ORIGINAL CONTRIBUTION

Should a History of Extraperitoneal Disease Be a Contraindication to Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Colorectal Cancer Peritoneal Metastases?

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BACKGROUND: Survival improvements have been reported in selected patients affected by colorectal peritoneal metastases who were undergoing cytoreductive surgery with intraperitoneal hyperthermic chemotherapy. Treatment of peritoneal metastases associated with extraperitoneal disease is still controversial.

OBJECTIVE: We assessed the prognostic impact of a history of extraperitoneal disease that was curatively treated either at the same time as or before the onset of peritoneal metastases.

DESIGN: We reviewed 2 prospective databases. Peritoneal involvement was scored by Peritoneal Cancer Index.

SETTINGS: Our study was conducted in 2 high-volume peritoneal malignancy management institutions.

PATIENTS: A total of 148 patients with peritoneal metastases were included. In 27 patients, extraperitoneal disease involving the liver (n = 23), lung (n = 1), both lung and liver (n = 2), or inguinal lymph nodes and liver (n = 1) was curatively treated either simultaneously with peritoneal metastases (n = 22) or before their onset (n = 5).

INTERVENTIONS: All of the macroscopic tumors were removed by means of peritonectomy procedures and visceral resections. Microscopic residual disease was treated by mitomycin C/cisplatin-based hyperthermic intraperitoneal chemotherapy.

MAIN OUTCOME MEASURES: Overall survival was the primary outcome measure.

RESULTS: After a median follow-up of 34.6 months (95% CI, 22.6–65.7 mo), 5-year survival of patients treated for both peritoneal and extraperitoneal disease versus peritoneal metastases alone was 16.5% versus 52.0% ($p = 0.019$). After multivariate analysis, reduced survival correlated with extraperitoneal disease ($p = 0.001$), Peritoneal Cancer Index >19 ($p = 0.004$), and peritoneal residual disease >2.5 mm ($p = 0.018$). Three prognostic groups were defined, and median survival was not reached for group 1 (Peritoneal Cancer Index ≤19 and no extraperitoneal disease), reached in 27.0 months for group 2 (Peritoneal Cancer Index ≤9 and extraperitoneal disease), and reached in 11.6 months for group 3 (Peritoneal Cancer Index >19 and no extraperitoneal disease or Peritoneal Cancer Index >9 and extraperitoneal disease).

LIMITATIONS: The main study limitation is its observational nature.

CONCLUSIONS: A history of extraperitoneal disease is associated with poorer prognosis. However, survival benefit may be obtained in selected patients with limited

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peritoneal involvement. See **Video Abstract** at http://links.lww.com/DCR/A655.

KEY WORDS: Colorectal cancer; Cytoreductive surgery; Hyperthermic intraperitoneal chemotherapy; Liver metastases;. Peritoneal metastases.

Metastatic disease is discovered in 20% to 25% of patients with colorectal cancer (CRC) at initial diagnosis and <50% during their clinical course.[1] Peritoneal surfaces are the second most common site of synchronous dissemination, after the liver.[2,3] Metachronous peritoneal metastases (PMs) develop in 5% to 19% of patients, but incidences are likely underestimated, because PMs are more difficult to detect than liver or lung metastases.[4] Historically, PMs were deemed as terminal disease only to be palliated, but nowadays selected patients with CRC-PMs are curatively treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC). Survival improvements over historical or contemporary nonrandomized control subjects and a successful randomized trial have been reported.[4–9]

Taking advantage of the recent advances in surgical and anesthesiology techniques, interventional radiology, medical oncology, and molecular biology, surgical resection has become the standard treatment option for isolated lung or liver metastases (LMs) from CRC. Today, even patients with metastatic CRC involving both liver and lung or other extrahepatic sites are increasingly considered for surgery.[10–12] In line with this emerging trend, surgical management of PMs with concurrent extraperitoneal (mainly hepatic) disease (EPD) has been reported. However, long-term results and selection factors for treatment are still unclear.[13,14]

Patients with CRC are often referred to peritoneal malignancy management centers with a history of systemic disease synchronous with PMs or previous resection. Therefore, we reviewed 2 prospective databases to compare long-term outcomes between patients who had CRS/HIPEC for PM alone and patients undergoing curative-intent treatments for EPD, either at the same time as CRS/HIPEC or before the onset of PM. In addition, we attempted to define reliable selection criteria for combined treatment in patients with both peritoneal and extra-PMs.

