Low Disease Burden in Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy Is Associated with Improved Outcomes: A Single Center Experience

Yossi Maman MD[1], Jawad Tome MD[1], Rina Neeman MD[2], Dan Mirelman MD[3], Danit Dayan MD[1], Guy Lahat MD[1,4], Ravit Geva MD[3,4], and Eran Nizri MD PhD[1,4]

[1]Department of Surgery B, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
[2]Department of Radiology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
[3]Department of Oncology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
[4]Gray Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel

ABSTRACT **Background:** Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) are established treatments for peritoneal metastasis from colorectal cancer (PM-CRC). The peritoneal carcinomatosis index (PCI) measures disease burden.

Objectives: To evaluate the effect of PCI on short- and long-term outcomes of patients with PM-CRC who underwent CRS-HIPEC.

Methods: We retrospectively analyzed 120 PM-CRC patients who underwent CRS-HIPEC, categorizing them into four PCI groups (PCI ≤ 3, PCI 4–6, PCI 7–11, PCI >11). We evaluated perioperative outcomes and long-term survival.

Results: Higher PCI scores were associated with increased surgical complexity, longer operative times, more organ resections, and higher blood transfusion requirements. Complete cytoreduction was achieved in 100% of the PCI ≤ 3 group, but only in 70.8% of the PCI > 11 group ($P = 0.001$). Postoperative outcomes showed a trend toward less major morbidity in low PCI patients (16.7% vs. 28%) and significantly shorter hospital stays (10–13 days vs. 19 days, $P = 0.006$). The 90-day mortality rate was 0% in the PCI ≤ 3 group compared to 11.5% in the PCI > 11 group. Long-term outcomes revealed significantly better disease-free survival (DFS) and overall survival (OS) for the PCI ≤ 3 group (DFS: 22 months vs. 4–6 months; OS: 79.6 months vs. 21–40 months, $P < 0.001$).

Conclusions: Patients with low PCI scores experience reduced morbidity and improved long-term survival, supporting the use of CRS-HIPEC in this subgroup. Further research is needed to enhance treatment strategies for patients with high PCI scores.

IMAJ 2026; 28: 18–23

KEY WORDS: colorectal cancer, cytoreductive surgery (CRS), hyperthermic intraperitoneal chemotherapy (HIPEC), peritoneal carcinomatosis index (PCI), peritoneal metastasis

Colorectal cancer (CRC) is among the most prevalent cancers worldwide, with an estimated lifetime risk of around 5%. Approximately 4–8% of CRC patients present with synchronous peritoneal metastasis (PM) as the sole site of metastasis at diagnosis, and up to 20% may develop metachronous PM during the course of their disease [1]. Unfortunately, the prognosis for patients with CRC-PM is poor, with a median overall survival (OS) of just 16.3 months [2]. However, in the past years a surgical approach was developed, that consists of cytoreductive surgery (CRS), directed against the macroscopic disease, and hyperthermic intraperitoneal chemotherapy (HIPEC) which addresses the microscopic disease [3]. A recent study demonstrated that CRS with or without HIPEC can more than double the median overall survival rates to about 41 months and, in certain cases, potentially achieve a cure for the disease, defined by disease-free survival (DFS) greater than 5 years [4]. However, despite significant improvements in outcomes over the years, current mortality and morbidity rates (2% and 24%, respectively) remain high [5], leading many healthcare providers, including both surgeons and oncologists, to hesitate in referring patients for CRS-HIPEC [6]. Contrary to that perception, studies show that approximately 80% of patients return to their baseline quality of life (QoL) within 6–12 months after CRS-HIPEC, particularly those with reduced disease burden [7] and no post-operative complications [8].

CRC-PM encompasses a wide range of disease severities, which are largely determined by the disease burden as measured by the peritoneal carcinomatosis index (PCI) [9]. As a result, the extent of CRS-HIPEC can vary significantly, with lower PCI scores being associated with less extensive surgery and reduced mor-

bidity and mortality. Both PCI and the completeness of cytoreduction are recognized as key factors influencing long-term survival [5].

In this study, we evaluated short- and long-term outcomes of patients with CRC-PM who underwent CRS-HIPEC in a single-center Israeli referral center and determined whether low disease burden confers the same improved prognosis in this cohort.

