Ann Surg Oncol (2019) 26:482–489
https://doi.org/10.1245/s10434-018-6860-4

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Sites of Recurrence After Complete Cytoreduction and Hyperthermic Intraperitoneal Chemotherapy for Patients with Peritoneal Carcinomatosis from Colorectal and Appendiceal Adenocarcinoma: A Tertiary Center Experience

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ABSTRACT

Background. This report describes patterns of disease recurrence after optimal cytoreduction (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) for peritoneal carcinomatosis (PC) of colorectal (CRC) and appendiceal adenocarcinoma (AC) origin.

Methods. Patients undergoing optimal CRS/HIPEC (2007–2016) at the authors' institution were retrospectively reviewed from a prospectively maintained database. Data regarding disease recurrence were analyzed.

Results. Of 74 patients who underwent CRS/HIPEC for PC from CRC (n = 46) or AC (n = 28), 49 (66%) had recurrence during a median follow-up period of 39.5 months. The sites of recurrence were peritoneal-only (n = 34, 69%), hematogenous-only (n = 6, 12%), and combined peritoneal and hematogenous (n = 9, 19%) sites. No patients with AC had hematogenous-only recurrence. The median disease-free survival (DFS) time for all the patients was 15 months (95% confidence interval [CI] 12.5–17.5 months). The recurrence rate after CRS/HIPEC was 41% at 1 year, 73% at 3 years, and 76% at 5 years. All the patients with hematogenous-only metastases experienced recurrence within 12 months after CRS/HIPEC. Mucinous or signet ring features predicted peritoneal recurrence (p = 0.041), whereas a complete cytoreduction of 1 was a predictor of early recurrence (p = 0.040). Patients who underwent repeat cytoreduction survived longer than those who received systemic chemotherapy alone. The median survival time after peritoneal-only recurrence was 33 months (95% CI 27.8–38.9 months).

Conclusion. Recurrence for patients with PC is common, even after optimal CRS/HIPEC. Hematogenous-only recurrence occurs early after CRS/HIPEC, suggesting occult disease at the time of treatment and highlighting the need for methods to identify micro-metastases and improve patient selection. Patients experiencing peritoneal-only recurrence had long survival period after CRS/HIPEC, suggesting its effectiveness at controlling peritoneal disease for a time.

The peritoneum is a common site of metastasis in patients with colorectal carcinoma (CRC) and those with appendiceal adenocarcinoma (AC) found in 10–25% and 72% of patients, respectively.[1,2] Traditionally, peritoneal carcinomatosis (PC) has been regarded as end-stage disease, with a relatively poor prognosis when treated with systemic chemotherapy.[3,4] However, for selected patients with isolated peritoneal disease, an aggressive combination of complete cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) can achieve longer survival.[3] The primary goal of CRS is complete tumor debulking (completeness of cytoreduction [CC]: CC-0 or CC-1 resection), recognized as one of the most important prognostic predictors after CRS/HIPEC[5–8] in numerous studies (http://www.sciencedirect.com/science/article/pii/S0960740415300141-bib2) as well as in our own institutional experience.[9] However, even after optimal CRS/HIPEC, disease recurrence is common, with reported rates reaching 75%.[10] In contrast to the natural history of primary CRC, in which the liver is the first site of metastasis,

First Received: 15 September 2017;
Published Online: 11 December 2018

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recurrences after successful CRS/HIPEC of peritoneal metastasis tend to favor the peritoneum.[10–15] Reports on specific patterns of recurrence after CRS/HIPEC for adenocarcinoma of colorectal and appendiceal origin are scarce. Additionally, the influence of patient characteristics, intraoperative findings, and pathologic features on hematogenous or peritoneal spread, location of peritoneal spread, and timing of recurrence remains unclear. This study aimed to analyze the patterns and timing of recurrence after complete CRS/HIPEC for PC of CRC and AC origin at a single tertiary referral center.

