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ORIGINAL ARTICLE

Survival prognostic factors in patients with colorectal peritoneal carcinomatosis treated with cytoreductive surgery and intraoperative hyperthermic intraperitoneal chemotherapy: a single institution exprerience

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Summary

Purpose: *The aim of this research was to examine overall (OS) and disease-free survival (DFS) in patients with colorectal peritoneal carcinomatosis (CRC-PC), treated with cytoreductive surgery (CRS) and intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC), as well as to analyse factors of prognostic significance.*

Methods: *We included 61 patients with pathological/and computerized tomography (CT) confirmation of CRC-PC, treated with CRS+HIPEC from 2005 to 2012. Peritoneal Cancer Index (PCI) score was used for quantitative assessment of the CRC-PC extent. We performed CRS following the Sugarbaker's principles in all patients with PCI ≤20 and only in 3/61 (4.92%) patients with PCI >20. HIPEC (oxaliplatin 410 mg/m² in 2000mL isotonic solution and 41˚C) was performed using RanD Performer® HT perfusion system during 30-60 min. Cox proportional hazard regression was used to determine significant factors for OS and DFS.*

Results: *The follow-up ranged from 1 to 83 months (median 22). Median OS was 51 months (95% confidence interval/CI 22⁺). Median DFS for patients without residual disease (57/61, 93.44%) was 23 months (95% CI 16⁺). One-, 2- and 6-year OS (DFS) were 78.6% (68.3%), 58.7% (46.7%) and 50.5% (38.1%), respectively. By the end of the study, 55.74% of the patients were still alive. Cox multivariate analysis indicated PCI score as a parameter of highly prognostic significance for patients treated with CRS+HIPEC (p<0.001). Patients with PCI <13 (vs PCI ≥13) had significantly longer OS and DFS (p<0.001), also confirmed for PCI subcategories (PCI <7 vs 7≤ PCI <13 vs PCI ≥13). All patients with PCI <7 are still alive.*

Conclusion: *Our study indicates that CRS+HIPEC significantly improves the survival of CRC-PC patients. This treatment modality should be considered as the most suitable in well-selected patients with this disease.*

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

Introduction

Peritoneum, together with liver, represents the most common site of CRC metastases. PC is mainly accumulated in the pelvic region, subphrenic space and the Morrison's pouch [1]. PC is present at the time of CRC diagnosis in approximately 10% of all patients [2]. In 40% of the cases it is the only site of metastatic disease [3]. Until recently, patient treatment was limited to palliative surgery and systemic chemotherapy, with median survival rates from 4 to 12 months [4]. Over the last decade, there have been new discoveries on limited intraperitoneal tumor spread, without systemic dissemination, which has led to new therapeutic approaches focused on the abdominal and pelvic cavity that can eradicate PC and provide longer survival in strictly selected

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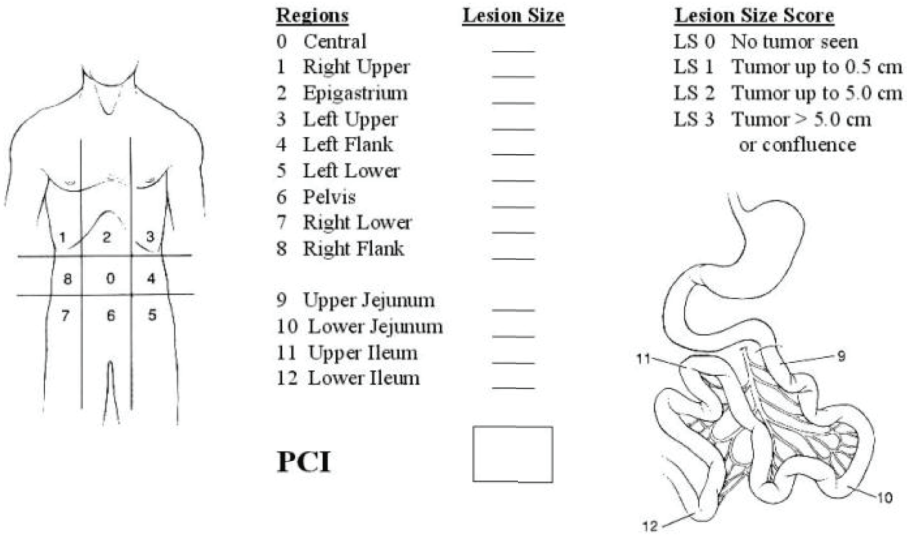

