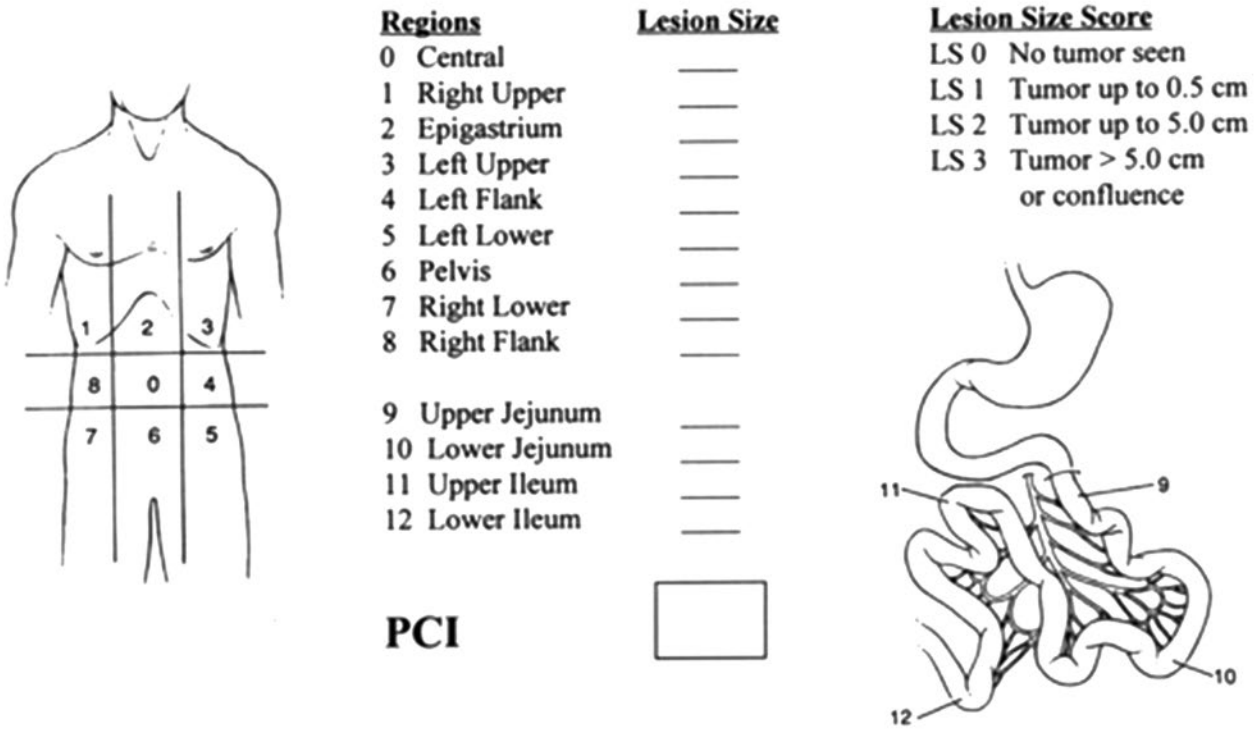

Figure 1. Graphical representation of peritoneal cancer index according to Sugarbaker [14].

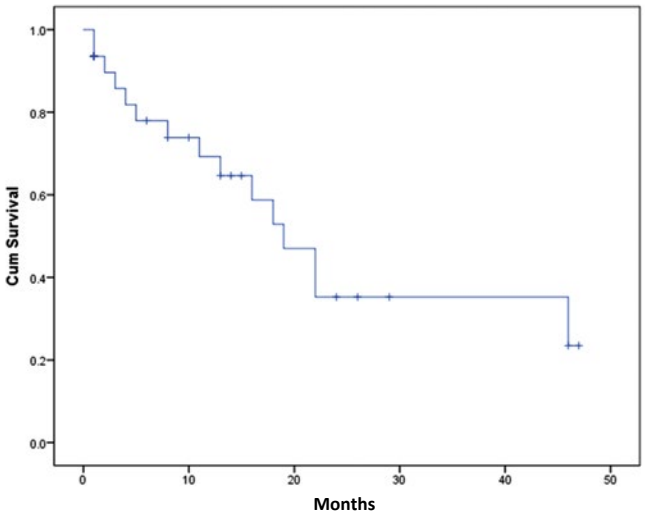

Figure 2. Kaplan-Meier disease-free survival (median 19.0 months).