PATIENTS AND METHODS

Data for the present analysis were collected within 2 databases that were prospectively maintained in 2 high-volume Italian centers from January 2004 to June 2016. Until 2007, surgeons from the Milan National Cancer Institute provided surgical training to Bentivoglio Hospital. Shared protocols were instituted regarding the selection of patients for treatment and surgical management, as reported elsewhere.[15] Ethics committees of both institutions approved the study, in accordance with the principles of the Helsinki Declaration. Informed consent forms were signed by all of the patients.

Study Population

Patients were selected through a systematic clinical–radiological workup including clinical history, physical examination, lung and abdominopelvic CT scan, colonoscopy, and serum tumor markers (CEA, CA19.9, and CA125). Additional studies, such as nuclear magnetic resonance and fluorodeoxyglucose positron emission tomography, were performed as needed. The final decision to submit each patient to CRS/HIPEC was discussed at multidisciplinary meetings involving both medical and surgical oncologists. Eligibility requirements included age ≤75 years, World Health Organization performance score ≤2, no significant comorbidities, and preoperative imaging showing PMs potentially amenable to complete cytoreductive surgery.

Additional selection criteria evolved during the study period based on both our experience and literature data. Peritoneal involvement was scored intraoperatively using the Peritoneal Cancer Index (PCI). PCI rates lesion size as 0 (no tumor), 1 (≤5 mm), 2 (>5–50 mm), or 3 (>50 mm) in 13 abdominopelvic regions, resulting in a final score ranging from 0 to 39.[16] Restrictions on PCI were adopted as it became increasingly clear that the extent of peritoneal involvement impacts prognosis, with a threshold beyond which optimal cytoreduction and HIPEC are poorly effective.[4,5,7]

Initially, EPD was an absolute contraindication. Later, patients with ≤3 easily resectable LMs and low-to-moderate PCI were treated.[17] More recently, no specific restriction on LM number was adopted because of the increasing effectiveness of current systemic chemotherapy (s-CT). Patients with invaded hepatic veins, inferior vena cava, or hepatic hilum were excluded. In patients with extrahepatic EPD, indications were individually tailored based on low volume of resectable disease and objective response or stabilization after s-CT.

Operative Treatment

Cytoreductive surgery was aimed at removing the macroscopic tumor, with peritonectomies and visceral resections, as necessary.[18,19] Bowel resections for primary lesions were performed respecting the oncologic principle of adequate lymphadenectomy. Completeness of cytoreduction (CCR) was rated as follows: CCR-0, macroscopically complete; CCR-1, nearly complete (residual disease ≤2.5 mm); and CCR-2, grossly incomplete (residual disease >2.5 mm).[16]

All of the patients with LMs were evaluated and treated by hepatobiliary surgeons. Intraoperative ultrasound examination was systematically performed to assess the number

and location of metastases and to plan liver resections. LMs were preferably treated by parenchyma-sparing wedge resections using an ultrasonic dissector. Intermittent vascular exclusion was selectively performed. Small central lesions (≤3.0 cm) were treated with radiofrequency ablation (RFA).

In both centers, HIPEC was performed only if CCR-0/CCR-1 cytoreduction was accomplished. HIPEC was administered at 42.5°C for 60 minutes, according to the close-abdomen technique, with 4–6 L of perfusate. A total of 117 patients received mitomycin C (3.3 mg/m^2 per liter) plus cisplatin (25 mL/m^2 per liter), 30 patients received mitomycin C (35 mg/m^2), and 1 patient received cisplatin (250 mg) because of intolerance to mitomycin C. Standardized dose reductions were applied to patients >70 year old, after previous s-CT, and/or after extensive surgery.[19]

The 7th edition of TNM classification (International Union Against Cancer/American Joint Committee on Cancer) was retrospectively used to stage patients who were operated on before 2010.[20] Indication to postoperative adjuvant s-CT was given at multidisciplinary meetings according to previous s-CT response and postoperative clinical conditions.[1] All of the patients attended regular follow-up visits, with physical examination, thoracic/abdominal CT scan, and tumor markers every 3 months for the first 2 years and every 6 months thereafter.