Figure 1. Peritoneal Cancer Index (PCI) quantification according to Sugarbaker [6]. Regions: abdominopelvic regions (0-12), LS: lesion nodule size (0-3).

group of patients [5].

The aim of the present research, conducted at the Institute for Oncology and Radiology of Serbia (IORS), was to examine OS and DFS in patients with CRC-PC, treated with combined CRS and HIPEC, as well as to analyse which factors are of prognostic significance for survival. All data were compared and discussed with those available in the literature on patients treated with other treatment modalities.

Methods

Patient selection

This study included 61 patients with CRC-PC treated with CRS and HIPEC (CRS+HIPEC) at the Surgical Oncology Clinic of IORS, from 2005 to 2012. All patients signed an informed consent for the treatment. The study was approved by the IORS Ethics Committee.

Inclusion criteria

Patients had to fulfill all of the following criteria: age from 18 to 75 years, good general condition, no unstable cardiac disease/acute myocardial infarction at least 6 months prior to the CRS+HIPEC, no neurological/mental disorders, no pregnancy/lactation (for women), histopathological/CT confirmation of CRC-PC, no previous CRS+HIPEC, no second malignancy/distant metastases (lungs, skeleton, CNS), and resectable liver disease (CT/angiographic confirmation).

Treatment of primary disease

All patients with CRC were treated following standard protocols according to the disease stage. The majority (61%) was treated for CRC in other institutions, the rest at IORS. Patients who initially had CRC-PC underwent CRS+HIPEC at IORS, following the inclusion criteria for this procedure.

Treatment of peritoneal carcinomatosis from colorectal cancer (CRS+HIPEC)

CT scan was used for preoperative planning of CRS. Intraoperatively, following surgical exploration of the abdominal and pelvic cavity, PCI score was determined, combining nodule size - score 0 to 3 with PC distribution in abdominopelvic regions - score 0 to12 (Figure 1) [6]. Ranging from 0 to 39, PCI score was used for quantitative assessment of the PC extent and deciding whether to perform CRS or palliative procedure. We performed CRS in all patients with PCI ≤20, as well as in 3/61 (4.92%) patients with PCI score > 20, although some authors indicate PCI >20 [7], or even >18 [8] as not suitable for CRS. Principles for peritonectomy procedures set out by Sugarbaker were followed [9]. After adequate CRS, "closed" HIPEC was applied during 30-60 min, according to the recommendations of some researchers [10]. The closed method implies intraperitoneal application of cytotoxic drug (oxaliplatin 410 mg/m^2) heated to 41°C in 2000 mL isotonic solution through drains, using RanD Performer ® HT perfusion system.

Treatment after CRS+HIPEC

After CRS+HIPEC, the majority of the patients received adjuvant chemotherapy, mainly the FOLFOX regimen. Exceptions were the patients with poor general condition. Some patients did not continue postoperative treatment at IORS, thus we had no information on their further therapy.

Parameters in the research

In addition to patient and primary tumor characteristics, we examined the influence of the following factors in relation to OS and DFS:

Period of time from primary tumor (PT) diagnosis to PC development

1. Synchronous PC: PC present at the time of CRC diagnosis and
2. Metachronous PC: PC appearance some time after PT diagnosis. Patients in this category were allocated in 2 subgroups:
   - Period from PT to PC ≤12 months - PC appearance within the first 12 months
   - Period from PT to PC >12 months - PC appearance after 12 months.

