Predictors of Recurrence of Peritoneal Carcinomatosis among Patients with Colorectal Cancer Following Cytoreductive Surgery alone versus Cytoreductive Surgery Plus HIPEC

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Abstract

Background Peritoneal carcinomatosis (PC) is a lethal regional progression in patients with colorectal cancer (CRC). Treatment with complete cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) achieves better local control than systemic palliative chemotherapy.

Objectives To assess the efficacy on the prognosis of CRS and HIPEC compared with CRS only and to identify possible clinicopathological factors associated with the recurrence of PC.

Methods The present retrospective study included all colorectal carcinoma cases with PC subjected to CRS with or without HIPC from January 2009 to June 2018 at the National Cancer Institute (NCI), Cairo University, Cairo, Egypt. The outcome is evaluated in terms of recurrence-free survival (RFS) and its predictors.

Results Out of the 61 patients, 45 patients (73.8%) underwent CRS plus HIPEC, and 16 (26.2%) underwent CRS alone. The 1-year RFS was 55.7%, with a median of 12 months. The risk factors for recurrence identified in the univariate analysis were T4 primary tumor, high-grade, positive lymphovascular invasion (LVI), positive extracapsular nodal spread, and patients treated with CRS only, without HIPEC. In the multivariate analysis, the independent risk factors for recurrence were high grade and patients treated with CRS only.

Conclusion T4 primary tumor, high grade, positive LVI, and positive extracapsular nodal spread seemed to be important predictors of recurrence following the treatment of PC. Our study also demonstrated that the addition of HIPEC to CRS improved the RFS.

Keywords
- colorectal cancer
- peritoneal carcinomatosis
- cytoreductive surgery
- HIPEC

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Introduction

Peritoneal carcinomatosis (PC) of colorectal origin is considered an advanced terminal disease. The reported incidence of synchronous and metachronous PC varies widely, from 3 to 28% and from 4 to 19%, respectively.[1] Treatment is based mainly on palliative chemotherapy, but, unfortunately, colorectal PC does not respond well to systemic chemotherapy like other sites of distant metastases.[2,3] Hyperthermic intraperitoneal chemotherapy (HIPEC) comprises the direct pumping of heated chemotherapy into the peritoneal cavity after surgery. Its rationale includes killing the micrometastatic disease and the minimal residual of gross disease by exposure of the diseased peritoneum to the higher concentration of chemotherapeutic agents while keeping its systemic plasma levels low. Another advantage is that the venous drainage of the peritoneum is via the portal vein to the liver, which provides a detoxifying effect to the administered drug and helps killing the potential micrometastatic hepatic deposits.[4] Hyperthermia can selectively destroy malignant cells at between 41 and 43°C by different mechanisms and enhance the cytotoxic effect of the chemotherapeutic agents.[5,6]

Many studies reported that treatment of colorectal PC with cytoreductive surgery (CRS) and HIPEC was associated with better local control and survival compared with systemic palliative chemotherapy.[7–9] Identifying patients at high risk for recurrence following CRS and HIPEC at an early stage could further improve the oncologic outcome. Many studies reported that repeated CRS and HIPEC were feasible, associated with low morbidity, and with superior oncologic outcome when compared with palliative chemotherapy alone.[10–12]

The present study aimed to assess the efficacy of CRS and HIPEC compared with CRS only on the prognosis of colorectal cancer patients diagnosed with PC and to identify possible clinicopathological factors associated with the recurrence of PC.

Patients and Methods

The present retrospective study included all cases of colorectal carcinoma with PC from January 2009 to June 2018 operated at the National Cancer Institute (NCI), Cairo University, Cairo, Egypt.

Inoperable cases and peritoneal disease of noncolorectal origins were excluded. The medical records of the patients were retrieved from the Epidemiology department, NCI, Cairo University. The extracted data were demographics, clinicopathological characteristics of the patients and of the primary tumor, investigation results, PC treatment and outcome.

All patients were operated on with complete CRS only or with CRS plus HIPEC. A midline skin incision was made from the xiphoid process to the pubic tubercle, resectioning the affected parts. Electrosurgery was used for implants on visceral or intestinal surfaces where resection or excisions of the nodules were done for infiltrative lesions. For those who underwent HIPEC, the drains and thermal probes were connected to the extracorporeal circuit of the HIPEC machine (Therma solution 2000).