Statistics

Differences between groups were tested by Fisher exact test, χ^2 test, or Student *t* test, as appropriate. The primary study end point was overall survival (OS), estimated using the Kaplan–Meier method from the date of CRS/HIPEC to the date of death or last follow-up.[21] Differences in survival distribution were assessed by 2-tailed log-rank test. Continuous variables were categorized into 2 classes by using their median value as a cutoff or according to literature data.[7] *P* values <0.05 were considered significant. Statistically significant factors by univariate analysis were included in a Cox proportional hazard model.

The National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm), were used to score complications occurring within the first 30 postoperative days. Operative outcomes were compared between patients who underwent CRS/HIPEC alone versus CRS/HIPEC combined with concurrent treatments for EPD to ascertain whether these additional procedures increased the operative risk. All of the statistical analyses were performed by SPSS version 20.0.0 (IBM Corporation, Armonk, NY.)

RESULTS

CRS/HIPEC was performed in 148 patients during the study period. Cytoreduction was rated as CCR-0 or CCR-1 in all but 2 patients. These patients were left with residual tumor <5 mm in limited abdominal regions. Both had HIPEC (and were included in the study) because we supposed that it might have been of benefit to them. On the contrary, 5 patients who underwent open-and-close laparotomy, palliative surgery, or grossly incomplete cytoreduction with no HIPEC were excluded.

Extraperitoneal Disease

Twenty-seven patients (18.2%) were treated for EPD, either before or at the same time as PM. As shown in Table 1, patients treated for PM alone and those treated for PM and EPD were comparable for all of the characteristics. In details, EPD involved the liver (n = 23), lung (n = 1), both lung and liver (n = 2), and both inguinal nodes and liver (n = 1).

Overall, a mean of 2.38 LMs (range 1–14) were treated in 26 patients. Mean metastasis diameter was 2.1 cm (range, 0.3–6.0 cm). Fourteen patients had single lesions. Twelve patients had single wedge resections, 9 had multiple wedge resections, 3 had bisegmentectomy/left lobectomy, and 1 had right hepatectomy. RFA alone and RFA in addition to hepatic resection were used in 1 patient. All of the liver resections were margin negative. RFA was considered as adequate surgery.

Because timing of EPD treatment is a concern, 18 patients were treated for LM at the same time as CRS/HIPEC. In all of them, the presence of LM was known preoperatively. Four patients underwent 2-stage treatment 4 to 8 weeks before CRS/HIPEC, liver resections for single metastases were performed in 2 patients, and single lung metastasectomy and metastatic left inguinal lymph node excision were performed in in 1. Five patients were treated for liver (n = 3) or both liver and lung (n = 2) metastases before PM development. In 3 patients, EPD was treated both simultaneously with CRS/HIPEC and before the onset of PM.

Survival and Failures

Median reverse Kaplan–Meier estimated follow-up was 34.6 months (95% CI, 22.6–65.7 mo) in the overall series. Five-year and median OSs were 47.8% and 35.6 months (95% CI, 17.1–58.4 mo). Five-year OS was 16.5% (median = 19.0 mo; 95% CI, 12.1–30.4 mo) for 27 patients treated for EPD either before or at the same time as CRS/HIPEC, as compared with 52.0% (median = 60.1 mo; 95% CI, 44.9–93.7 mo) for 121 patients treated for PM alone. Survival difference was highly significant ($p = 0.019$). OS is plotted in Figure 1.