PCI score

- PCI Category 1: PCI <13 and PCI ≥13,
- PCI Category 2: PCI <7. 7, PCI<13 and PCI≥13.

Completeness of the cytoreduction (CC) score
(defined by Sugarbaker's recommendations [6])

1. CC0 - no visible PC (R0 resection),
2. CC1 - residual PC nodules < 2.5mm (R1 resection),
3. CC2 - residual PC nodules between 2.5-25 mm (R2 resection),
4. CC3 - residual PC nodules >25mm or confluent unresected nodules.

In CRC, a complete cytoreduction includes both R0 and R1 surgical resection, with all visible sites of disease successfully cleared and residual nodule size less than 2.5 mm penetrable by intracavitary chemotherapy [11].

Statistics

To summarize the data, the following descriptive methods of statistical analysis were used: frequencies, percentages, mean, median, standard deviation (SD) and range. The statistical significance level was set at $p<0.05$. Curves of probabilities for OS and DFS were constructed using the Kaplan-Meier product-limit method and the median of survival analysis, with corresponding 95% CI was used for their description. Log-rank test was used for testing the differences between curves for OS and DFS, regarding several parameters. Univariate and multivariate Cox proportional hazard regression models were used. The hazard ratio with corresponding 95% CI was used for description and the Wald and Likelihood ratio test were used for the statistical testing. The statistical analysis was done in the program R, version 2.15.1 (2012-06-22) - "Roasted Marshmallows"; Copyright (C) 2012 The R Foundation for Statistical Computing; ISBN 3-900051-07-0; downloaded: June 27, 2012. Tables and curves were designed in Microsoft Office Excel 2007.

Results

After CRS+HIPEC, patients were followed up for 1-83 months (median 22). Median OS (with 95% CI) was 51 (>22) months (Figure 1) and within 2 months after CRS+HIPEC 4/61 (6.56%) patients died. Four out of 61 (6.56%) patients had residual disease after CRS (R1 and R2 resection), thus median DFS (with 95% CI) for the remaining 57/61 (93.44%) patients was 23 (>16) months (Figure 1).

One-, 2- and 6-year OS (and DFS) were 78.6% (68.3%), 58.7% (46.7%) and 50.5% (38.1%), respectively (Figure 2). By the end of the research, 27/61 (44.26%) patients had died, while the remaining 55.74% were alive.

Characteristics of patients and primary tumors are depicted in Table 1. Only localization of

Table 1. Patient, disease characteristics and univariate survival analysis

Characteristics	*N (%)*	*Log-rank, p*	
		OS	*DFS*
Patient characteristics			
Gender			
Male	11 (18.13)	NS	NS
Female	50 (81.87)		
Age (years)			
Mean (SD)	53.51 (12.67)	-	-
Median (range)	55 (27 - 76)		
Age at surgery, years			
≤55	31 (50.82)	NS	NS
>55	30 (49.18)		
Primary tumor characteristics			
Localisation			
Colon	56 (91.80)	NS	p<0.05
Appendix	5 (8.20)		
Mucinous tumor component			
No	48 (78.69)	NS	p<0.05
Yes	13 (21.31)		
LN status in 61 patients			
Positive	10 (16.39)	-	-
Negative	14 (22.95)		
No data*	37 (60.66)		
Extirpated LNs in 24 patients			
Mean (SD)	19.75 (19.59)	-	-
Median (range)	14 (3 - 66)		
Positive LNs in 10 patients			
Mean (SD)	5.22 (5.65)	-	-
Median (range)	3 (1 - 18)		
Total patients	61 (100)	-	-

NS: not statistically significant, SD: standard deviation, LN: lymph nodes. * Data on initial LNs number and their status were not available for 37/61 (60.66%) of patients treated outside IORS, so this parameter was not statistically analyzed