Intraoperatively, the extent of peritoneal involvement was assessed by the peritoneal carcinomatosis index (PCI).[13] The PCI is calculated as the summation of the size of implants in the abdominopelvic regions in a score that ranges from 0 to 3 (0: no malignant deposits, 1: nodules < 0.5 cm in their greatest dimension, 2: nodules of 0.5 to 5.0 cm, 3: nodules > 5.0 cm).

The completeness of surgical resection was assessed by the completeness of cytoreduction (CC) score.[14] A CC-0 is apparent when there is no peritoneal seeding visualized within the operative field. CC-1 indicates nodules persisting after cytoreduction < 2.5 cm. CC-2 indicates nodules measuring between 2.5 and 5 cm, whereas CC-3 indicates nodules > 5 cm or a confluence of unresectable tumor nodule at any site within the abdomen or the pelvis. After treatment, the patients were followed-up by clinical examination, radiological imaging, and serum tumor markers (CEA and CA 19.9).

Peritoneal recurrence was defined as any new lesion detected by noninvasive radiological imaging (computed tomography [CT] or positron emission tomography [PET-CT] scan) with or without biopsy compared with the first imaging performed 3 months after treatment. In lesions detected by endoscopy or reoperations, recurrence was defined by pathological tissue examination. Extraperitoneal recurrence was defined as metastasis to the liver, the lungs, bone, and as the recurrence in the retroperitoneum and local colonic recurrence.

Follow-up and Survival

The patients were followed-up at 3 monthly intervals by clinical examination, radiological imaging, and serum tumor markers (CEA and CA 19.9) for 2 years, and then every 6 months for an additional 3 years.

Objectives

To detect recurrence-free survival (RFS) and its predictors among patients with colorectal cancer following CRS only versus CRS plus HIPEC.

Statistical Methods

Statistical analysis was done using IBM SPSS Statistics for Windows, version 22 (IBM Corp., Armonk, NY, USA). Data were expressed as frequency and percentage. The Pearson chi-squared test or the Fisher exact test were used to test the relationship between qualitative variables.

Recurrence-free survival was calculated from the date of surgery until the date of recurrence. Survival analysis was done using the Kaplan-Meier method, and a comparison between two survival curves was made using the log-rank test.

Multivariate analysis was done using the Cox-proportional hazard regression model with the forward likelihood ratio method for the factors affecting survival on univariate analysis. Hazard ratios (HR) with their 95% confidence intervals (CIs) were used for risk estimation. All tests were two-tailed. A p-value < 0.05 was considered significant.

Results

The present study included 61 patients. Two patients were lost to follow-up very early after the procedure, so they were excluded from the RFS analysis. About 59% of the patients were $\geq$ 45 years old. Females represented 54.1% of the sample. Adenocarcinoma corresponded to about half of the cases of primary tumors. About three-fourths of the participants had a low-grade primary tumor. Out of 46 patients with positive nodes, 33 (75.0%) had an extracapsular invasion. About one-third of the patients presented with a T4 primary tumor. Almost all patients (93.4%) were asymptomatic regarding the presentation of the primary peritoneal disease. The peritoneal disease was synchronous in 43.3% of the participants and metachronous in 56.7%. More than 12 lymph nodes (LNs) were harvested during resection of the primary tumor in 36 cases (61.0%), compared with 23 cases (39.0%) with <12 harvested LNs. A PCI ≤ 10 was evident in 37 patients (61.7%), and >10 in 23 patients (38.3%). CC0 and CC1 were achieved in 54 patients (88.5%) and in 7 patients (11.5%), respectively. Most of the patients (73.8%) were treated by CRS + HIPEC (►**Table 1**).

The median follow-up period was of 14 months (range: 6 to 72 months). The cumulative RFS of the whole group was 55.7% at 1 year and 19.9% at 3 years, with a median of 12 months. Most of the recurrences (76.9%) occurred within the 1st year after treatment. Most cases developed peritoneal relapse either alone or in association with distant metastasis or local relapse; only one patient developed local relapse only (►**Tables 2** and **3**).

