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Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy outcomes in peritoneal carcinomatosis: 11-year tertiary-center experience

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Abstract

Background Cytoreductive Surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) are techniques developed for curative treatment of peritoneal carcinomatosis (PC). Studies have shown that CRS + HIPEC provides a survival advantage in PC, and long-term survival can be achieved in selected cases. This study aimed to evaluate CRS + HIPEC cases performed for curative purposes and to examine the prognostic factors.

Methods PC patients who underwent CRS + HIPEC with curative intent between January 2011 and September 2022 were included. Demographic, clinical, and pathological findings, procedure-specific parameters, complications, mortality, progression-free survival (PFS), and overall survival (OS) were analyzed.

Results Optimal cytoreduction was achieved in 70% of the patients. The median PFS for the entire series was 9.2 months, while the median OS was 20.5 months, with a 3-year OS rate of 36%. Appendiceal origin, cytoreduction score, absence of lymph node metastasis, and absence of complications were factors associated with a positive impact on both PFS and OS. In multivariate analysis, cytoreduction score emerged as the sole independent factor influencing both PFS and OS.

Conclusions Considering the results in our series, cases of PC in which complete cytoreduction can be achieved should be evaluated for CRS + HIPEC.

Keywords Cytoreductive surgery, Hyperthermic intraperitoneal chemotherapy, Peritoneal surface malignancy

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Introduction

Peritoneal carcinomatosis (PC) is a condition characterized by intraabdominal spread of advanced-stage gastrointestinal and gynecological malignancies. Rarely, it can also occur due to primary tumors of the peritoneum [1]. Before the 1980s, PC was considered untreatable, often resulting in mortality within an average of 6 months and standard treatment approaches were systemic chemotherapy and palliative surgeries [2–4]. Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) techniques were developed under the concept that peritoneal carcinomatosis is a locoregional rather than systemic condition [5–7]. In CRS + HIPEC case series, longer survival was observed compared to traditional palliative treatment methods. Complication rates were also found to be within acceptable levels [8, 9]. Despite the favorable outcomes in terms of survival, determining the optimal treatment method for PC remains challenging due to the diverse primary tumor types and their varying biological behaviors. Currently, CRS + HIPEC is not considered a standard practice in routine clinical settings, and its application is typically limited to experienced centers conducting patient-based evaluations [10–12]. There are different opinions and limited data about which patients will benefit from HIPEC and which chemotherapy drug should be preferred in patients who will undergo HIPEC [8, 13–15]. This retrospective study aims to analyze the outcomes of CRS + HIPEC procedures performed at our institution. Our objectives include evaluating prognostic factors and assessing the therapeutic impact of this intervention on survival.

Materials and methods

Patients who underwent CRS + HIPEC with a diagnosis of PC at our center between January 2011 and September 2022 were retrospectively analyzed. Patients aged 18 and over, diagnosed with peritoneal carcinomatosis, and underwent CRS + HIPEC were included in the study, regardless of the primary tumor origin and Peritoneal Cancer Index (PCI). Any of the following conditions accepted as exclusion criteria: Eastern Cooperative Oncology Group (ECOG) performance score of 3–4, Extraabdominal and/or liver metastasis on preoperative imaging or exploration, retroperitoneal pathological lymph node involvement, widespread involvement of the small intestine, and involvement of the mesenteric root, HIPEC for palliative purposes [16].

Demographic data, comorbidities, intraoperative findings (PCI, completeness of cytoreduction score [CC], type of intraperitoneal chemotherapy drug), pathological findings, Progression-free Survival (PFS), and Overall Survival (OS) of the patients were reviewed retrospectively. PCI, as defined by Sugarbaker, was utilized to assess the extent of peritoneal disease [17, 18]. Residual disease following a CRS was evaluated using the CC score. In this scoring system, cases with no residual implants were classified as CC-0, with the largest residual implant smaller than 2.5 mm as CC-1, with residual implants between 2.5 mm and 2.5 cm as CC-2, and with residual implants larger than 2.5 cm as CC-3 (15). Resections classified as CC-0 and CC-1 were considered as complete cytoreduction [17].

Postoperative complications were graded on the Clavien-Dindo classification scale, with grades 3–4 were considered as major complications [19]. Deaths occurring within 30 days after surgery were considered as early postoperative mortality.