PATIENTS AND METHODS

PATIENTS

Data for all patients who underwent CRS-HIPEC for CRC-PM at our institution from January 2010 to January 2024 were prospectively collected and retrospectively analyzed. Patient staging prior to the procedure included imaging (contrast-enhanced computed tomography [CT] of the chest and abdomen, ^{18}F-fluorodeoxyglucose positron-emission tomography/computed tomography, or magnetic resonance imaging) and serum tumor markers (carcinoembryonic antigen [CEA], CA19-9, and CA125). Perioperative systemic chemotherapy treatment and timing of CRS-HIPEC were discussed by a multidisciplinary tumor board. Decisions regarding dosage and treatment adjustments as well as treatment discontinuation were made at the discretion of the oncologist in charge. Surgery was performed within 4–6 weeks after the last treatment in patients who received neoadjuvant therapy, and adjuvant chemotherapy was started up to 12 weeks after surgery. The institutional review board of the Tel Aviv Medical Center approved the study and waived informed consent (TLV-19-0463).

CRS+HIPEC

CRS consists of both visceral resections and peritonectomies with the aim of resecting all macroscopic diseases. In this study, the extent of peritoneal spread was classified according to the PCI, and completeness of cytoreduction (CCR) was used to measure residual disease at the end of the procedure [9]. In recent years, we have performed HIPEC for 90 minutes using the closed technique with mitomycin C at a fixed dose of 40 mg [10]. Postoperative complications were graded according to the Clavien-Dindo (CD) classification [11], with severe complications defined as CD grade 3 or higher.

FOLLOW-UP EVALUATION

All study patients were followed postoperatively with physical examinations, thoracic/abdominal CT scans, and serum marker measurements every 3 months during the first 2 years and every 6 months from the third year. Postoperative disease progression was confirmed based on clinical, imaging, or laboratory criteria. Local recurrence was defined as any peritoneal recurrence, while systemic recurrence was defined as any liver or extra-abdominal recurrence. Combined peritoneal and systemic disease identified in the first imaging that defined recurrence was also classified as systemic recurrence.

STATISTICAL ANALYSIS

Categorical variables were described by incidences and percentages and compared using the chi-square test. Quantitative variables were described by means and standard deviations or by medians and inter-quartile ranges (IQR) and compared using the independent *t*-test and Mann-Whitney U test. Survival analysis was conducted using the Kaplan-Meier method, and multivariate analysis was performed using the Cox model. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 29 (SPSS, IBM Corp, Armonk, NY, USA). A P-value < 0.05 was considered statistically significant.

RESULTS

PATIENT DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

Table 1 depicts patient clinical and pathological characteristics. The study included 120 patients with a median age of 60 years. In our cohort PCI ranged from 0 to 32, median PCI was 6 and interquartile range (IQR) was 3–11. Patients were categorized into four groups based on their PCI, using the median and quartiles as cutoffs: PCI ≤ 3 (n=42), PCI 4–6 (n=28), PCI 7–11 (n=24), and PCI > 11 (n=26). Among the high PCI (> 11) group, median PCI was 16 (IQR 13–20.5). Age tended to be younger in higher PCI groups, as did the use of neoadjuvant treatment, although neither reached statistical significance. Tumor origin (right, left, rectum) or grade did not differ between groups (data not shown). Higher PCI scores were significantly associated with the presence of lymphovascular invasion (LVI) (70% vs. 19.2%, $P = 0.003$) and clinical symptoms of PM, such as pain and weight loss (52% and 31.8% vs. 19.4% and 2.9%, $P = 0.002$ and $P = -0.018$, respectively). Maximal CEA levels and time to diagnosis of PM-CRC were not correlated with high disease burden.

OPERATIVE AND POSTOPERATIVE OUTCOMES

Table 2 depicts the characteristics of the surgical procedures performed according to PCI groups. As expected, the complexity of surgery and postoperative outcomes were closely linked to the PCI score. Patients with lower PCI scores experienced significantly shorter surgeries and required fewer organ resections and anastomoses. In addition, these patients required significantly fewer blood transfusions. Achieving complete cytoreduction (CCR=0) was possible in 100% of the PCI ≤ 3 group, whereas only 70.8%