Median progression-free survival was 11.5 months (95% CI, 6.6–26.4 mo) in the overall series; 5-year PFS was 22.9%. Median PFS was 9.6 months for patients treated for EPD either before or at the same time as CRS/HIPEC and 13.8 months for patients treated for

TABLE 1. Patient and treatment characteristics

Category	*Overall series (N = 148)*	*Only PM (N = 121)*	*PM and EPD (N = 27)*	*p*
Sex				
Men	61	51	10	0.626
Women	87	70	17	
Age, y				
Mean (SD)	57.7 (10.9)	57.4 (11.4)	59.5 (8.7)	0.361
Median (range)	59.0 (51.0–65.5)	58.0 (49.0–65.0)	61.0 (55.0–66.0)	
WHO score				
0	106	87	19	0.792
1	39	32	7	
2	3	2	1	
Previous surgery				
≤1 abdominal region dissected	77	67	10	0. 201
>1 abdominal region dissected	71	54	17	
Previous systemic chemotherapy				
Adjuvant after primary surgery[a]	61	47	14	0.280
5-FU/capecitabine based	26	20	6	
Oxaliplatin/irinotecan containing	33	28	6	
5-FU, FA, oxaliplatin/irinotecan, and bevacizumab/cetuximab	4	2	2	
Treatment for PM[b]	87	79	22	0.115
5-FU/capecitabine based	12	8	4	
5-FU/capecitabine based and bevacizumab/cetuximab	7	6	1	
Oxaliplatin/irinotecan containing	49	39	10	
5-FU, FA, oxaliplatin/irinotecan *and* bevacizumab/cetuximab	53	39	14	
Other	1	0	1	
Both adjuvant and treatment	43	32	11	0.162
Either adjuvant or treatment	117	92	25	0.068
Site of primary[c]				
Right	68	56	12	0.832[3]
Left	77	61	15	
Multiple	1	1		
Unknown	2	2		
Histologic type				
Intestinal	112	90	22	0.598
Mucinous	33	28	5	
Signet ring cell	3	3	0	
Grade of primary				
Well differentiated	5	4	1	0.662
Moderately differentiated	81	68	13	
Poorly differentiated	60	43	13	
Signet ring cells	2	2	0	
Stage of primary				
II/III	62	55	7	0.084
IV	86	66	20	
PM synchronous with primary				
Yes	78	64	14	1.000
No	70	57	13	
PCI				
Mean (SD)	11.9 (8.8)	12.4 (9.3)	9.8 (6.5)	0.181
Median (range)	10.0 (5–17)	10.0 (5–18)	8.5 (5–16)	
Completeness of cytoreduction				
No visible residual tumor	117	94	23	0.610
Residual tumor ≤2.5 mm	29	25	4	
Residual tumor >2.5 mm	2	2	0	

PM = peritoneal metastasis; EPD = extraperitoneal disease; 5-FU = 5-fluorouracil; FA = folinic acid; WHO = World Health Organization performance score; PCI = Peritoneal Cancer Index.

[a]Two patients underwent 2 different systemic chemotherapy regimens.

[b]A total of 23 patients underwent >1 different systemic chemotherapy regimen.

[c]Right colon was considered the part of large bowel extending up to the left flexure, left colon was considered the part of the large bowel extending from the left flexure to the peritoneal reflection, and 3 patients with multiple or unknown primary site were excluded.

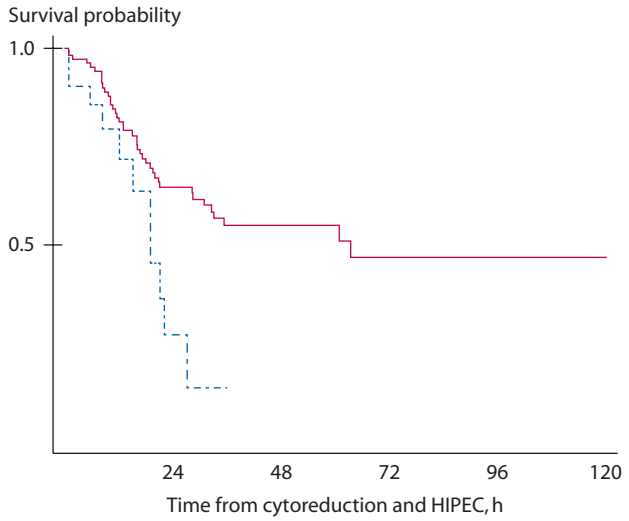

FIGURE 1. Overall survival Kaplan–Meier curves of patients treated by cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC) for peritoneal metastases alone (continue line) and cytoreductive surgery with HIPEC associated with curative-intent treatments for extraperitoneal disease (dashed line). Survival difference was significant: *p* (log-rank test) = 0.019.