METHODS

A retrospective review of all patients undergoing HIPEC at our institution was performed from a prospectively maintained, institutional review board (IRB)-approved database. The patients included in this analysis underwent complete cytoreduction (CC $\leq$ 1) CRS/HIPEC for PC of CRC or AC origin (including both mucinous and non-mucinous adenocarcinoma) between March 2007 and January 2016. Patients with low-grade appendiceal mucinous neoplasms were excluded from the study. Patients with incomplete cytoreduction (n = 28), those lost to follow-up evaluation (n = 4), those who died within 90 days after surgery (n = 2), and those who underwent palliative CRS/HIPEC for symptom management (n = 29) also were excluded from the analysis (Fig. 1). No distinction was made between the patients who initially presented with PC and the patients who progressed to PC after primary resection. The variables collected were demographics, medical and surgical history, perioperative treatments, surgical and pathologic details, and follow-up information, including survival and recurrence data.

Preoperative planning and operative technique for CRS/HIPEC have been previously described.[9,16,17] Briefly, diagnostic laparoscopy was performed routinely and converted to laparotomy when complete cytoreduction was deemed possible. The peritoneal cancer index (PCI) was recorded according to the Sugarbaker classification.[18] Cytoreduction then was performed, and the CC score was recorded. Next, HIPEC was administered via the closed abdomen technique using a fixed dose of 40-mg mitomycin C according to consensus guidelines.[19]

Routine follow-up surveillance included carcinoembryonic antigen (CEA) level and contrast-enhanced computed tomography (CT) of the chest, abdomen, and pelvis every 3–4 months for 2 years, and then every 6 months thereafter for a total of 5 years. Additional imaging was obtained if patients presented with symptoms suspicious for recurrence. Recurrence was defined as the presence of new lesions on diagnostic imaging or the presence of pathologically confirmed metastasis.

We defined three categories for the sites of recurrence: (1) peritoneal recurrence-only, (2) hematogenous recurrence-only (including distant lymph node metastasis), and (3) combined peritoneal and hematogenous recurrence sites. Peritoneal recurrences were further categorized by