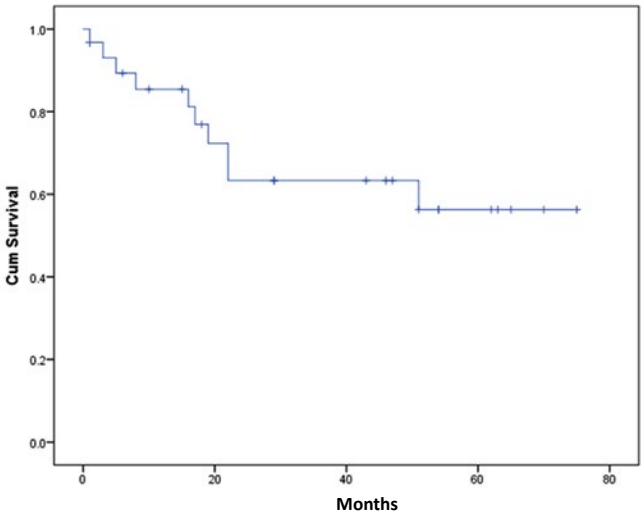

Figure 3. Kaplan-Meier overall survival (median not reached).

construction of probability curves for DFS and OS. and differences of DFS and OS regarding different PCI scores were tested by log rank test.

In all analyses, the significance level was set at 0.05, while the applied confidence interval (CI) was 95%. Statistical analyses were performed using SPSS for Windows, version 20.0 (IBM Corp.).

Results

The mean age of the 31 patients was 54.4 years (median 56.44, range 32-76) with more than half of them being older than 55 years (Table 1). After combined CRC and HIPEC treatment all the enrolled patients were followed-up from 1 to 63 months (median 22). Median DFS was 19 months (95%CI=13-25) (Figure 2). The calculated DFS for 1 and 2-year period was 69.2 and 35.2%, respectively. Unfortunately, the 5-year DFS could not be calculated as the longest recorded disease-free period was 48 months with estimated DFS of 23.5%. The mean OS was approximately 51 months (95%CI=39-63) (Figure 3). OS for 1, 2, and 5 years was 85.4, 63.3 and 56.3%, respectively. No statistically significant relationship (p>0.05) between patient age and OS, as well as DFS was detected. On closing the study 10 patients (32.26%) had died.

Although little more than half (54.8%) of the patients expressed preoperative symptoms, at the time of hospital admission the most frequently recorded ECOG PS was 0 (61.5%). It was noticed that patients who felt discomfort preoperatively had unfavorable prognosis. However, neither ECOG PS nor presence of preoperative symptoms showed significant relationship with OS or DFS (p>0.05).

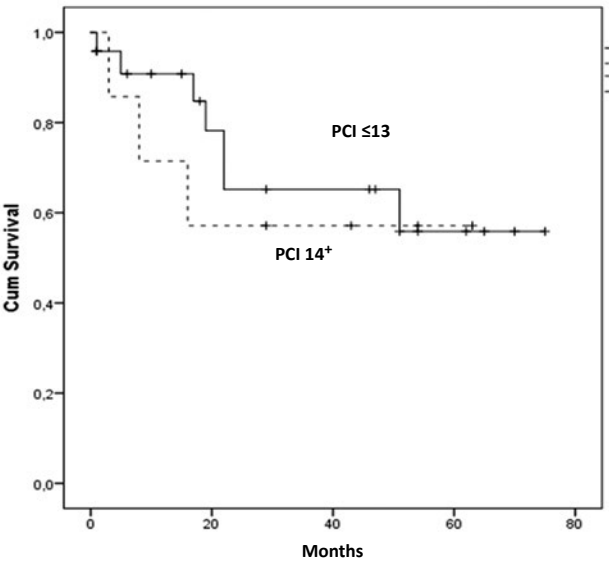

Figure 4. Kaplan-Meier overall survival according to PCI (p=0.663).