Table 1. Patient clinic-pathological characteristics

		All patients (n=120)	PCI ≤ 3 (n=42)	PCI 4–6 (n=28)	PCI 7–11 (n=24)	PCI > 11 (n=26)	*P*-value
Age (years), median (IQR)		60 (49–70)	64 (50–68)	62 (45–73)	51.5 (42–64)	58 (49–74)	0.091
Sex M/F, n (%)		63 (52.5)	23 (36.5)	17 (27)	8 (12.7)	15 (23.8)	0.198
N stage of primary tumor	0	31 (26.7)	12 (38.7)	6 (19.4)	8 (25.8)	5 (16.1)	0.34
	1	53 (45.7)	19 (35.8)	16 (30.2)	8 (15.1)	10 (18.9)	
	2	32 (27.6)	9 (28.1)	5 (15.6)	7 (21.9)	11 (34.4)	
LVI, n (%)		27 (44.3)	5 (19.2)	6 (46.2)	9 (75)	7 (70)	0.003
Clinical presentation of PM-CRC	Pain n (%)	46 (42.2)	7 (19.4)	11 (42.3)	15 (68.2)	13 (52)	0.002
	Weight loss, n (%)	13 (13.1)	1 (2.9)	3 (12.5)	2 (11.1)	7 (31.8)	0.018
Metachronous, n (%)		87 (72.5)	34 (81)	22 (78.6)	17 (70.8)	14 (53.8)	0.086
Maximal CEA, mean ± SD		19.3 ± 70.4	26.1 ± 109	18.2 ± 42.8	14.5 ± 37.7	13.8 ± 23.4	0.892
NA Treatment n (%)		49 (40.8)	17 (40.5)	6 (21.4)	13 (54.2)	13 (50)	0.071
Time between diagnosis to PM-CRC (months), median (95%CI)		29 (22.43–35.6)	24.4 (16.3–32.5)	37.5 (19.7–55.3)	21.7 (15.5-27.9)	34.6 (11–58)	0.95

95%CI = 95% confidence interval, IQR = interquartile range, LN = lymph node, LVI = lymphovascular invasion, N stage = nodal involvement according to TNM, NA = neoadjuvant, PM-CRC = peritoneal metastases of colorectal cancer, SD = standard deviation

Table 2. Procedure characteristics and post-operative outcomes

		All patients (n=120)	PCI ≤ 3 (n=42)	PCI 4–6 (n=28)	PCI 7–11 (n=24)	PCI > 11 (n=26)	*P*-value
Number of organs resected, mean ± SD		2 ± 1.4	1.5 ± 1.1	1.7 ± 1.3	2.3 ± 1.4	2.9 ± 1.3	< 0.001
Number of anastomoses, mean ± SD		0.78 ± 0.77	0.54 ± 0.64	0.68 ± 0.72	0.88 ± 0.74	1.2 ± 0.9	0.005
Number of RBC, mean ± SD		0.32 ± 0.82	0.05 ± 0.31	0.19 ± 0.63	0.33 ± 0.73	0.85 ± 1.29	0.001
CCR, n (%)	0	98 (92.5)	35 (100)	26 (96.3)	20 (100)	17 (70.8)	0.001
	1	5 (4.7)	0 (0)	1 (3.7)	0 (0)	4 (16.7)	
	2	3 (2.8)	0 (0)	0 (0)	0 (0)	3 (12.5)	
	3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Duration of surgery (hours), mean ± SD		5.9 ± 1.9	5.2 ± 1.7	5.9 ± 1.3	6.2 ± 1.8	6.9 ± 2.1	0.002
Major morbidity (CD ≥ 3, n (%)		28 (23.3)	7 (16.7)	5 (17.9)	6 (25)	10 (28.5)	0.181
LOS (days), mean ± SD		15.4 ± 11.3	13.6 ± 10	10.8 ± 5	19.1 ± 16	19.7 ± 11	0.006
90-day mortality, n (%)		4 (3.3)	0 (0)	0 (0)	1 (4.2)	3 (11.5)	0.048

CD = Clavien-Dindo, CCR = completeness of cytoreduction, LOS = length of stay, RBC = red blood cells, SD = standard deviation

Table 3. Univariate and multivariate analysis of factor associated with long term outcomes

	Disease-free survival				Overall survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR	*P*-value	HR	*P*-value	HR	*P*-value	HR	*P*-value
Grade	1.2	0.5			1.64	0.1	1.82	0.09
N stage	1.31	0.07	1.19	0.25	1.6	0.01	1.16	0.58
CCR	1.47	0.13			3.3	< 0.001	3.08	0.002
PCI	1.54	< 0.001	1.5	< 0.001	1.74	< 0.001	1.44	0.02
Neoadjuvant before HIPEC	1.47	0.09	1.21	0.41	1.06	0.81		
Adjuvant after HIPEC	0.64	0.12			0.82	0.54		

CCR =completeness of cytoreduction, HIPEC = heated intraperitoneal chemotherapy, HR = hazard ratio, N stage = nodal involvement according to TNM, PCI = peritoneal carcinomatosis index

of patients in the high PCI group achieved this outcome ($P = 0.001$). This reduced surgical burden was also associated with a trend toward less major morbidity (16.7% vs. 28%) and a significantly shorter length of stay (LOS), averaging 10–13 days for patients in the low PCI groups compared to 19 days in the higher PCI groups ($P = 0.006$).