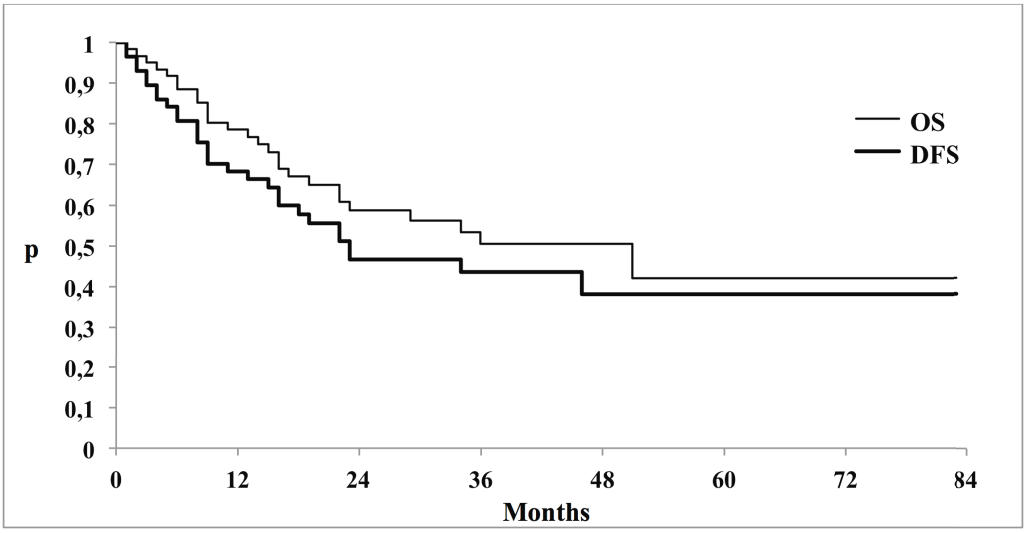

Figure 2. Overall survival (OS) and disease free survival (DFS) of patients with colorectal peritoneal carcinomatosis treated with CRS+HIPEC.

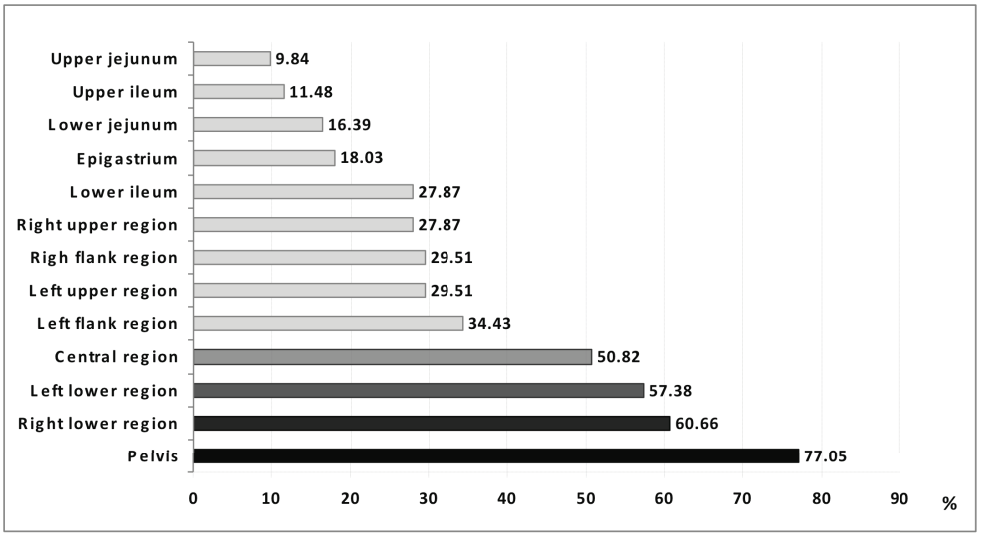

Figure 3. Localization of peritoneal carcinomatosis nodules (%) in abdominopelvic regions in our group of patients (according to Sugarbaker [7]).