PM alone ($p = 0.009$). Among the 4 patients with extrahepatic EPD, 3 were alive at 15 to 36 months and 1 died at 21 months.

Other than EPD, right-sided primary tumors ($p = 0.018$), mucinous histology ($p = 0.022$), grade 3 to 5 complications ($p = 0.013$), PCI >19 ($p < 0.001$), and suboptimal (CCR-1/2) cytoreduction ($p = 0.020$) correlated with poorer OS at univariate analysis. Multivariate analysis recognized EPD as an independent adverse prognostic factor ($p = 0.001$), with completeness of cytoreduction ($p = 0.018$) and PCI >19 ($p = 0.004$; Table 2).

The site of first disease progression was known for 92 patients, excluding operative deaths (n = 5), deaths unrelated to cancer (n = 3), patients who did not experienced recurrence (n = 42), and those whose site of first recurrence remained undetermined (n = 6). First disease progression involved the peritoneum in 4 patients with a history of EPD, extraperitoneal sites in 14 patients, and both in 2 patients. Conversely, first disease progression involved the peritoneum in 35 patients treated for PM alone, extraperitoneal sites in 35 patients, and both in 2 patients. The proportion of patients relapsing at extraperitoneal sites was higher in patients with a history of EPD (16/20 (80%)), as compared with those treated for PM alone (37/72 (48.6%)), although statistical significance was not reached ($p = 0.204$).

Operative Outcomes

In the overall series, major complications (grade 3–5) occurred in 41 patients (27.7%) and operative death in 5 (3.4%). Twenty major complications occurred in 11 (61.1%) of 18 patients undergoing CRS/HIPEC and synchronous treatment of LM; 44 major complications occurred in 30 (23.1%) of 130 patients undergoing CRS/HIPEC alone ($p = 0.002$). In detail, surgical morbidity occurred in 10 (55.6%) and 27 patients (20.8%) of the 2 groups ($p = 0.003$). Systemic toxicity occurred in 5 patients of each group (3.8% vs 27.8%; $p = 0.003$). Complications apparently related to liver resections occurred in 3 patients, namely biliary leakage (n = 2) and perihepatic collection (n = 1). In the 2 groups there were 3 (17.6%) and 2 (1.6%) operative deaths ($p = 0.013$). Deaths were caused by sepsis and multiorgan failure in 4 patients, as well as respiratory failure in 1. Conversely, differences between groups were not significant regarding reoperation rates (27.8% vs 10.0%; $p = 0.131$), operative time (mean = 585.7 min (range, 378–990 min) vs 535.4 min (range, 300–960 min); $p = 0.127$), and hospital stay (mean = 25.0 d (range, 9–52 d) vs 21.2 d (range, 9–89 d); $p = 0.248$).

Survival According to Disease Extent

The analysis of potential prognostic variables for 27 individuals treated for both PM and EPD is shown in Table 3. PCI >8 was the only significant variable. Notably, the survival difference between EPD treated synchronously with PM or before the onset of PM was not significant (median = 21.0 vs 19.0 mo; $p = 0.624$). We were able to identify 3 prognostic groups (Fig. 2), including patients with PCI ≤18 and no EPD (5-year OS = 59.3%; median not reached), patients with PCI ≤8 and EPD (5-year OS = 32.9%; median, 27.0 mo), and patients with PCI >19 and no EPD or PCI >8 and EPD (5-year OS = 0; median, 11.6 mo; $p = 0.001$).