In the univariate analysis, the following variables were associated with worse RFS: T4 tumor (1 year RFS: 62.4% for T2,3 versus 37.2% for T4, $p = 0.035$), presence of lymphovascular invasion (1 year RFS: 34.2% for LVI+ versus 89.7% for LVI-, $p = 0.001$), presence of extracapsular nodal invasion (1 year RFS: 39 versus 83.3%, $p = 0.005$), high grade tumors (1 year RFS: 64.5 for low grade versus 13.2% for high grade, $p = 0.007$), and patients treated for their PC with CRS only (1 year RFS: 23.8 for CRS only versus 66.2% for CRS + HIPEC, $p = 0.002$). Other variables that tend toward statistical significance of worse RFS include patients with N2 nodal stage at the initial surgery (1 year RFS: 76.9, 51, and 44% for N0, N1, and N2, respectively, $p = 0.087$), harvesting <12 LNs during resection of the primary tumor (1 year RFS: 24.8 versus 67.4%, $p = 0.060$), patients with mucinous histology (1 year RFS: 73.6, 40, and 38.5% for adenocarcinoma, signet ring carcinoma, and mucinous carcinoma, respectively, $p = 0.061$), and patients with synchronous peritoneal disease (1 year RFS: 38.9 versus 68.3% for synchronous and metachronous disease, respectively, $p = 0.073$). (►**Table 3**). Using the Cox-regression model, RFS was independently affected by tumor grade and type of surgical management of the primary peritoneal disease (►**Table 4** and ►**Figs. 1** and **2**).

Discussion

The present study demonstrated that the RFS was 52.2% at 1 year in patients with peritoneal carcinomatosis on top of CRC treated with CRS and/or HIPEC. The RFS was independently worsened by higher tumor grade and primary peritoneal disease management with CRS only. Other factors that appeared to worsen the prognosis were T4 tumor, lymphovascular invasion, and extracapsular nodal invasion.

These results agreed with the study by Verwaal et al.,[15] who reported a recurrence rate of $\sim$ 64% after a median follow-up of 47.5 months with a median time to recurrence of 13.7 months, despite the longer follow-up period in their study. They found that most recurrences occurred within the 1st year. A systematic review and meta-analysis including 27 studies reported a recurrence rate of between 22.5 and 82% after CRS and HIPEC for PC of colorectal origin.[16]

In the present study, the most common histopathological type was adenocarcinoma (52.5%), followed by the mucinous (37.7%) and signet ring (9.8%) types. Many studies confirmed the higher frequency of adenocarcinoma (between 70 and 90%) compared with the mucinous (between 10 and 20%) and signet ring (between 1 and 7%) types.[17–19]

We observed a higher recurrence rate in patients with T4 primary tumors than in those with T2 and T3 tumors (RFS: 37.2 versus 62.4%, $p = 0.033$). Our results are in line with those of Segelman et al.[20] reported that the Independent predictors for metachronous PC were colonic cancer (hazard ratio (HR) 1.77, 95 per cent confidence interval 1.31 to 2.39; $P = 0.002$ for right-sided colonic cancer), advanced tumour (T) status (HR 9.98, 3.10 to 32.11; $P < 0.001$ for T4) as compared to 0.60 (0.15, 2.32) for T2 in the multivariate analysis. Taylor et al.[21] also reported a lower recurrence rate with a higher 5 year disease free survival for T1, T2, and T3a.

The present study demonstrated that the onset of peritoneal metastases negatively affected recurrence with borderline significance. Synchronous onset tends to have higher recurrences after treatment than the metachronous counterpart (RFS: 38.9 versus 68.3%, respectively, $p = 0.071$). Hentzen et al. described earlier recurrence after CRS with HIPEC for metachronous PC compared with synchronous PC (HR: 1.63; 95%CI: 1.18–2.26); however, Hompes et al. reported no impact of the onset of peritoneal metastasis on disease-free survival.[22,23]

In the present study, the use of HIPEC with CRS resulted in better RFS compared with CRS only (RFS: 23.8 versus 66.2%, $p = 0.002$). These findings are consistent with those of Chua et al., who found a poorer RFS in a group of 2,298 patients with pseudomyxoma peritonii treated with CRS compared with those treated with CRS and HIPEC (HR: 0.65; $p = 0.030$). The results obtained by Quenet et al. reported a median RFS of 11.1 months (95%CI: 9.0–12.7) in the non-HIPEC arm and of 13.1 months (95%CI: 12.1–15.7) in the HIPEC arm (HR: 0.90; 95% CI: 0.69–1.90; $p = 0.486$), while the 1-year RFS rates were 46.1 and 59% in each arm, respectively.[24,25]