PT in colon (vs appendix), as well as presence (vs absence) of mucinous component in tumor, were associated with significantly longer DFS.

The characteristics of PC are displayed in Table 2. PC nodules were mostly localized in the lower parts of abdominopelvic cavity, mainly in the pelvis (77.05%), while half of the patients had the central region affected by PC (Figure 3). PCI score ranged from 2 to 27 (median 8; Table 2). Only 3 patients had PCI> 20 (24, 26 and 27). They all were females, aged 60, 62 and 73 years, with lethal outcome 6-8 months after CRS+HIPEC.

Statistical analysis showed no difference in OS/DFS between groups of patients with synchronous and metachronous PC ($p<0.05$), neither impact of PC nodules size on OS/DFS. However, patients with a time period from PT to PC ≤12 months had significantly longer DFS (Table 2). Patients with PCI <13 (vs PCI ≥13) had significantly longer OS and DFS (Table 2), also confirmed for PCI subcategories (PCI <7 vs 7≤PCI <13 vs PCI ≥ 13). OS and DFS in association with all PCI categories and subcategories are given in Figures 4 and 5. The group of patients with PCI <13 (vs PCI ≥13) had median OS and DFS >51 (vs 11) and >23 (vs >8) months. Medians for OS/DFS in PCI<7 subcategory were not reached due to lack of events by the end of the research in that subcategory, meaning that all patients were alive.

Treatment characteristics are shown in Table 3. The majority of our patients (25/61, 40.98%) had peritoneal resection of only one abdominal

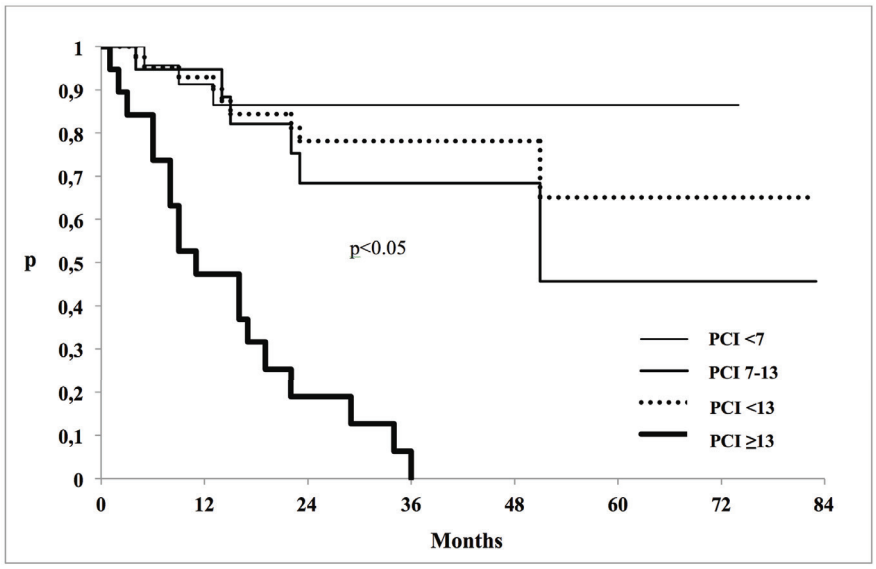

Figure 4. Overall survival in all Peritoneal Cancer Index (PCI) score categories.