DISCUSSION

The concept of locoregional metastatic disease represents one of the most relevant advancements in contemporary oncology practice.[1,12] Surgery and/or locoregional therapies have become standard options for isolated CRC metastases in the liver, lung, and peritoneum. Additional evidence was provided that extrahepatic metastases should no longer be considered as absolute contraindications to curative treatment of colorectal LM.[12] Nevertheless, surgical resection is still controversial in patients affected by both PM and EPD.[13,14]

In the present series, OS of patients treated for both PM and EPD was statistically reduced, as compared with patients treated for PM alone, irrespective of whether EPD was treated before the onset of PM or simultaneously with CRS/HIPEC. Unlike most studies that simply compared outcomes between patients undergoing CRS/HIPEC with or without concurrent treatment of EPD,[13,14] we have addressed the clinically relevant question of the prognostic impact of EPD treated at any time in the disease history. Because the recent advances in

TABLE 2. Univariate and multivariate analysis of factors influencing overall survival

Category	5-y overall survival	p (log-rank)	HR (95% CI)	p (Cox)
Sex				
Men	39.5	0.189		
Women	53.0			
Age, y				
≤59	48.3	0.674		
>59	48.4			
WHO score				
0	46.2	0.357		
1–2	53.8			
Previous surgery				
≤1 abdominal region dissected	53.4	0.395		
>1 abdominal region dissected	37.6			
Site of primary[a,b]				
Right	32.4	0.018	0.95 (0.57–1.57)	0.842
Left	67.2			
T stage of primary[b]				
2–3	59.0	0.777		
4a/b	43.3			
N stage of primary				
0	59.5	0.154		
1–2	38.8			
Grading				
1–2	69.1	0.155		
3	31.9			
TNM stage of primary				
2–3	61.4	0.122		
4	46.9			
Histological type				
Intestinal	75.4	0.022	0.86 (0.50–1.49)	0.590
Mucinous/ signet ring	41.9			
PM synchronous with primary				
Yes	49.3	0.313		
No	35.6			
Completeness of cytoreduction				
No visible residual tumor	52.3	0.020	2.28 (1.36–3.82)	0.018
Residual tumor ≤2.5 mm	33.4			
Residual tumor >2.5 mm	0			
PCI				
1–20	55.5	0.001	3.14 (1.67–5.91)	0.004
21–39	0			
History of EPD				
Yes	52.0	0.019	3.04 (1.74–5.32)	0.001
No	16.5			
Grade 3–5 complication[c]				
Yes	28.1	0.013	0.93 (0.58–1.48)	0.765
No	55.4			
Previous systemic CT (adjuvant)				
Yes	52.3	0.362		
No	38.9			
Previous systemic CT (treatment for PM)				
Yes	48.7	0.210		
No	51.2			

WHO = World Health Organization performance score; PM = peritoneal metastasis; EPD = extraperitoneal disease; CT = chemotherapy; CCR = completeness of cytoreduction; PCI = Peritoneal Cancer Index.
[a]Right colon was considered the part of large bowel extending up to the left flexure and left colon was considered the part of large bowel extending from the left flexure to the peritoneal reflection.
[b]Three patients with multiple or unknown primary site were excluded.
[c]Classifications are according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

cancer medicine have greatly prolonged survival in metastatic CRC, it has become increasingly common that patients with either a history of systemic disease synchronous with PM or previously resected are referred to our center and other peritoneal malignancy management centers.

As poor prognosis for colorectal PM with a history of EPD was demonstrated, we sought to recognize a subset of patients who are more likely to benefit from an intensive treatment approach. In agreement with previous series suggesting that total tumor load is the predominant prognostic factor in CRC with multiple metastatic sites regardless of disease location, we found that PCI was the only prognostically significant variable in patients with a history of EPD.[12,22] However, this finding may be specific to our series, because peritoneal disease extent likely exerted a stronger prognostic impact than number of LMs because of the limited number of LMs in our patients, with a median of 1 lesion per patient. This may also reflect the biological behavior of PM, resulting in more rapid disruption to function, as compared with LM, because of anatomic features, higher metastatic efficiency, or both.[23]

Median survival of patients with PCI ≤8 and EPD was 27.0 months. Currently, very few data are available to compare outcomes of patients with both PM and EPD, treated with curative surgery and HIPEC versus s-CT. In a Dutch population-based study collecting 440 individuals with PM and LM undergoing noncurative treatments, median survival was 5 months.[24] Also, our results compare favorably with those obtained in peritoneal-only metastases by