In the present study, we observed a 1-year RFS of 64.5% for low grade versus 13.2% for high grade tumors ($p = 0.007$) both in the univariate ($p = 0.007$) and in the multivariate analysis ($p = 0.037$). Günther et al. reported that primary tumor grading reflected the individual tumor phenotype and its biological behavior better than the immunohistochemical

Table 1 Demographic, clinicopathological, and treatment characteristics of the studied group

		Number	Percentage
Age (years old)	< 45	25	41.0
	≥ 45	36	59.0
Gender	Male	28	45.9
	Female	33	54.1
Primary tumor characteristics			
T stage	T2 + T3	43	70.5
	T4a + T4b	18	29.5
N stage ($n = 59$)*	N0	13	22.0
	N1	22	37.3
	N2	24	40.7
M stage	-ve	33	54.1
	+ve	28	45.9
Histopathological type	Signet ring	6	9.8
	Mucinous	23	37.7
	Adenocarcinoma	32	52.5
Grade	Low (G1,2)	47	77.0
	High (G3,4)	14	23.0
LNs harvested during resection ($n = 59$)*	≤ 12	23	39.0
	> 12	36	61.0
Lymphovascular invasion ($n = 51$)*	Yes	32	62.7
	No	19	37.3
Extracapsular node invasion ($n = 44$)**	Yes	33	75.0
	No	11	25.0
Peritoneal disease characteristics			
Presentation	Symptomatic	4	6.6
	Asymptomatic	57	93.4
Onset	Synchronous	27	44.2
	Metachronous	34	55.7
PCI score ($n = 60$)*	≤ 10	37	61.7
	> 10	23	38.3
CC score	CC0	54	88.5
	CC1	7	11.5
Surgical procedure	CRS only	16	26.2
	CRS + HIPEC	45	73.8

Abbreviations: CC, completeness of cytoreduction; CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy; LN, lymph nodes; LVI, lymphovascular invasion; PCI, peritoneal carcinomatosis index.
*Some data missing.
**for N1 and N2 only.

studies, and it was the independent predictor of metachronous distant metastasis in the studied group.[26]

The present study demonstrated that the presence of lymphovascular invasion negatively affected recurrence (1-year RFS: 34.2 for LVI+ versus 89.7% for LVI-; $p = 0.001$). Another single-center analysis of 1,616 patients also reported a negative impact of lymphatic invasion on the RFS (HR: 2.0449; 95%CI= 1.4932–2.8365; $p = 0.01$).[27]

Conclusion

The clinicopathological characteristics of the primary tumor appear to be significant predictors of recurrence following

Table 2 Recurrence after treatment of primary peritoneal disease

Recurrence after CRS ± HIPEC	**Yes**	26	42.6%
	No	35	57.4%
Time to recurrence (months) ($n = 26$)	**Early < 12 m**	20	76.9%
	Late ≥ 12 m	6	23.1%
Site of recurrence ($n = 26$)	**HIPEC + CRS**	**CRS**	**Total**
Peritoneum only	6	8	14
Peritoneum plus distant metastasis	4	1	5
Peritoneum plus local recurrence	2	1	3
Local recurrence	0	1	1
Distant metastasis only	2	1	3

Abbreviations: CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy.

Table 3 Patients and disease characteristics in relation to 1-year recurrence-free survival (RFS) after treatment of colorectal peritoneal carcinomatosis