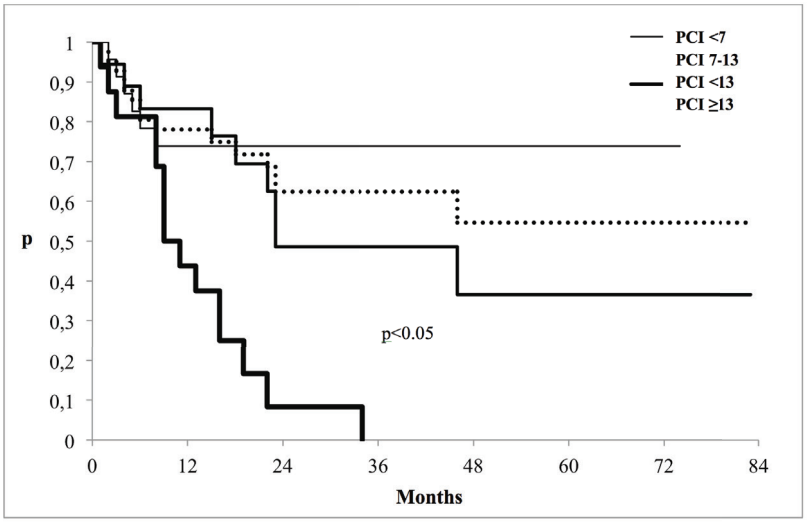

Figure 5. Disease free survival in all Peritoneal Cancer Index (PCI) score categories.

region, dominantly the left upper (48/61, 78.69%) and left lower quadrant (42/61, 68.85%). Regarding visceral resections, colon (39/61, 63.93%) and omentum (37/61, 60.66%) resections were the most frequent, while prostate, pancreas and stomach were rarely infiltrated with PC (Table 3). Statistical analysis did not show longer OS/DFS in association with certain peritoneal and visceral resections (log-rank test; p>0.05 for all parameters in Table 3). The average time of the cytotoxic drug application in our group was 48.25 (SD=7.47) min. Only 6/57 (10.53%) patients underwent HIPEC under 45 min.

Complete surgical cytoreduction was achieved in 57/61 (93.44%) patients (Table 4). Fifty-three out of 61 (86.88%) patients had no postoperative complications, while the rest had grade I and II complications that did not cause lethal outcome. No statistically significant difference in OS/DFS regarding presence (vs absence) of postoperative complications, or receiving adjuvant chemotherapy (vs no chemotherapy) was found (log-rank test; p>0.05 for both).

All parameters identified as statistically significant for OS/DFS (log-rank test, Tables 1 and 2), were tested with Cox proportional hazards regression method for survival data in the subgroup of 54 patients in whom all necessary data for selected parameters were available. Results of Cox univariate and multivariate analysis are given in Table 5. Mucinous component of the PT (for OS and DFS) and time period from PT to PC (only for DFS)

Table 2. Characteristics of peritoneal carcinomatosis and Peritoneal Cancer Index in patients

Characteristics	*N (%)*	*Log-rank, p*	
		OS	*DFS*
Appearance of PC in comparison to PT			
Synchronous	28 (45.90)	NS	NS
Metachronous	27 (44.26)		
No data#	6 (9.84)		
Period from PT to PC (months)*			
Mean (SD)	15.41 (12.87)	-	-
Median (range)	12 (2 - 48)		
Period from PT to PC, months			
≤12	14 (51.85)	NS	<0.05
>12	13 (48.15)		
PCN size, cm			
≤0.5	18 (29.51)	NS	NS
0.5-5	34 (55.74)		
>5	9 (14.75)		
PCI			
Mean (SD)	9.77 (6.05)	-	-
Median (range)	8 (2 - 27)		
PCI – category 1			
<13	42 (68.85)	<0.001	<0.001
≥13	19 (31.15)		
PCI – category 2			
<7	23 (37.70)		
7-13	19 (31.15)	<0.001	<0.001
≥13	19 (31.15)		
Total patients	61 (100)		

NS: not statistically significant, SD: standard deviation, PC:peritoneal carcinomatosis, PT: primary tumor, PCN: peritoneal carcinomatosis nodule, PCI: peritoneal cancer index. *Period from PT to PC for patients with metachronous PC. # For some patients treated outside IORS (≈10%), data on the time period from PT to PC were not available