Surgical technique

All patients underwent an xiphopubic median incision. For patients with prior surgeries, existing incision scars were also excised. PCI was assessed for all patients at the beginning of the surgery. If any inoperability criteria are detected during exploration, surgical intervention was either terminated, or palliative measures were initiated.

Cytoreductive surgery is conducted utilizing the peritonectomy techniques defined by Sugarbaker [6]. Disease-free peritoneal regions were preserved whenever possible. In cases requiring organ resection for complete cytoreduction, additional resections were performed. Gastrointestinal anastomoses were conducted before intraperitoneal chemotherapy.

Intraperitoneal chemotherapy

Closed HIPEC techniques are the standard approach in our institution. After cytoreductive surgery, four silicone HIPEC catheters are inserted, extending from the right and left upper quadrants to subdiaphragmatic areas, and from the right and left lower quadrants to the pelvis. Routine abdominal reexploration is not conducted post-HIPEC. Stable hyperthermia between 41 and 43 °C is maintained throughout the perfusion process. The volume of perfusate is determined based on the body surface area. Various HIPEC drugs are selected according to tumor types, as outlined in Table 1. HIPEC is administered to all patients for a duration ranging from 60 to 90 min.

Follow-up

Following surgery, patients' pathology data were evaluated in a multidisciplinary tumor board to devise their oncological treatments. Patients underwent follow-up visits every 3 months for the first 2 years, followed by visits every 6 months for the subsequent 3 years, and then annually after 5 years. During each follow-up visit, patients received a physical examination, tumor marker assessment, and radiological evaluations. For patients

Table 1 Demographic and clinicopathologic features of the study population

Variable		*N*(%)
Age (Median 55, Range 18–75)	All patients	89 (100)
	< 60	55 (62)
	≥ 60	34 (38)
Gender	Female	50 (56)
	Male	39 (44)
Tumor site	Apendiceal neoplasm	18 (20)
	LAMN	8 (9)
	Mucinous adenocarcinoma	10 (11)
	Colorectal cancer	38 (43)
	Gastric cancer	20 (22)
	Peritoneal cancer	13 (15)
Intraperitoneal Chemotherapy Agents	Mitomisin-C	28 (32)
	Mitomisin-C + Cisplatin	55 (62)
	Cisplatin	2 (2)
	Oxaliplatin	1 (1)
	Paclitaxel	2 (2)
	Paclitaxel + Cisplatin	1 (1)
Completeness of cytoreduction (CC)	CC-0	24 (27)
	CC-1	38 (43)
	CC-2	15 (17)
	CC-3	12 (13)
Perioperative Chemotherapy	Yes	70 (79)
	No	19 (21)
Peritoneal Cancer Index (Median 14, Range 0–30)	All patients	89 (100)
	0–10	32 (36)
	10–20	27 (30)
	21–39	30 (34)
Lymph node metastasis	Positive	54 (61)
	Negative	35 (39)

LAMN: Low-grade appendiceal mucinous neoplasm

achieving complete cytoreduction (CC-0 and CC-1), the formation of new implants or the development of ascites was considered as progression. In patients with incomplete cytoreduction (CC-2 and CC-3), an increase in the size of residual implants or the development of ascites, as well as an increase in existing ascites, was regarded as progression.

Statistical analysis

Statistical analysis was conducted using SPSS (Statistical Package for the Social Sciences) version 25.0 (IBM Corp., Armonk, NY, USA). Survival analyses were calculated using the Kaplan-Meier method. The impact of prognostic factors on progression-free survival and overall survival was assessed using the log-rank test. Independent prognostic factors were evaluated using the Cox regression test. Categorical comparisons were made using the chi-square test. Results were evaluated at a significance level of $p < 0.05$, with a 95% confidence interval.

Table 2 Complications, follow-up and recurrence rates of the study population

Variable		*N* (%)	Median	Range
Length of In-hospital Stay (Days)		89 (100%)	16	11–38
Complications	Yes	32 (36%)		
	No	57 (64%)		
Complication subgroups	Grade 1–2	16 (18%)		
	Grade 3a	13 (15%)		
	Grade 3b	3 (3%)		
Postoperative mortality	Yes	5 (6%)		
	No	84 (94%)		
Follow-up time (Months)		84 (94%)	23.2	1-140
Locoregional Recurrence	Yes	24 (27%)		
	No	65 (73%)		
Systemic metastasis	Yes	10 (11%)		
	No	79 (89%)		

Research ethics

Our study was conducted under the Helsinki Declaration and was approved by the Istanbul Faculty of Medicine Institutional Review Board (28.07.2022-No: 1085943).