		n	Failures (*n*)	RFS (%)	Median survival (months)	*p-value*
Whole Group		59	26	55.7	12	
Surgery for primary peritoneal disease	CRS	15	12	23.8	9	0.002
	CRS + HIPEC	44	14	66.2	35	
Age (years old)	< 45	23	14	48.8	11	0.415
	≥ 45	36	12	58.2	35	
Gender	Female	32	16	36.6	11	0.105
	Male	27	10	69.0	56	
Primary tumor characteristics						
T stage	T2 & T3	31	14	62.4	35	0.035
	T4 a & b	28	12	37.2	11	
N stage	N0	13	2	76.9	NR	0.087
	N1	22	9	51.0	35	
	N2	24	14	44.0	12	
M stage	Negative	31	7	75.5	35	0.009
	Positive	28	19	33.0	9	
Final stage	Stages 1 & 2	10	1	80.0	NR	0.024
	Stage 3	21	6	73.4	35	
	Stage 4	28	19	33.0	9	
Histopathological type	Adenocarcinoma	31	9	73.6	35	0.061
	Signet ring	6	4	40.0	9	
	Mucinous	22	13	38.5	20	
Grade	Low grade	46	17	64.5	16	0.007
	High grade	13	9	13.2	9.0	
LNs harvested during resection ($n = 59$)*	≤ 12	23	11	24.8	10	0.06
	> 12	36	14	67.4	35	
LVI ($n = 51$)*	Yes	32	20	34.2	10	0.001
	No	19	4	89.7	35	

(*Continued*)

Table 3 (*Continued*)

		n	Failures (*n*)	RFS (%)	Median survival (months)	*p-value*
Extracapsular node invasion ($n = 44$)*	Yes	32	21	39.0	10	0.005
	No	11	3	83.3	35	
Peritoneal disease characteristics						
Onset	synchronous	26	16	38.9	11	0.073
	metachronous	33	9	68.3	35	
PCI score	≤ 10	37	17	48.3	12	0.546
	> 10	22	9	61.2	35	
CC score	CC0	53	23	55.4	13	0.270
	CC1	6	3	66.7	NR	

Abbreviations: CC, completeness of cytoreduction; CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy; LN, lymph node; LVI, lymphovascular invasion; PCI, peritoneal carcinomatosis index.
NR: No median RFS because more than half of the patients of this group did not develop recurrence until the end of the study.
*Some data missing.

Table 4 Independent factors affecting recurrence-free survival of the whole studied group

	p-value	HR	95%CI for HR	
			Lower	Upper
Management of primary peritoneal disease (CRS versus CRS + HIPEC)	0.011	2.924	1.282	6.667
Grade of primary colonic disease (high grade versus low grade)	0.037	2.488	1.057	5.857

Abbreviations: CI, confidence interval; CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy; HR, hazard ratio.