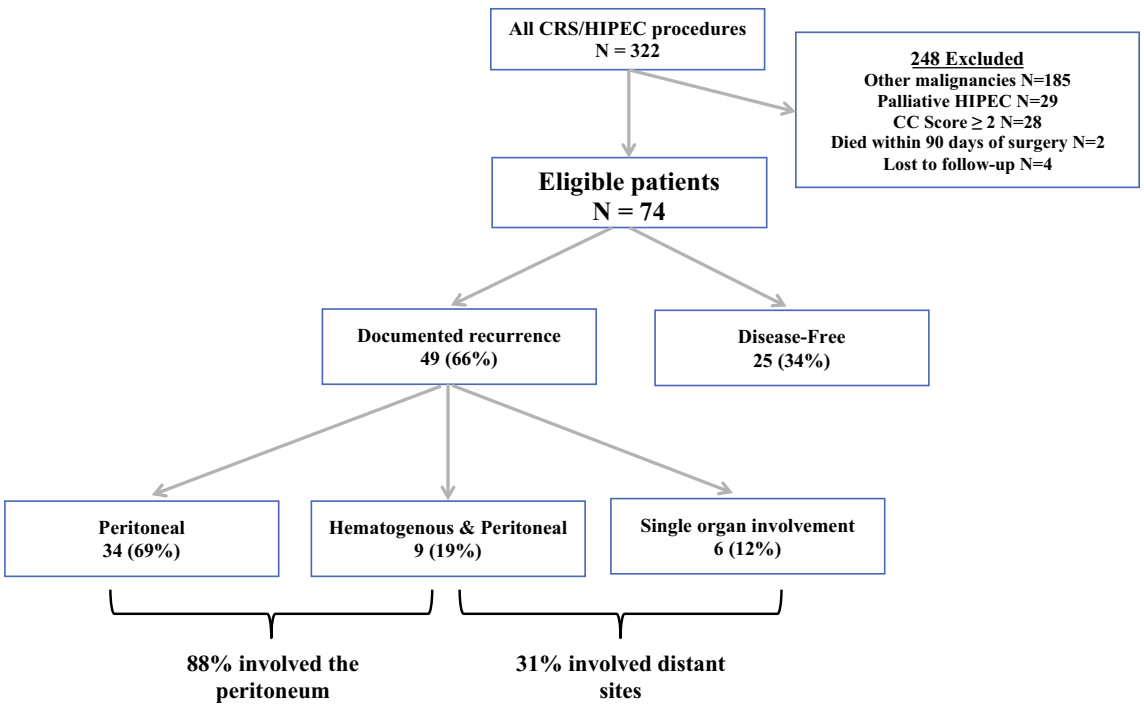

FIG. 1 Study population. CRS/HIPEC cytoreductive surgery and hyperthermic intraperitoneal chemotherapy, CRC colorectal cancer

disease location as follows: lower abdomen (including pelvis), upper abdomen (including diaphragm), or diffuse disease.

Statistical Analysis

Descriptive data analysis was performed by calculating frequencies and percentages for categorical variables and measures of central tendency (means or medians) for continuous variables. Chi square, Fisher's exact test, and independent two-sample *t* test were used to determine significant differences between the groups. Overall survival (OS) was calculated as the time from CRS/HIPEC to the date of death using the Kaplan–Meier method, and disease-free survival (DFS) was calculated as the time from CRS/HIPEC to the first evidence of recurrence using the hazard function. The recurrence rate was defined as the percentage of patients who experienced recurrent disease within the observation period.

Uni- and multivariate analyses were performed with Cox regression. Univariate logistic regression was performed to identify predictors of peritoneal or hematogenous recurrence. A p value lower than 0.05 was considered statistically significant. All p values were two-sided. The statistical software for the social sciences (SPSS) version 22.0 (IBM Corp., Armonk, NY) was used for all statistical analyses.

RESULTS

Patient Characteristics

The study population and baseline characteristics are reported in Fig. 1 and Table 1. The study comprised 74 patients, 46 (62%) with CRC and 28 (38%) with AC. Resection of the primary tumor was performed at an outside institution for 55 patients (74%). This was more common among the patients with AC (89% vs 67%; $p = 0.028$). Of all the study patients, 17 (23%) had their diagnosis initially determined during emergent surgery. The patients with a diagnosis of AC showed a trend toward more emergent surgeries (32% vs 17%; p not significant). Synchronous peritoneal metastases were found at diagnosis for 45 patients (61%). At diagnosis, 44 patients (59%) had node-positive disease (N1/N2), 20 patients (27%) had node-negative disease, and 10 patients (14%) had undetermined node status (Nx).

Node-positive disease was more common among the patients with CRC (67% vs 45%; $p = 0.007$). In terms of histology, 26 patients (35%) had adenocarcinoma with mucinous features, 5 patients (6%) had signet ring cells, and 11 patients (15%) had mixed mucinous and signet ring cell features, and these were more commonly associated with AC ($p = 0.014$). Tumor differentiation was categorized as well-differentiated in 4 cases (5%), moderate in 32 cases (43%), and poorly differentiated in 31 cases (36%). The CRC primary tumors were less differentiated than the AC primary tumors ($p = 0.009$). The median PCI was 8.5 ± 6, and the majority of the patients had a PCI lower than 20 ($n = 67$, 91%,).

Sites of Recurrence

The sites of recurrence are summarized in Fig. 1 and Table 1. During the observation period, 49 patients (68%) had documented recurrence. Of these 49 patients, 34 (69%) had peritoneal-only recurrence, 6 (12%) had hematogenous metastasis with single-organ involvement, and 9 (18%) had a combination of peritoneal and hematogenous recurrence. Recurrence was diagnosed on follow-up imaging, except for 4 patients. Of these four patients, three had their diagnosis determined during exploratory laparoscopy, performed in two cases due to increasing tumor marker and in one case due to small bowel obstruction. The fourth patient had an enlarged palpable inguinal lymph node, which prompted excisional biopsy.