Results

A total of 89 patients were included in the study. Fifty of the patients (56%) were female. The median age was 55 (Range 18–75) years. The primary tumors of the patients were as follows: 38 (43%) colorectal cancer (CRC), 20 (22%) gastric cancer, 18 (20%) appendiceal neoplasms, and 13 (15%) primary peritoneal cancer. The median PCI was 14 (0–30). The rate of patients achieving complete cytoreduction (CC-0/1) was 70%. CC-0 resection was performed in 24 (27%) patients, while CC-1 resection was performed in 38 (43%) patients. LNM was detected in 54 (61%) patients (Table 1).

In the postoperative period, complications occurred in 32 (36%) patients, with 16 (18%) patients experiencing major complications. Among these 16 patients, 3 required early reoperation: 2 for evisceration and 1 for anastomotic leakage. The 30-day postoperative mortality rate was 6%. The median follow-up period was 23.2 months (Range 1-140 months). During the follow-up, 24 (28%) patients developed recurrent peritoneal carcinomatosis, while 10 (11%) patients developed systemic metastases Table 2).

The median PFS was 9.2 months, the median OS was 20.5 months, and the 3-year OS rate was 36% for the entire series. PFS was 17.6 months and OS was 114.8 months for appendiceal tumors. PFS was 15.7 months and OS was 19.3 months for peritoneal cancers. In colorectal cancers, PFS was 6.5 months and OS was 10.9

months. For gastric cancers, having the shortest survival, exhibited a PFS of 6.4 months and OS of 7.2 months. Appendiceal cancers exhibited significantly longer survival compared to other tumor types ($p = 0.009$ for PFS, $p = 0.002$ for OS) (Table 3; Fig. 1).

For all patients, patients with PCI values of 0–10 demonstrated a median OS of 16.4 months, while those with PCI values of 11–20 exhibited an OS of 14.2 months. Patients with PCI values of 21 and above had a significantly lower OS of 7.3 months ($p = 0.001$). The median PFS was 27 months and OS was 37.9 months for CC-0 patients, while for CC-1 patients PFS was 6.7 months and OS was 9.2 months. CC-0 resection resulted in significantly longer PFS ($p < 0.001$) and OS ($p < 0.001$) when compared to CC-1 resection. Patients with LNM and complications had significantly shorter PFS ($p = 0.001$ for both) and OS ($p < 0.001$ for both) compared to those without LNM or complications (Table 3).

In cases of appendiceal tumors, patients who underwent complete cytoreduction (CC-0 and 1) not reached to median OS, while those with incomplete cytoreduction (CC-2 and 3) had a median OS of 8.3 months, demonstrating a significant difference in favor of longer survival in patients who underwent complete cytoreduction ($p < 0.001$). CC-0 patients also still not reached to median OS, while CC-1 patients had a median OS of 42 months, and there was a significant difference between these two groups ($p = 0.022$) (Table 4).

CRC cases who underwent complete cytoreduction (CC-0 and 1) had a median OS of 24.6 months, while those with incomplete cytoreduction (CC-2 and 3) had a median OS of 6.7 months, demonstrating a significant difference in favor of longer survival in patients who underwent complete cytoreduction ($p < 0.001$). CC-0 patients had a median OS of 38.8 months, while CC-1 patients had a median OS of 19.4 months, and although there was no statistical significance between CC-0 and CC-1 ($p = 0.066$), there was a significant difference between CC-0 and CC-1,2,3 patients ($p = 0.009$) (Table 4).

Gastric cancer patients with complete cytoreduction (CC-0 and 1) had a median OS of 11,7 months, while those with incomplete cytoreduction (CC-2 and 3) had a median OS of 6,8 months, and although there was no statistical significance between CC-0,1 and CC-2,3 ($p = 0.097$), there was a significant difference between CC-0 and CC-1,2,3 patients ($p = 0.011$) (Table 4).