TABLE 3. Univariate analysis of factors influencing overall survival in 27 patients treated for peritoneal metastases and extraperitoneal disease

Category	No.	5-y survival	Median survival	p (log-rank)
Sex				
Men	10	0	13.9	0.558
Women	17	26.1	19.9	
Age, y				
<61	15	0	19.0	0.377
>61	12	20.5	9.6	
WHO score				
0	19	16.1	19.0	0.961
1–2	8	12.5	16.2	
Previous surgery				
≤1 abdominal region dissected	10	0	27.0	0.797
>1 abdominal region dissected	17	24.4	19.0	
Site of primary[a]				
Right	12	0	19.0	0.753
Left	15	33.3	13.9	
T stage of primary				
2–3	18	11.0	19.0	0.084
4a/b	9	34.3	13.9	
N stage of primary				
0	4	25.0	9.6	0.153
1–2	23	11.9	19.0	
TNM stage of primary				
2–3	7	0	19.0	0.456
4	20	15.4	21.0	
PM synchronous with primary				
Yes	14	0	21.0	0.733
No	13	16.8	19.0	
EPD synchronous with primary				
Yes	8	43.7	16.2	0.548
No	19	0	19.0	
Grading				
1–2	13	11.8	13.9	0.849
3	14	19.9	19.0	
Histological type				
Intestinal	22	13.4	21.0	0.085
Mucinous	5	0	13.9	
Diameter of liver metastases				
<2.7	14	0	27.3	0.398
>2.7	13	20.0	13.9	
Previous systemic CT (adjuvant)				
Yes	21	24.9	16.2	0.578
No	6	0	19.0	
Previous systemic CT (treatment for PM)				
Yes	22	22.7	19.0	0.648
No	5	0	19.0	
CCR				
0	23	12.5	21.0	0.364
1	4	0	9.6	
PCI				
1–8	14	20.6	27.3	0.002
>8	13	0	9.6	
Extrahepatic EPD				
Yes	4	50.0	21.0	0.178
No	22	0	16.2	
Timing of EPD treatment				
Before PM onset	5	0	19.0	0.421
2-stage/ simultaneous with CRS/ HIPEC	22	30.0	21.0	
No. of liver metastases				
1	15	17.6	19.0	0.286
>1	11	0	19.0	0.243
1–2	19	16.6	19.0	0.379
>2	7	0	16.2	
1–3	21	13.6	19.0	
<3	5	0	16.2	
Grade 3–5 complications[b]				
Yes	14	18.8	19.0	0.706
No	13	0	19.0	

WHO = World Health Organization performance score; PM = peritoneal metastasis; EPD = extraperitoneal disease; CCR = completeness of cytoreduction; PCI = Peritoneal Cancer Index; CT = chemotherapy; CRS = cytoreductive surgery; HIPEC = hyperthermic intraperitoneal chemotherapy.

[a]Right colon was considered the part of large bowel extending up to the left flexure and left colon was considered the part of large bowel extending from the left flexure to the peritoneal reflection.

[b]Classifications are according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

systemic combinations, ranging from 5.2 to 7.0 months in unselected patients treated with old 5-fluorouracil–based combinations to 16.8 to 23.9 months in more recent series of potentially resectable patients receiving modern systemic and targeted agents.[4,6,8] These data support a curative-intent strategy for patients with limited peritoneal tumor and EPD.

Pathophysiological, molecular, and clinical differences exist between peritoneal and systemic metastases.