Of six patients with hematogenous recurrence to a single organ, four had isolated liver recurrence, and two had isolated lung recurrence. Three patients had metastasis to multiple distant organs, and all the metastases were associated with peritoneal recurrence. Recurrences in the patients with AC favored the peritoneum ($n = 19$, 100%) compared with the patients who had primary CRC ($n = 24$, 80%), although this trend was not significant, and none of the patients had hematogenous-only recurrence.

In a separate analysis of peritoneal recurrences, 20 patients (27%) had recurrence in the lower abdomen and pelvis, 10 patients (14%) had recurrence in the upper abdomen, and 12 patients (17%) presented with diffuse metastasis. Mucinous or signet ring cell features shown by pathology were significantly associated with a peritoneal pattern of metastases compared with hematogenous-only recurrences ($p = 0.027$) and were found to be predictive of peritoneal failure shown by univariate logistic regression ($p = 0.041$). No significant differences were found when peritoneal and hematogenous patterns were compared via primary location, synchronous metastasis during resection of the primary tumor, histologic features, differentiation, perioperative chemotherapy, PCI, or CC scores (Table 2).

Survival Analysis

The median DFS was 14 months (95% CI, 9.2–18.8 months) for the patients with AC and 15 months (95% CI, 11.6–18.3 months) for the patients with CRC

TABLE 1 Patient, treatment, and recurrence characteristics

Variables	Overall $n = 74$	Primary appendiceal $n = 28$ (38)	Primary CRC $n = 46$ (62)	p value[a]
Median age: years ± SD	54 ± 11.6	57.5 ± 10.6	52.5 ± 12.1	
Female sex	46 (62)	20 (71)	26 (57)	0.150
Primary tumor resection OSH	55 (74)	25 (89)	30 (65)	0.028
Emergent surgery	17 (23)	9 (32)	8 (17)	0.155
Adenocarcinoma, histologic subtype				0.014
Nonmucinous	32 (43)	6 (21)	26 (57)	
Mucinous features	26 (35)	13 (46)	13 (28)	
Signet ring cell features	5 (6)	4 (14)	1 (2)	
Mucinous and signet ring cell	11 (15)	5 (18)	6 (13)	
Differentiation				0.009
Well	4 (5)	4 (14)	0	
Moderate	32 (43)	8 (29)	24 (52)	
Poorly	31 (36)	8 (29)	19 (41)	
Unknown	11 (15)	8 (29)	3 (7)	
Lymph node status				0.007
N0	20 (27)	11 (39)	9 (20)	
N1/N2	44 (59)	13 (46)	31 (67)	
Nx	10 (14)	4 (14)	6 (13)	
Systemic chemotherapy before CRS	40 (54)	12 (43)	28 (61)	0.580
Synchronous diagnosis of PC	45 (61)	17 (61)	28 (61)	0.989
Median PCI ± SD	8.5 ± 6	9.5 ± 6.5	7 ± 6.4	0.774
Recurrence	$n = 49$ (66)	$n = 19$ (68)	$n = 30$ (65)	0.816
Location of recurrence				0.180
Peritoneal only	34 (70)	16 (84)	18 (60)	
Hematogenous with single-organ involvement	6 (12)	0	6 (20)	
Combined peritoneal and hematogenous	9 (18)	3 (16)	6 (20)	
Any peritoneal recurrence	$n = 43$ (58)	$n = 19$ (68)	$n = 24$ (52)	0.515
Lower abdomen	20 (47)	8 (42)	12 (50)	
Upper abdomen	10 (23)	6 (32)	4 (17)	
Diffuse/retroperitoneal	13 (30)	5 (26)	8 (33)	
Median DFS: months ± SE	15 (1.3)	14 (2.4)	15 (1.7)	0.644
Median follow-up: months ± SD	39.5 (27.5)	33.5 (15.2)	45 (30.7)	

All data are n (%) unless otherwise specified

CRC colorectal cancer, *SD* standard deviation, *OSH* outside hospital, *Nx* undetermined node status, *CRS* cytoreductive surgery, *PC* peritoneal carcinomatosis, *PCI* peritoneal carcinomatosis index, *SE* standard error

[a]Results are considered statistically significant at $p < 0.05$

(nonsignificant p) during a median follow-up period of 39.5 months after CRS/HIPEC. The recurrence rate after CRS/HIPEC was 41% at 1 year, 73% at 3 years, and 76% at 5 years. The survival rate after CRS/HIPEC was 94% at 1 year, 71% at 3 years, and 41% at 5 years.