Table 3 Factors associated with progression-free survival and overall survival

Variable			PFS		Median PFS		OS		Median OS	
		N	1 year (%)	3 years (%)	Month (%95 CI)	*P*-value	1 year (%)	3 years (%)	Month (%95 CI)	*P*-value
All Patients	All Patients	89	80	43	9.20 (6,56 – 11,84)		56	36	20,47 (8,80 – 32,13)	
Age	< 60	55	76	46	10,17 (7,47 – 12,87)	0,056	63	39	14,17 (4,76 – 23,58)	**0,017***
	≥ 60	34	82	29	6,50 (5,31 – 7,69)		48	32	7,20 (4,11 – 10,30)	
Gender	Female	50	71	43	7,40 (4,17 – 10,63)	0,408	53	36	9,67 (6,63 – 12,71)	0,802
	Male	39	91	42	10,87 (5,20 – 16,53)		59	37	12,07 (0,44 – 23,69)	
Tumor site	Appendiceal	18	89	47	17,69 (6,08–28,92)	**0,009***	78	71	114.8 (41.87-NR)	**0,002***
	Peritoneal	13	100	45	15.71 (5,12–26,87)		67	39	19,35 (8,92 – 40,63)	
	Colorectal	38	73	34	6,50 (4,04–8,96)		56	34	10,87 (5,43 – 16,30)	
	Gastric	20	57	38	6,40 (2,82 – 9,97)		29	9	7,20 (3,48 – 10,93)	
CC	CC-0	24	91	64	27,00 (19,88 – 34,1)	**< 0,001***	95,8	78,8	37,87(18,50 – 7,23)	**< 0,001***
	CC-1	38	72	18	6,67 (5,16 – 8,18)		65	33	9,20 (2,61 – 15,80)	
	CC-2	15	43	***	7,83 (1,01–14,65)		13	7	7,83 (0,22 – 15,45)	
	CC-3	12	**	***	2,17 (0,00–8,50)		8	**	2,17 (0,00–8,50)	
Perioperative Chemotherapy	Yes	70	77	37	9,07 (5,82 – 12,31)	0,252	54	34	10,87 (7,93 – 13,81)	0,204
	No	19	90	51	10,20 (5,98 – 14,42)		62	41	10,37 (0,00–27,00)	
PCI	0–10	32	82	40	12,07 (3,65 – 20,48)	0,522	77	56	16,43 (4,50 – 28,36)	**0,001***
	10–20	27	81	40	9,20 (4,39 – 14,01)		70	45	14,17 (0,00–32,32)	
	21–39	30	73	41	7,20 (4,20 – 10,20)		27	17	7,27 (5,84 – 8,70)	
LNM	Positive	54	69	28	6,50 (5,18 – 7,82)	**0,001***	44	21	7,70 (4,90-1050)	**< 0,001***
	Negative	35	89	56	18,23 (8,19–28,28)		72	52	24,13 (16,06–32,2)	
Complication	Yes	32	73	29	6,67 (4,73 – 8,61)	**0,031***	39	18	8,67 (6,17 – 11,16)	**0,029***
	No	57	84	47	10,37 (6,46 – 14,28)		64	44	15,80 (5,13–26,47)	

*:$p < 0.05$, Log-rank test, **:No events, ***:Not reached 3 years period, CC: Completeness of cytoreduction, PCI: Peritoneal cancer index, LNM: Lymph node metastasis, PFS: Progression-free survival, OS: Overall survival, NR: Not reached