The presence of mucinous component in the primary tumors was associated with longer OS and PFS although without statistical significance (p >0.05). Nevertheless, this tumor characteristic was underrepresented (12.9%) in our patients. Patients with synchronous and metachronous carcinomatosis were equally represented in the sample and no statistical difference was shown in OS and PFS for patients of both groups. In addition, the mean time that passed since the primary operative treatment until the occurence of metachronous carcinomatosis was 20.3 months (median 16, range 2-48) (Table 2).

PCI score ranged from 1 to 24 (mean 7.23, median 5.00) (Table 2). Furthermore, only one pa-

Table 2. Carcinomatosis characteristics and Cox regression analysis

Characteristics		*Cox regression analysis*	
	N (%)	*Deceased HR (95% CI)*	*Progressed HR (95% CI)*
Metachronous carcinomatosis			
No	15 (48.4)		
Yes	15 (48.4)		
Missing data	1 (3.2)		
Synchronous carcinomatosis			
No	15 (48.4)		
Yes	15 (48.4)	1.238 (0.331-4.638)	1.136 (0.379-3.404)
Missing data	1 (3.2)		
Time from primary disease to metachronous carcinomatosis (months)			
Mean±SD	20.3±13.8	0.981 (0.904-1.065)	1.009 (0.954-1.066)
PCI			
Mean±SD	7.23±5.93	1.012 (0.913-1.120)	1.036 (0.964-1.113)
PCI			
≤13	24 (77.4)		
>13	7 (22.6)	1.348 (0.348-5.218)	1.418 (0.443-4.534)
PCI			
≤7	18 (58.1)		
8-12	6 (19.4)	0.415 (0.050-3.452)	2.414 (0.677-8.602)
>13	7 (22.6)	1.121 (0,280-4.491)	1.850 (0.521-6.573)

tient had a score above 20, which was at the same time the highest recorded in this study. PCI score was less than 7 in 58.1% of the patients, while scores 8-12 and 13 and above were noted in 19.4% and 22.6% of the patients, respectively. Overall, the majority of patients had PCI score below 13 (77.4%) and patients with PCI score 13 and above showed unfavorable OS (Figure 4) and DFS (Figure 5), yet without statistical significance (p>0.05).

The distribution of carcinomatosis of abdominal and pelvic organs revealed that the most frequent location was observed in the omentum (80.6%) followed by adnexae (61.3%), uterus (58.1%), and colon (58.1%) (Table 3). Further analysis showed that only adnexal carcinomatosis was statistically related with low DFS (p=0.013). Colon carcinomatosis presented borderline significance (p=0.053). Carcinomatosis of other organs was much less frequent. Spleen was involved in 25.8% of the cases, diaphragm in 25.8%, small intestine in 19.4% and bursa omentalis in 19.4%, while liver (9.7%) and pancreas (3.2%) were underrepresented. Nevertheless, statistical analysis revealed significant association between carcinomatosis of the small intestine and unfavorable DFS (p=0.011).

The mean duration of HIPEC application was 44.67 min (median 45) (Table 4). No side effects of HIPEC procedure had been observed. Transfusion