Moreover, the 90-day mortality rate was notably higher in the high PCI group at 11.5%, compared to 0% in the low PCI group. These findings underscore the importance of PCI as a determinant of both surgical complexity and short-term postoperative outcomes in CRS-HIPEC procedures.

LONG TERM OUTCOMES

Our data demonstrate a clear correlation between the PCI and patient survival outcomes. Patients in the PCI ≤ 3 group exhibited significantly better DFS than those in the PCI 7–11 and PCI > 11 groups (median DFS = 22 months, 95% confidence interval [95%CI] 0–45 vs. 6 months, 95%CI 1.65–10.34 and 4 months, 95%CI 2.55–5.44, $P < 0.001$, respectively). The same was observed for OS (median OS = 79.6 months, 95%CI 40.4–117.6 vs. 40 months, 95%CI 33.9–46.1 and 21 months, 95%CI 0.64–41.4; $P < 0.001$, respectively). Table 3 shows the multivariate analysis of PCI along with other factors known to determine long–term outcomes in patients with PM–CRC [12]. PCI group was the only statistically significant factor for DFS (hazard ratio [HR] 1.54, 95%CI = 1.22–1.84, $P < 0.001$) and OS (HR 1.41, 95%CI 1.05–1.98, $P = 0.02$).

DISCUSSION

The main finding of this study is that abdominal disease burden, as measured by the PCI, has implications for both short- and long-term outcomes. Thus, PM-CRC has different prognostic implications and post-CRS-HIPEC outcomes across various PCI groups.

The clinical characteristics of patients generally did not vary according to the PCI except for clinical symptoms of pain and weight loss, which were significantly associated with the high PCI group (> 11). Interestingly, tumor markers did not assist in classifying patients into the various PCI groups, nor did the time to PM-CRC diagnosis. These findings, in addition to the limitation of PCI determination by various imaging modalities [13,14], indicate that definitive PCI is often an intraoperative finding, complicating preoperative decision-making, such as the use of neoadjuvant therapy.

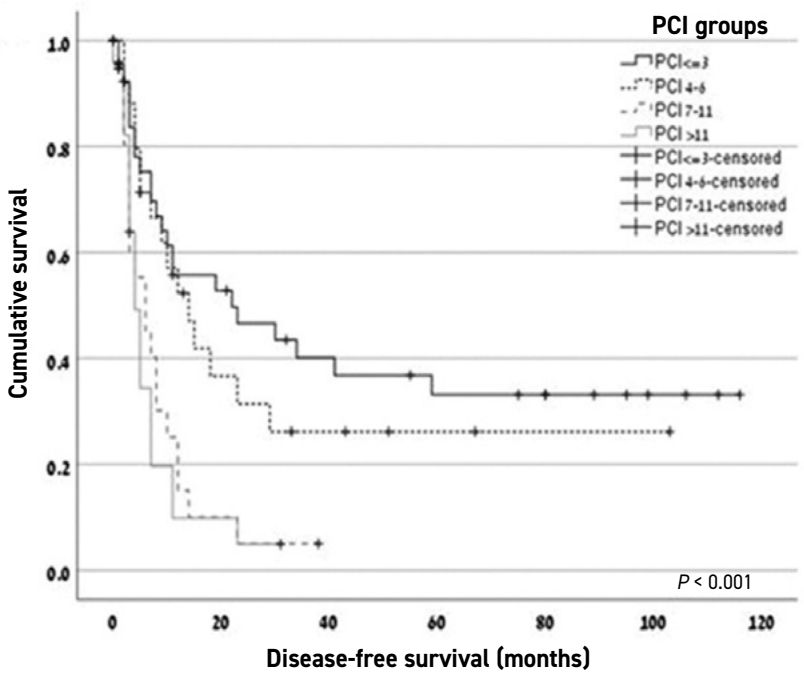
The extent of CRS+HIPEC, measured by the number of organs resected, number of anastomoses, and the need for diversion, varies according to the PCI, as expected. Consequently, patients with a low PCI burden can be safely referred for the procedure and usually experience an uneventful postoperative course. Accordingly, the ability to achieve CCR = 0 is influenced by the PCI groups, which has strong implications for OS (HR 3.08, $P = 0.002$).