All *p*-values less than 0.05 was bold

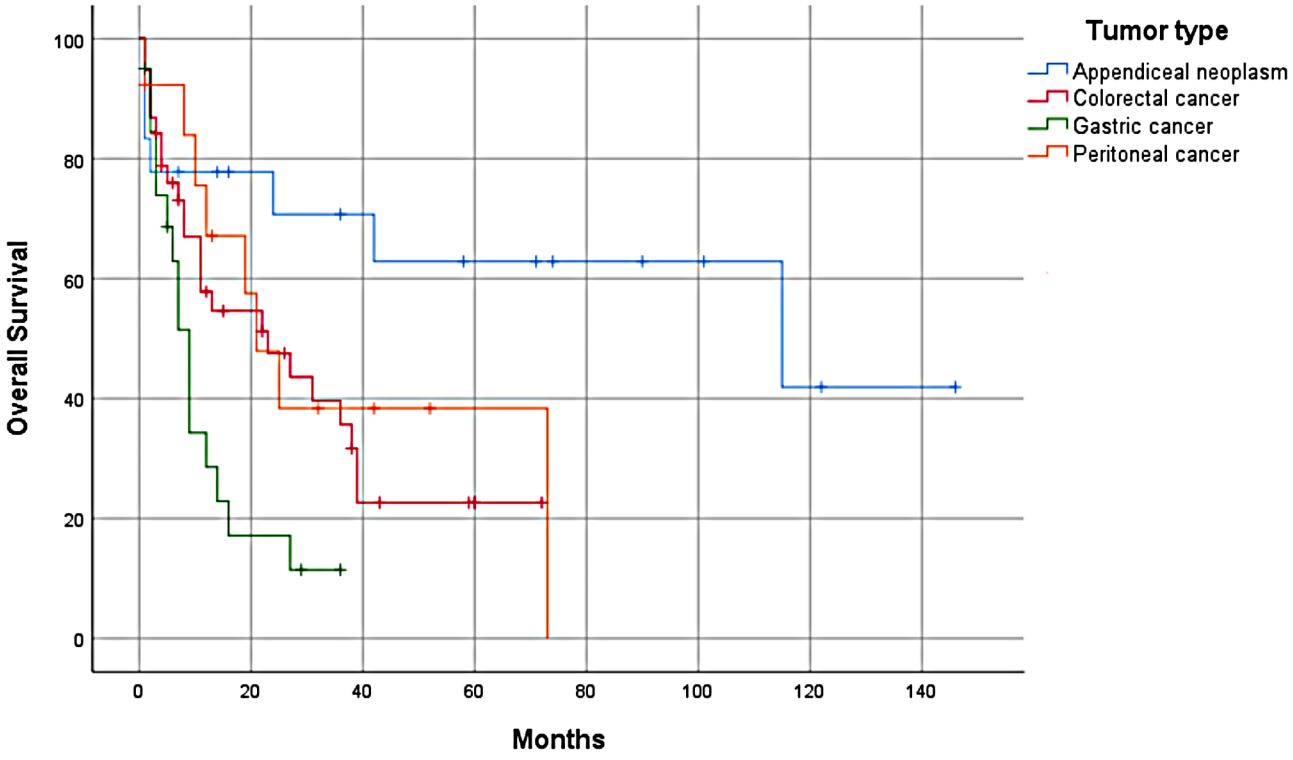

Fig. 1 Overall survival according to primary tumor types

Table 4 Relationship of cytoreduction score with overall survival according to tumor types

		Completeness of Cytoreduction Score			
		CC-0/1		CC-2/3	
Tumor site	**N**	**Median (%95 CI)**	**N**	**Median (%95 CI)**	**P-value**
Appendiceal	15	NR (115-NR)	3	8.3 (2.7–17.8)	**< 0.001***
Peritoneal	10	25.6 (12.7–38.3)	3	7.4 (2.5–15.3)	**< 0.001***
Colorectal	26	24.6(16.8–32.4)	12	6.7(2.4–10.9)	**< 0.001***
Gastric	11	11.7(4.6–18.7)	9	6.8(2.9–10.7)	0.097
		CC-0		**CC-1**	**P-value**
Tumor site	**N**	**Median (%95 CI)**	**N**	**Median (%95 CI)**	
Appendiceal	9	NR (115-NR)	6	42 (28.7–69.4)	**0.022***
Peritoneal	3	73.9 (21.5-NR)	7	19.1 (8.6–29.5)	**0.049***
Colorectal	7	38.8(18.4–59.3)	19	19.4(11.8–26.9)	0.066
Gastric	5	19.4(5.8–33.1)	6	5.2(1.6–8.8)	0.057
		CC-0		**CC-1/2/3**	
Tumor site	**N**	**Median (%95 CI)**	**N**	**Median (%95 CI)**	**P-value**
Appendiceal	9	NR (115-NR)	9	23.5(11.8–45.9)	**0.003***
Peritoneal	3	73.9 (21.5-NR)	10	18.7 (9.9–37.4)	**0.032***
Colorectal	7	38.8(18.4–59.3)	31	14.5(9.2–19.7)	**0.009***
Gastric	5	19.4(5.8–33.1)	15	6.2(3.7–8.6)	**0.011***

*$p < 0.05$, Log Rank test, CC: Completeness of cytoreduction, CI: Confidence interval, NR: Not reached

All *p*-values less than 0.05 was bold

Peritoneal cancer cases who underwent complete cytoreduction (CC-0 and 1) had a median OS of 25.6 months, while those with incomplete cytoreduction (CC-2 and 3) had a median OS of 7.4 months, demonstrating a significant difference in favor of longer survival in patients who underwent complete cytoreduction ($p < 0.001$). CC-0 patients had a median OS of 73.9 months, while CC-1 patients had a median OS of 19.1 months ($p = 0.049$), and there was also a significant difference between CC-0 and CC-1,2,3 patients ($p = 0.032$) (Table 4).