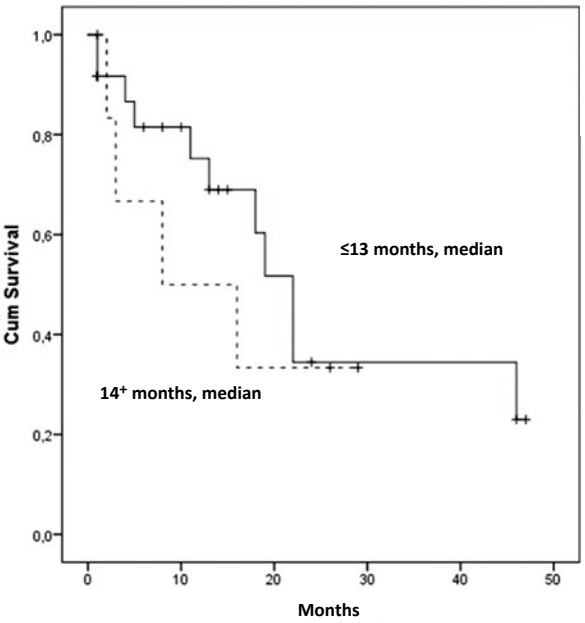

Figure 5. Kaplan-Meier disease-free survival according to PCI (p=0.549).

and autotransfusion of blood were used during operative treatment. However, only the volume of the blood used in conventional transfusion showed statistically significant negative association with OS (p=0.039, HR=1.001, 95%CI=1.000-1.003).

Finally, complete cytoreduction was achieved in 28 (90.3%) patients, while R1 resection was

Table 3. Carcinomatosis of abdominopelvic organs and Cox regression analysis

Organs	*N (%)*	*Cox regression analysis* *Deceased HR (95% CI)*	*Progressed HR (95% CI)*
Colon	18 (58.1)	2.316 (0.596-8.999)	3.128 (0.984-9.941)*
Small int.	6 (19.4)	2.336 (0.597-9.134)	5.383 (1.480-19.586)*
Stomach	0		
Liver	3 (9.7)	0.040 (0.001-217)	0.043 (0.001-233.7)
Spleen	8 (25.8)	1.202 (0.310-4.661)	1.338 (0.416-4.304)
Pancreas	1 (3.2)	-	
Uterus	18 (58.1)	0.915 (0.258-3.251)	0.390 (0.140-1.082)
Adnexa	19 (61.3)	0.755 (0.212-2.680)	0.271 (0.096-0.763)*
Bladder	5 (16.1)	1.164 (0.247-5.493)	0.779 (0.173-3.504)
Diaphragm	8 (25.8)	1.814 (0.511-6.445)	0.815 (0.253-2.629)
Omentum	25 (80.6)	27.53 (0.02-40899)	0.640 (0.176-2.327)
Bursa oment.	6 (19.4)	0.954 (0.202-4.503)	1.054 (0.293-3.797)

*statistically significant (p<0.05)

Table 4. Treatment characteristics and Cox regression analysis

Characteristics	*N (%)*	*Cox regression analyses* *Deceased HR (95% CI)*	*Progressed HR (95% CI)*
Transfusion	31 (100)	-	-
Transfusion (ml)			
Mean±SD	1093.3±582.2	1.001 (1.001-1.003)*	1.001 (1.000-1.002)
Auto transfusion (ml)			
Mean±SD	532.4±369.8	1.001 (0.999-1.003)	1.001 (0.999-1.003)
HIPEC duration (min)			
Mean±SD	44.67±3.46	0.972 (0.822-1.149)	1.124 (0.936-1.350)
Completeness of cytoreduction			
CC-0	28 (90.3)		
CC-1	2 (6.5)		
CC-2 and CC-3	1 (3.2)		
Hospitalizations days			
Mean±SD	18.3 ±6.1	1.035 (0.944-1.136)	1.039 (0.969-1.113)
Postoperative complications			
No	23 (74.2)		
Yes	5 (16.1)	2.055 (0.410-10.302)	1.224 (0.335-4.473)
Missing data	3 (9.7)		
Postoperative chemotherapy			
No	7 (22.6)		
Yes	20 (64.5)	1.312 (0.271-6.360)	1.907 (0.413-8.804)
Missing data	4 (12.9)		
Postoperative chemotherapy (number of cycles)			
Mean±SD	5.60±3.79	0.986 (0.784-1.240)	0.960 (0.792-1.164)

*statistically significant (p<0.05)

possible in 2 (6.5%) patients and R2 resection in only 1 (3.2%) patient. Grade I and II postoperative complications were observed in 5 (16.1%) patients. Yet, these complications did not cause any lethal event. Postoperatively 20 (64.5%) patients received adjuvant chemotherapy with 5.6 cycles on average. There was no significantly longer OS or DFS in these patients.