Table 3. Treatment characteristics

Characteristics	*N (%)*
Cytoreductive surgery – Peritoneal resections	
Extent of resection	
1 region	25 (40.98)
2 regions	16 (26.23)
≥ 3 regions	20 (32.79)
Resected regions	
Region 1 (RUQ)*	41 (67.21)
Region 2 (RLQ)*	33 (54.10)
Region 3 (LUQ)*	48 (78.69)
Region 4 (LLQ)*	42 (68.85)
Region 5 (pelvis)	12 (19.67)
Cytoreductive surgery – Visceral resections	
Colon	39 (63.93)
Omentum	37 (60.66)
Adnexa	27 (44.26)
Uterus	25 (40.98)
Small intestine	24 (39.34)
Diaphragm	14 (22.95)
Spleen	13 (21.31)
Bladder	10 (16.39)
Liver	6 (9.84)
Omental bursa	6 (9.84)
Stomach	2 (3.28)
Pancreas	2 (3.28)
Prostate	1 (1.64)
HIPEC	
Cytotoxic drug (N=61)	
Oxaliplatin	53 (86.89)
Mitomycin	8 (13.11)
Administration time (min)	
Mean (SD)	48.25 (7.47)
Median (Range)	45 (30-60)
No data^	4 (6.56)
Application time by categories, min (N=57)	
30	1 (1.75)
40	5 (8.77)
45	36 (63.16)
60	15 (26.32)
Adjuvant chemotherapy	
Yes	41 (67.21)
No	11 (18.03)
No data#	9 (14.75)
Chemotherapy regimens (N=40)	
Folfox	33 (82.50)
Folfiri	1 (2.50)
5-FU	6 (15.00)

* Abdominal cavity: RUQ - right upper quadrant, RLQ - right lower quadrant, LUQ - left upper quadrant, LLQ - left lower quadrant, ^ Data were not available from operative reports, # These patients did not present to the Medical Board at IORS and therefore data on their postoperative treatment are lacking

Table 4. Treatment outcome

Treatment outcome	*N (%)*
Completeness of cytoreduction (CC) score	
CC0: no residual disease	57 (93.44)
CC1: residual <2.5 mm	2 (3.28)
CC2: residual 2.5 mm-2.5 cm	2 (3.28)
CC3: residual > 2.5 cm	0 (0)
Postoperative complications	
No	53 (86.88)
Yes	8 (13.11)
Outcome	
Alive	34 (55.74)
Dead	27 (44.26)
Patients, total	61 (100)

Table 5. Results of univariate and multivariate Cox regression analyses for overall survival and disease free survival in relation to primary tumor and peritoneal carcinomatosis characteristics (N=54)

Parameters	*Univariate analysis*		*Multivariate analysis*	
	Hazard ratio (95% CI)	*Wald Test*	*Hazard ratio (95% CI)*	*Likelihood ratio test*
Overall survival				
Mucinous component in PT No vs Yes	2.77 (0.8-9.58)	p=0.1078	-	0.05743312
Time from PT to PC Metachronous ≥12 vs metachronous <12 Synchronous vs metachronous <12	2.78 (0.81-9.57) 1.70 (0.54-5.37)	p=0.106 p=0.365	-	0.1141776
PCI score ≤13 vs >13	10.22 (3.85-27.14)	$3.09 \cdot 10^{-6}$	10.22 (3.85-27.14)	$5.898 \cdot 10^{-7}$
Disease free survival				
Mucinous tumor component No vs Yes	4.93 (1.15-21.16)	p=0.032	-	0.05506885
Time from PT to PC Metachronous ≥12 vs metachronous <12 Synchronous vs metachronous <12	3.89 (1.25-12.05) 1.80 (0.63-5.10)	p=0.106 p=0.365	-	0.06234948
PCI score ≤13 vs >13	4.39 (1.93-9.95)	$4.04 \cdot 10^{-4}$	4.39 (1.93-9.95)	$5.25 \cdot 10^{-4}$

PT: primary tumor, PC: peritoneal carcinomatosis, PCI: peritoneal cancer index

are on the borderline of statistical significance in Cox multivariate analysis (Table 5). PCI score was confirmed as parameter of significance in the prognosis of patients treated with CRS+HIPEC for CRC-PC.