Table 5 Relationship of lymph node metastasis with overall survival according to tumor types

		Lymph Node Metastasis			
		Absent		Present	
Tumor site	***N***	**Median (%95 CI)**	***N***	**Median (%95 CI)**	***P*-value**
Appendiceal	12	115 (42-NR)	6	8.3 (2.7–17.8)	**0.006***
Peritoneal	11	20,8 (11,6–38,9)	2	10 (9,2–12,7)	0.217
Colorectal	8	27,3 (16.8–37.4)	30	11,8 (5.4–20.9)	**0.045***
Gastric	2	7,6 (2,5–13,7)	18	9,4 (6,1–25,8)	0.482

*$p < 0.05$, Log Rank test, CC: Completeness of cytoreduction, CI: Confidence interval, NR: Not reached

All *p*-values less than 0.05 was bold

When lymph node metastasis was evaluated according to tumor types, it was found that the presence of lymph node metastasis significantly reduced survival in appendiceal neoplasms and colorectal cancers ($p = 0.006$ and $p = 0.045$, respectively) (Table 5).

In the multivariate analysis, CC was emerged as the sole independent factor significantly affecting both PFS ($p < 0.001$) and OS ($p < 0.001$) Table 6).

Table 6 Factors associated with Progression-Free survival and overall survival (Multivariate analysis Results)

	Progression-Free Survival (PFS)			Overall Survival (OS)		
Age	**HR**	**%95-CI**	***P*-value**	**HR**	**%95-CI**	***P*-value**
< 60	1			1		
≥ 60	1,36	0,86 – 2,16	*0,191*	1,49	0,92 – 2,42	0,104
Tumor site						
Appendiceal	1			1		
Peritoneal	1,02	0,22 – 4,70	0,973	2,49	0,85 – 7,30	0,097
Colorectal	2,20	0,55 – 8,82	0,268	1,96	0,71 – 5,43	0,198
Gastric	4,23	0,82 – 21,75	0,084	4,71	1,60 – 13,91	**0,031***
CC						
CC-0	1			1		
CC-1	3,07	1,67 – 5,64	**< 0,001***	2,63	1,43 – 4,83	**0,002***
CC-2	4,68	2,09–10,49	**< 0,001***	5,92	2,45 – 14,32	**< 0,001***
CC-3	4,75	2,06–10,99	**< 0,001***	6,54	2,27 – 18,84	**0,001***
LNM						
Negative	1			1		
Positive	1,61	0,91 – 2,85	0,099	1,58	0,93 – 2,71	0,093
Complication						
No	1			1		
Yes	1,11	0,67 – 1,84	0,693	1,07	0,63 – 1,82	0,812
PCI						
≤ 20				1		
> 21				1,13	0,60 – 2,15	0,708

*p:<0.05; Cox Regression Analysis, HR: Hazard ratio, CI: Confidence interval, 1:Reference value, CC: Completeness of cytoreduction, PCI: Peritoneal cancer index, LNM: Lymph node metastasis

All *p*-values less than 0.05 was bold

Discussion

CRS and HIPEC have been considered as a potentially curative treatment method for isolated peritoneal carcinomatosis. However, the large number of both patient-related and technique-related factors makes it challenging to demonstrate the impact of these variables on survival [12]. In this study; cytoreduction score, PCI, LNM, and complications were identified as significant prognostic factors affecting PFS and OS in univariate analysis. However, after multivariate analysis, the cytoreduction score was identified as the only independent variable. Some studies in the literature also emphasize the cytoreduction score as the main prognostic marker, with other factors exerting an influence on the cytoreduction score [20, 21].