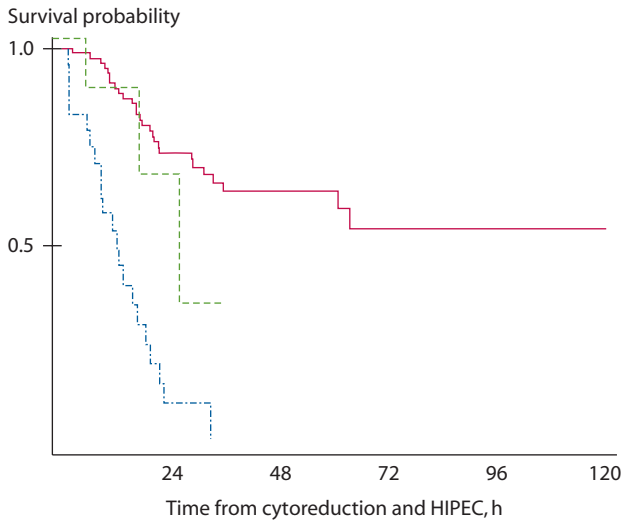

FIGURE 2. Overall survival according to Peritoneal Cancer Index (PCI) and extraperitoneal disease (EPD): PCI ≤19 and no EPD (continue line); PCI ≤8 and EPD (dashed line); and PCI >19 and no EPD or PCI >8 and EPD (dotted line); *p* (log-rank test) = 0.001.

The former occur by transcelomic cell dissemination from primary tumors penetrating peritoneal surfaces and the latter by hematogenous spread.[4,9] At the molecular level, BRAF-mutated metastatic CRC is associated with worse prognosis, higher likelihood to present with PM, and lower likelihood to present with liver-only metastases.[1,23] Tumors with both PM and EPD have proven to be able to spread through both routes of dissemination, and this may explain decreased survival. Finally, it has been reported that modern s-CT and targeted therapies are less efficient in peritoneal versus extra-PMs.[25,26] Nevertheless, several authors have demonstrated similar survival after curative-intent resection of colorectal LM versus PM, thus suggesting that both disease entities may deserve aggressive treatment approaches.[27–29]

As compared with CRS/HIPEC for isolated PM, treatment of PM with EPD has been associated with lower survival in some series[30–32] and no difference in others.[7,33–35] In a recent controlled nonrandomized study, survival was significantly reduced in patients who were treated for LM and PM as compared with control subjects treated for PM alone.[36] Finally, only a trend toward reduced survival after CRS/HIPEC has been found by a systematic meta-analysis of patients with both PM and LM, whereas a second meta-analysis by the same Dutch group showed a significant negative impact on prognosis.[13,14]

The selection factors for patients with both PM and EPD have been thoroughly addressed by Elias et al.[17] In their early article, >3 hepatic metastases contraindicated curative-intent treatment.[17] Their most recent update demonstrated that 5-year OS was dramatically low in patients with >10 LMs (18.1%) and in those with PCI >15 (11.8%).[23] Our findings may further improve prognostic stratification and clinical decision-making, suggesting that our intermediate prognosis group (PCI ≤8 and EPD) may be considered for curative-intent treatments. Conversely, patients with PCI >19 or PCI >8 and EPD are better treated in a palliative setting because survival rates were not higher than those obtained by s-CT.[4,6,8,25,26]

Our analysis of postoperative complications confirms that great caution is needed in considering concurrent resection of PM and hepatic metastasis combined with HIPEC. Of note, operative death rate was several-fold higher for patients who had liver resections at the same time as CRS/HIPEC. However, the reason why the addition of hepatic resections to CRS/HIPEC increased morbidity and mortality rates remains unclear, because only a minority of complications were apparently related to liver surgery. Interestingly, Navez et al[37] reported the same discrepancy. In the present article, however, numbers were too small to determine whether a 2-staged surgical procedure may be safer than performing hepatic resections simultaneously with CRS/HIPEC.

We realize a few weaknesses of the present study, such as the retrospective design and evolution of patient selection criteria during the study period. Nevertheless, uniform cytoreductive surgical procedures were applied to all our patients, and prognostic factors of CRC were homogeneously distributed between groups, thus limiting any potential bias. Second, inadequate statistical power, attributed to small sample size, might have accounted for the lack of prognostic correlation of clinicopathological variables, such as number of LMs. Third, our series was highly selected, and the results might not be applicable to the general population with PM and EPD.

CONCLUSION

The results of the present investigation do not support CRS/HIPEC in patients with a history of EPD and moderate-to-severe PM (PCI >8). On the contrary, a survival benefit may be obtained in selected patients with EPD and limited PM (PCI ≤8). In line with the current literature, our findings suggest a PCI cutoff of 19 for patients with PM only. These data would warrant prospective confirmation.

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