Discussion

Up until recently most of the patients with

OC and peritoneal carcinomatosis were treated either with palliative surgery, chemotherapy or a combination with CRS and postoperative platinum/taxol-based chemotherapy. Despite all of these conventional methods, more than half of the patients recurred [11,16]. Since the 1980s and the introduction of HIPEC [17] many of the studies showed significant improvement both in OS and DFS with CRS plus HIPEC [18,19]. According to a multicentric French study [19], depending on completeness of CRS and chemosensitivity, median DFS was brought up to 11.8 months, with survival rates for 1, 3 and 5 years of 52, 18, and 12%, respectively. Similarly, median OS survival rates went to 45.7 months. Furthermore, the same authors reported 1, 3 and 5-year survival rates up to 89, 59 and 37%, respectively [19]. The results of the current study revealed higher median DFS (19 months) as well as calculated recurrence-free survival rate for the first year (69.2%). Because the median OS was not reached, the present study could not provide but only the mean value of 50.7 months. The calculated one-year survival rate for OS from the French study [19] was in accordance with our result (85.4%). However, the present study reported higher 5-year rate of 56.3%. Some other researchers also reported high OS rates with more than 50 months after performed CRS [20,21], or even more than 60 months if HIPEC was applied [11]. In addition, Vergote et al. [22] reported lower median survival (29-30 months) after administration of standard upfront treatment.

As previously stated, in the present study the CRS was predominantly performed in cases of PCI under 20, since only one patient was included in the study with PCI value of 24. However, some authors stated that CRS should be performed on patients with PCI below 18 [23]. Nonetheless, this was partially in concordance to our study as the majority (77.4%) of the enrolled patients had PCI below 13. Although omental carcinomatosis was most frequently observed, our results demonstrated statistically significant worse DFS as well as OS only in patients with adnexal and small intestine carcinomatosis, while colon carcinomatosis bore borderline significance. Carcinomatosis of other organs was recorded much less frequently. Furthermore, complete cytoreduction, which contributes to better DFS and OS, was achieved in the vast majority of the patients (90.3%). As expected, almost three quarters of the enrolled patients underwent adjuvant chemotherapy. However, the conducted analyses failed to demonstarte statistically significant relationship of adjuvant chemotherapy with longer OS or DFS.

Grade I and II surgical complications were recorded in 16.1% of the cases, which is slightly less than what was reported in a study of multicenter evaluation of postoperative morbidity and mortality after the combined CRS and HIPEC treatment published by Rafii et al. [24].

The current study also marked the presence of mucinous component in the primary tumors as favorable feature, associated with longer OS and DFS. However, no statistical significance was confirmed after the conducted analyses. This could be a result of the low number of patients with this histology (12.9%).

Patients with synchronous and metachronous carcinomatosis were equally represented in this study and no significant difference in OS and DFS was demonstrated between the two groups.

Analysis of other operative and postoperative treatment factors showed that only the blood volume used in conventional transfusion was a factor with statistically significant association to OS. Their negative relation could only be explained by the fact that patients with more extensive disease demanded more extensive surgical treatments which increased the amount of transfusion.

According to the data provided in the current as well as in other studies, the importance of combined CRS and HIPEC treatment is clearly marked as favorable. The reported data suggest that this method could be successfully applied in our region and outline necessity of education and training of the medical personnel in all major regional hospitals. As the current study presents a single tertiary institution experience, the sample size remained relatively low. The appropriate power to measure patient outcomes requires involvement of several major regional hospitals, therefore highlighting the importance of future multicentric studies.

Conflict of interests

The authors declare no confict of interests.

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