One of the most important factors in the success of CRS + HIPEC is to achieve complete cytoreduction in CRS (CC-0/1). The surgeon's experience plays a crucial role in achieving complete cytoreduction during CRS, leading to variations in complete cytoreduction rates across different centers. A study conducted in the Netherlands assessed the initial experiences of four centers, revealing complete cytoreduction rates ranging from 66 to 86% for the first 100 cases. Subsequently, higher rates of complete cytoreduction were observed after the initial 100 cases [22]. Among 89 cases treated with CRS + HIPEC in our center, a complete cytoreduction rate of 70% was observed, which is consistent with the literature.

Although there is an increased risk of morbidity and mortality after CRS + HIPEC, morbidity and mortality rates after CRS + HIPEC have decreased to acceptable levels with increasing experience [23, 24]. In a retrospective study evaluating 2149 patients in Germany, it was reported that the major complication rate was 19.3% and the 30-day postoperative mortality rate was 2.3% [25]. In a single-center study conducted by Deo et al. [26], involving 232 patients, the treatment-related mortality rate was reported to be 3.5%. The impact of postoperative complications on recurrence and shortened survival has been investigated in various cancer types. Schneider MA et al. [27] conducted a study examining the influence of complications following CRS + HIPEC procedures on survival, revealing that lymph node metastasis (LNM) and complications were associated with reduced disease-free survival. Additionally, in this study, PCI > 10 was independently associated with poor prognostic outcomes on cancer-specific survival. In a separate study by Gamboa AC et al. [28] patients with PC from non-invasive and invasive appendiceal neoplasms were analyzed. It was found that complications did not significantly affect survival in CRS + HIPEC cases involving non-invasive appendiceal neoplasms. However, in cases of invasive appendiceal neoplasms, complications were identified as

an independent factor contributing to decreased overall survival. In our series, complications were observed in 36% of all patients, with 18% classified as major complications. Early (30-day) postoperative mortality was observed in 5 patients (6%). Early mortality was observed in 7% of cases (3 out of 44) performed between 2011 and 2019, whereas only 4% of cases (2 out of 45) performed between 2019 and 2022. This suggests that the increasing experience over time impacted these outcomes. While the development of complications was identified as a factor associated with reduced survival in univariate analysis, it did not emerge as an independent variable in multivariate analysis.

Pseudomyxoma peritonei (PMP) is the first patient group in which long-term survival was achieved with CRS + HIPEC applications. In a series of 385 PMP patients reported by Sugarbaker et al. [9] in 1999, it was observed that the 5-year survival rate was 86% with complete cytoreduction in diffuse peritoneal adenomucinosis, and 50% after complete cytoreduction in PMP cases due to invasive appendiceal neoplasia. In an international multicenter study, patients undergoing CRS with or without HIPEC for PMP treatment were compared, revealing a significant survival benefit associated with HIPEC application [29]. Currently, CRS + HIPEC applications are considered the primary treatment modality for PMP in the majority of medical centers [30]. In our series, 18 PMP patients were treated with CRS + HIPEC, with 9 undergoing CC-0 resection and 6 undergoing CC-1 resection. Among those who underwent CC-0 resection, 4 patients had a PCI between 18 and 26, and all are currently alive. Among those who underwent CC-1 resection, three patients are also alive. According to the literature, a high PCI does not preclude surgery in PMP cases, and CRS + HIPEC is recommended when complete cytoreduction is feasible, which aligns with our findings [31].

CRC and gastric cancer are malignancies that can progress to PC during the course of the disease, and the efficacy of systemic chemotherapy is limited in PC cases. A randomized controlled trial comparing CRS + HIPEC with systemic chemotherapy in CRC cases showed longer overall survival with CRS + HIPEC [10]. Similarly, a study comparing neoadjuvant systemic chemotherapy with neoadjuvant intraperitoneal + systemic chemotherapy in PC cases related to gastric cancer demonstrated increased R0 resection rates and overall survival with the addition of intraperitoneal chemotherapy [32]. In our series, complete cytoreduction with CRS + HIPEC positively impacted survival in CRC and gastric cancer cases. However, since HIPEC was administered to all cases, isolating the effect of HIPEC alone was not feasible. Moreover, most of our patients received systemic chemotherapy perioperatively, making it challenging to compare the contributions of CRS + HIPEC and systemic chemotherapy in our series.