Many studies have reported the importance of PCI as a prognostic marker for long-term outcomes in PM-CRC [3,15,16]. Our study affirms these data and highlights the prognostic significance of different PCI groups, at a single Israeli center [3]. Quantitative comparisons between studies regarding the impact of PCI are challenging due to variations in peri-operative chemotherapy protocols. However, it is evident that PM-CRC can be cured in a subset of patients with low PCI, when cure is defined as 5-year DFS. In our cohort, this number reached 33%. We believe that the low morbidity of the procedure, coupled with its curative potential, should encourage practitioners to refer patients with low disease burden to surgical treat-

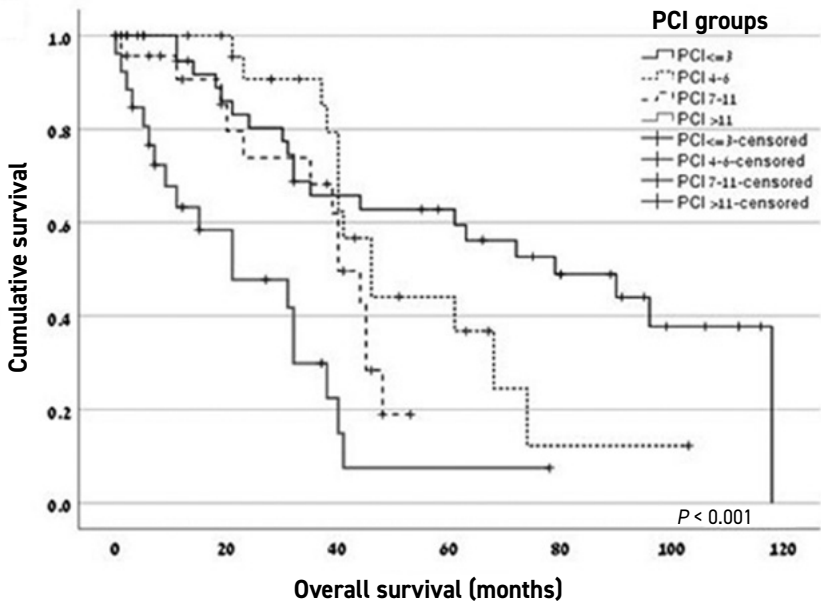
Figure 1. Disease-free survival and overall survival of patients according to peritoneal carcinomatosis index groups; *P*-value by log-rank test; see text for intergroup comparisons

DFS = disease-free survival, OS = overall survival, PCI = peritoneal carcinomatosis index

[A] Disease-free survival



[B] Overall survival



ment. Whether HIPEC has a benefit in patients with low disease burden is questionable. In the PRODIGE7 study, patients with PCI < 11 were shown to derive benefit from HIPEC [4]. However, some units abandoned HIPEC for PM-CRC [17]. It should be noted that the 5-year DFS in the low PCI group was 33% even when complete cytoreduction was achieved, highlighting the limitation of the procedure to achieve high cure rates. This finding encouraged us to incorporate new treatment modalities in an experimental PM-CRC model to optimize results [18].

While patients with low disease burden may benefit from surgery, it is clear from many series that there is a cut-off PCI above which patients do not benefit from CRS+HIPEC. This cut off value was 17–20 in various series [19,20]. In our cohort patients in the high PCI (> 11) group had median DFS of 4 months (95%CI 2.5–5.4) and median OS of 21 months (95%CI 0.6–41.4). Thus, one may question the efficacy of CRS+HIPEC even to delay chemotherapy in these patients. As the median PCI in this high PCI group is 16, our results are in line with the literature.

This study has several limitations. First, it is a single-center cohort with a relatively small number of patients. In addition, the cohort spans various practice changes in staging (regarding imaging modalities) and treatment of PM-CRC.

CONCLUSIONS

Patients with low-burden PM-CRC can safely undergo CRS+HIPEC, which offers a curative potential for a significant number of patients. Further research should focus on exploring novel treatment modalities for this aggressive disease.