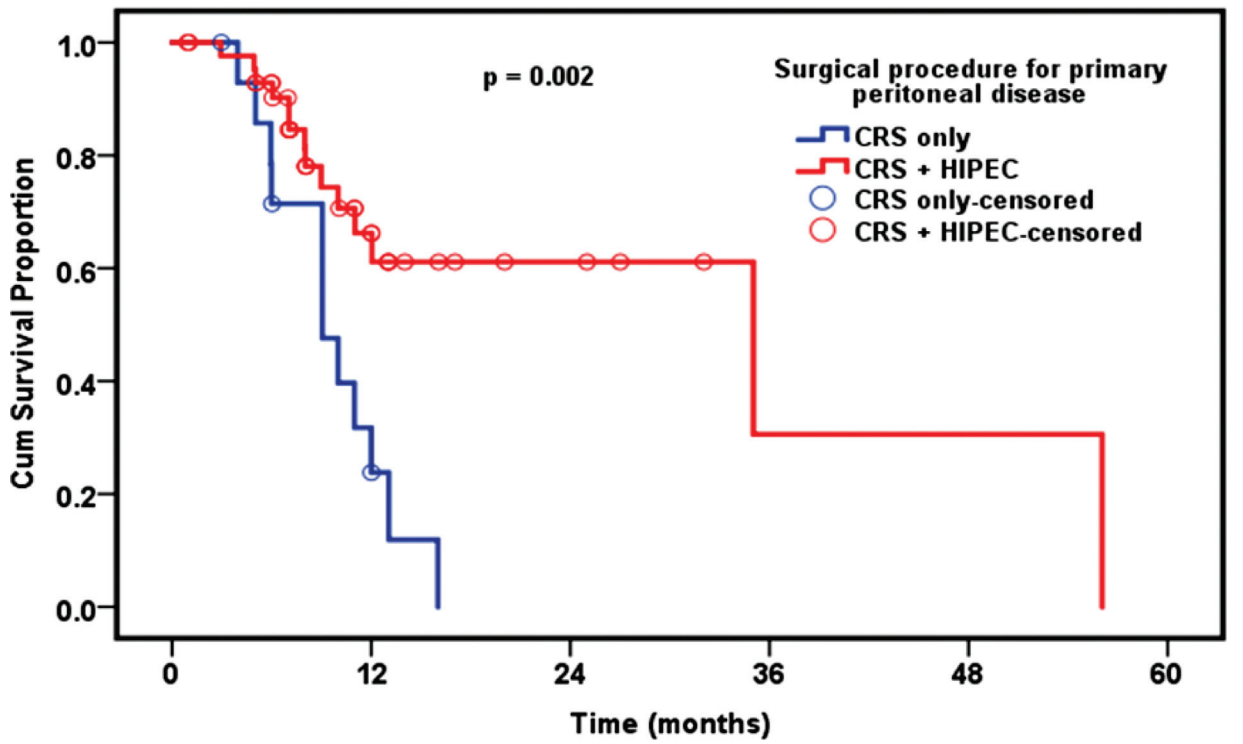

Fig. 1 Recurrence-free survival in relation to the surgical management.

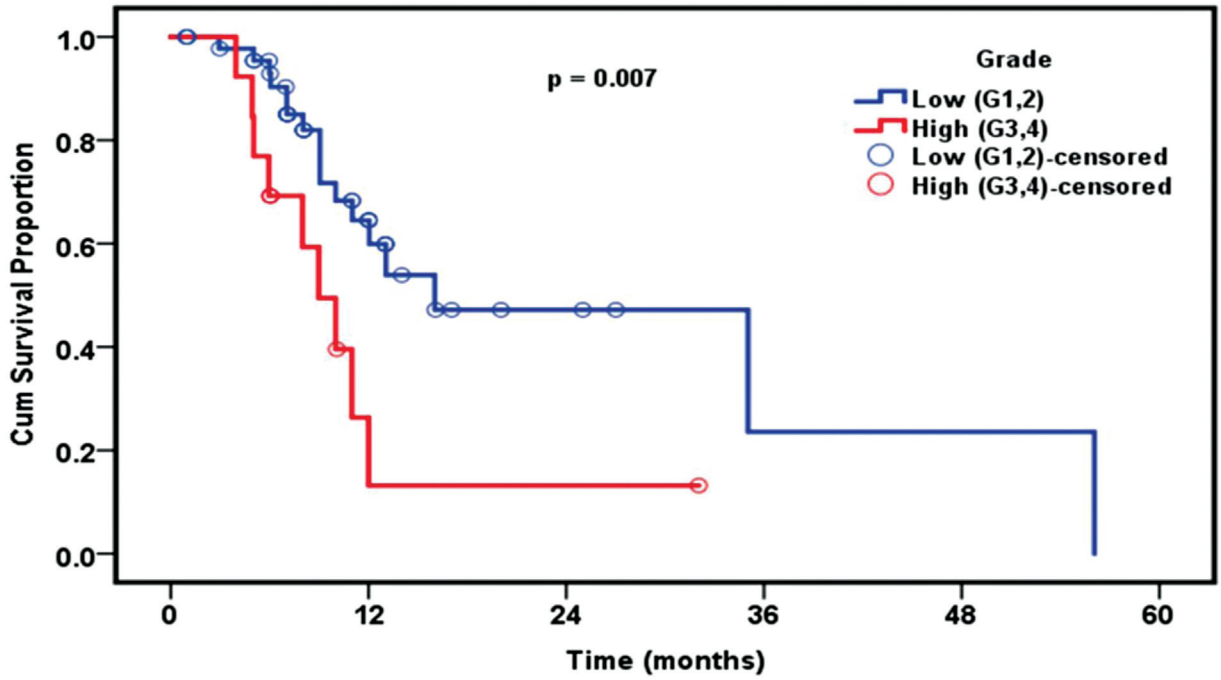

Fig. 2 Recurrence-free survival in relation to the grade of the primary colonic disease.

treatment of PC. These include the T4 stage, high grade, +ve lymphovascular, +ve extracapsular nodal invasion, and treatment with CRS only. On the multivariate analysis, the RFS was independently affected by the primary tumor grade and by the type of surgical management of the primary peritoneal disease.

Ethical Issues

Approval by the Institutional Review Board of the National Cancer Institute was obtained before the start of the present study (IRB Number: IRB00004025, approval number: 201819016.3).

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Conflict of Interests

The authors have no conflict of interests to declare.

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