Discussion

Patients with CRC-PC are mainly treated with systemic chemotherapy and palliative surgery, with their survival being mostly under 6 [12,13] or 7 months [14]. Several studies, however, confirmed better prognosis of these patients if treated with CRS+HIPEC. Median OS was 19.2 [7] and 22.2 [15]; median DFS was 20 months [16]; and 5-year OS up to 33% [7]. Our research showed median OS (DFS) over 22 (16) months, while 5-year OS (DFS) was 50.5% (38.1%). Better OS/DFS in patients treated with CRS+HIPEC (oxaliplatin) was substantiated by studies that compared these two treatment options (systemic chemotherapy and palliative surgery vs CRS+HIPEC) [17,18].

Our results showed localization of the PT in appendix (vs colon) as statistically significant for better OS/DFS, irrespective of age (≤55 vs >55 years) and gender (females vs males). This finding is consistent with available data on these parameters from one Italian multicentric study [19] and may be the result of the fact that appendiceal tumors are mainly mucinous, with better prognosis than adenocarcinomas of colorectum.

We confirmed the results of previous publications showing significantly worse OS/DFS in patients with PC affecting the central and left/right subphrenic region [20], and infiltration of small intestine and its mesentery as one of the most significant factors leading to shorter OS/DFS [7,12,21].

The results of our research are consistent with prior knowledge on the prognostic value of PCI score, thus it is significant in critical patient selection for CRS+HIPEC treatment [6-8]. In our patients with PCI <13 (vs PCI ≥13) the median OS was >51 (vs 11) months, while the median DFS was >23 (vs >8) months. All patients from the group with PCI <7 were alive at the end of the research.

Regarding CRS, according to literature data [22], which correspond with our study, the extent of surgery, in terms of resected regions and number of anastomoses, had no statistical relevance in OS or DFS, but did increase the morbidity and postoperative complications. Many authors [17,23] assign prognostic significance of CRS on OS. In 93.44% of our patients R0 surgical resection was achieved, which is related to good preoperative staging and correct PCI assessment. However, statistical significance of CRS completeness in relation with OS/DFS has not been shown.

Postoperative complications are expected in regard to long-lasting surgical procedures followed by HIPEC procedure. The complication rates ranged from 12 to 66% in different centers [24-26]. In our patients, grade I and II compli-

cations were recorded in 13.11% of the patients, but there was no statistical relevance regarding OS and DFS. We didn't observe significant toxic effects of HIPEC, probably due to less toxicity of local administration (vs systemic), although the doses were much higher.

Given that carcinomatosis equals stage 4 disease, postoperative chemotherapy is administered in all major medical centers almost as a standard protocol, following intraoperative chemotherapy. No studies to date, including ours, showed better prognosis of patients who received postoperative chemotherapy, in comparison to those who did not. Further research on postoperative chemotherapy administration (after CRS and HIPEC) is needed.

Our study revealed that mucinous component of PT (for OS and DFS) and time elapsed from PT to PC (only for DFS) had borderline statistical significance in the Cox regression analysis (p=0.055 and p=0.062, respectively). On the other hand, statistical analysis indicated PCI score as a significant prognostic parameter (p<0.001) of patients treated with CRS+HIPEC for CRC-PC. This data corresponds with data from other international studies [6-8,11,16,23].

All of our patients had complete surgical resection of peritoneal carcinomatosis due to good preoperative staging and correct assessment of PCI score. The results of the present research indicate that CRS and HIPEC significantly improve the survival of patients with PC of CRC origin (median: OS>22, DFS>16 months), therefore this treatment modality should be considered as the most suitable in well-selected patients with this disease [27].

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