Correspondence

Dr. E. Nizri
Dept. of Surgery B, Tel Aviv Sourasky Medical Center, Tel Aviv 6423906, Israel
Phone: (972-3) 694-7341
Email: eran.nizri@mail.huji.ac.il

References

1. Siegel RL, Wagle NS, Cercek A, Smith RA, Jemal A. Colorectal cancer statistics, 2023. *CA Cancer J Clin* 2023; 73: 233-54.
2. Franko J, Shi Q, Meyers JP, et al; Analysis and Research in Cancers of the Digestive System (ARCAD) Group. Prognosis of patients with peritoneal metastatic colorectal cancer given systemic therapy: an analysis of individual patient data from prospective randomised trials from the Analysis and Research in Cancers of the Digestive System (ARCAD) database. *Lancet Oncol* 2016; 17 (12): 1709-19.
3. Elias D, Lefevre JH, Chevalier J, et al. Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin. *J Clin Oncol* 2009; 27: 681-5.
4. Quenet F, Elias D, Roca L, et al. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy versus cytoreductive surgery alone for colorectal peritoneal metastases (PRODIGE 7): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol* 2021; 22: 256-66.
5. Chua TC, Moran BJ, Sugarbaker PH, et al. Early- and long-term outcome data of patients with pseudomyxoma peritonei from appendiceal origin treated by a strategy of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. J Clin Oncol 2012; 30: 2449-56.
6. Siddiqui J, Brown K, Zahid A, Young CJ. Current practices and barriers to referral for cytoreductive surgery and HIPEC among colorectal surgeons: a binational survey. *Eur J Surg Oncol* 2020; 46: 166-72.
7. Leimkuhler M, Hentzen J, Hemmer PHJ, et al. Systematic review of factors affecting quality of life after cytoreductive surgery with hyperthermic intraperitoneal chemotherapy. *Ann Surg Oncol* 2020; 27: 3973-83.
8. Newton AD, Bartlett EK, Karakousis GC. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: a review of factors contributing to morbidity and mortality. J Gastrointest Oncol 2016; 7: 99-111.
9. Sugarbaker PH. Peritonectomy procedures. Ann Surg 1995; 221: 29-42.
10. Turaga K, Levine E, Barone R, et al. Consensus guidelines from the American Society of Peritoneal Surface Malignancies on standardizing the delivery of hyperthermic intraperitoneal chemotherapy (HIPEC) in colorectal cancer patients in the United States. *Ann Surg Oncol* 2014; 21: 1501-5.
11. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; 240: 205-13.
12. Simkens GA, van Oudheusden TR, Nieboer D, et al. Development of a prognostic nomogram for patients with peritoneally metastasized colorectal cancer treated with cytoreductive surgery and HIPEC. *Ann Surg Oncol* 2016; 23: 4214-21.
13. Fallon EA, Awiwi MO, Bhutiani N, et al. Peritoneal cancer index correlates with radiographic assessment of colorectal carcinomatosis. *Ann Surg Oncol* 2025; 32 (4): 2923-31.
14. Dohan A, Hobeika C, Najah H, Pocard M, Rousset P, Eveno C. Preoperative assessment of peritoneal carcinomatosis of colorectal origin. J Visc Surg 2018; 155: 293-303.
15. Allievi N, Sidhom M, Samuel MV, et al. Survival Analysis and Recurrence Patterns in 555 Patients with colorectal peritoneal metastases treated by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Ann Surg Oncol* 2024; 31: 8585-95.
16. Goere D, Souadka A, Faron M, et al. Extent of colorectal peritoneal carcinomatosis: attempt to define a threshold above which HIPEC does not offer survival benefit: a comparative study. *Ann Surg Oncol* 2015; 22: 2958-64.
17. van de Vlasakker VCJ, Lurvink RJ, Cashin PH, et al. The impact of PRODIGE 7 on the current worldwide practice of CRS-HIPEC for colorectal peritoneal metastases: a web-based survey and 2021 statement by Peritoneal Surface Oncology Group International (PSOGI). *Eur J Surg Oncol* 2021; 47: 2888-92.
18. Geva R, Alon G, Nathanson M, et al. PD-1 Blockade combined with heated intraperitoneal chemotherapy improves outcome in experimental peritoneal metastases from colonic origin in a murine model. *Ann Surg Oncol* 2023; 30: 2657-63.
19. Steffen T, Eden J, Bijelic L, et al. Patient selection for hyperthermic intraperitoneal chemotherapy in patients with colorectal cancer: consensus on decision making among international experts. *Clin Colorectal Cancer* 2020; 19: 277-84
20. Simkens GA, Rovers KP, Nienhuijs SW, de Hingh IH. Patient selection for cytoreductive surgery and HIPEC for the treatment of peritoneal metastases from colorectal cancer. *Cancer Manag Res* 2017; 9: 259-66.