An increase in PCI correlates with a decrease in PFS and OS. However, in the multivariate analysis, PCI was not identified as a significant factor affecting survival. The increase in PCI score may be speculated to reduce the rates of complete cytoreduction, with the primary influencing factor potentially being the extent of cytoreduction itself [21]. However, the literature suggests that especially for tumor types with more aggressive biological behavior, such as colorectal and gastric cancers, a high PCI may have an impact on survival, regardless of achieving complete cytoreduction [33, 34]. Evaluating the relationship between PCI and survival among larger cohorts, stratified by tumor types, would be advantageous.

CC-0 and CC-1 resections are generally considered complete cytoreduction and complete cytoreduction is associated with longer survival [35]. But there is limited data on the difference between CC-0 and CC-1 resections and their effect on survival. In a study assessing patients with a history of peritoneal metastasis from gastric cancer who achieved long-term survival after CRS + HIPEC, CC-0 resection was associated with improved long-term survival [36]. In our series, a significant difference in PFS and OS was found between CC-0 and CC-1 cytoreduction in the appendix and peritoneal tumors. However, there was not a statistically significant difference between CC-0 and CC-1 patients with colorectal cancer and gastric cancer, even though CC-0 patients had longer PFS and OS. The absence of statistical significance between CC-0 and CC-1 resections in our study could be due to the limited number of cases. Further comparison of CC-0 and CC-1 resections in patients with PC from colorectal and gastric cancer in larger cohorts is warranted.

Studies have shown that LNM is poor prognostic in various types of carcinomas, including appendiceal tumors, colorectal cancers, gastric cancers, and malignant peritoneal mesotheliomas [37–40]. Publications indicate that the presence of LNM indicates an aggressive tumor biology and shorter survival as well as increased local and systemic recurrences [41]. In a study examining 160 cases of PC from CRC, it was found that patients with LNM from peritoneal implants had a higher risk of systemic recurrence [42]. In our study, lymph node metastasis was found to be prognostic in univariate analysis but lost its significance in multivariate analysis. Our cohort consisted of histologically and biologically diverse tumors, and therefore, the prognostic effect of lymph node metastasis should be evaluated in larger series, preferably with specific tumor types.

The primary limitation of our study is the small sample size, comprising diverse patient groups. Since all patients received CRS and HIPEC concurrently, it is challenging to independently assess the individual contributions of

each treatment modality to prognosis within the current cohort. The changes in systemic chemotherapy applications and drug preferences during the study's timeframe may have exerted a heterogeneous effect on our results. Furthermore, incomplete data in pathological parameters necessitate further evaluation of our findings in larger cohorts.

Conclusions

CRS + HIPEC procedures positively impact survival outcomes when complete cytoreduction is achieved. Specifically, CC-0 resection in PC cases is likely to yield a more favorable survival outcome compared to CC-1 resection, particularly in appendiceal and primary peritoneal tumors.

Abbreviations

CC	Completeness of cytoreduction
CRC	Colorectal cancer
CRS	Cytoreductive surgery
ECOG	Eastern cooperative oncology group
HIPEC	Hyperthermic intraperitoneal chemotherapy
LNM	Lymph node metastasis
LVI	Lymphovascular invasion
mPC	Metachronous peritoneal carcinomatosis
OS	Overall survival
PC	Peritoneal carcinomatosis
PCI	Peritoneal cancer index
PFS	Progression-free survival
PMP	Pseudomyxoma peritonei
pN	Pathologic nodal stage
PNI	Perineural invasion
TIL	Tumor-infiltrating lymphocytes

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Author contributions

Conceptualization – BD, CE; Data curation – BD, AFKG, Mİ, LDE, CBK, CCE, NB; Formal Analysis – BD; Investigation – BD, CE; Methodology – BD, AFKG, Mİ, LDE, CE; Supervision – AFKG, Mİ, LDE, CBK, CE; Validation – LDE, CBK, CCE, NB; Visualization – BD, AFKG, Mİ, LDE, CBK, CE; Writing – original draft - BD, AFKG, LDE; Writing – review & editing BD, AFKG, Mİ, LDE, CBK, CCE, NB, CE. All authors read and approve the final version of the manuscript.

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Data availability

The datasets generated and/or analysed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Our study was conducted under the Helsinki Declaration and was approved by the Istanbul Faculty of Medicine Institutional Review Board (28.07.2022-No: 1085943). Written informed consent was obtained from all patients. Informed consent obtained from next of kin on deceased patients.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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