In the univariate Cox regression, DFS correlated negatively with perioperative treatment ($p = 0.034$) and a CC score of 1 ($p = 0.014$). In the multivariate analysis, only a CC score of 1 negatively affected DFS (Table 3). A Kaplan–Meier analysis for different spread patterns found that the patients with hematogenous-only recurrence experienced the recurrence markedly earlier (median DFS, 4.5 months; 95% CI, 0.1–10.1 months), whereas the patients with peritoneal-only spread or combined peritoneal and hematogenous spread had recurrence later (DFS, 10.6 months; 95% CI, 6.5–14.6 months; $p = 0.04$) (Fig. 2). < F3 > The median survival period for the patients who experienced peritoneal-only recurrence after CRS/HIPEC was 33 months (95% CI, 27.8–38.9 months).

TABLE 2 Recurrence patterns, contingency, and prediction

	Contingency			Predicted probability	
	Any peritoneal (n =43) n (%)	Hematogenous-only (n = 6) n (%)	p value[a]	OR (95% CI)	p value[a]
Age > 50 years	28 (65)	3 (50)	0.656	1.867 (0.335–10.412)	0.477
Positive LN at primary resection	25 (58)	4 (67)	0.302	N/A	N/A
Synchronous metastasis at primary resection	28 (65)	5 (83)	0.649	0.373 (0.040–3.495)	0.388
Before debulking chemotherapy	32 (74)	5 (83)	0.634	0.582 (0.061–5.540)	0.638
PCI > 20	5 (11)	0	0.378	N/A	N/A
CC score = 1	20 (46)	3 (50)	0.873	0.870 (0.157–4.802)	0.873
Mucinous or signet ring cell	29 (67)	1 (17)	0.027	10.357 (1.103–97.266)	0.041
Poor differentiation	18 (42)	1 (17)	0.197	3.6 (0.87–33.509)	0.260
	Contingency			Predicted probability	
	Any hematogenous (n = 15) n (%)	Peritoneal-only (n = 34) n (%)	p value[a]	OR (95% CI)	p value[a]
Age > 50 years	9 (60)	22 (65)	0.759	1.222 (0.350, 4.265)	0.753
Positive LN at primary resection	9 (60)	20 (59)	0.231	0.202 (0.023, 1.811)	0.153
Synchronous metastasis at primary resection	13 (87)	20 (59)	0.097	4.550 (0.884, 23.407)	0.070
Before debulking chemotherapy	11 (73)	26 (76)	0.814	0.846 (0.210, 3.404)	0.814
PCI > 20	3 (20)	2 (6)	0.160	4 (0.593, 26.965)	0.154
CC score = 1	7 (47)	16 (47)	0.980	0.984 (0.291, 3.326)	0.980
Mucinous or signet ring cell	8 (53)	11 (32)	0.210	1.546 (0.830, 2.878)	0.170
Poor differentiation	4 (27)	15 (44)	0.495	2 (0.494, 8.089)	0.331

OR odds ratio, *CI* confidence interval, *LN* lymph node, *N/A* not applicable, *PCI* peritoneal carcinomatosis index, *CC* completeness of cytoreduction

[a]Results are considered statistically significant at $p < 0.05$

TABLE 3 Cox regression analysis: uni- and multivariate predictors of disease-free survival (DFS)

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p* value[a]	HR	95% CI	*p* value[a]
Female sex	0.763	0.423–1.375	0.368			
Age > 50 years	1.047	0.588–1.862	0.876			
Primary, colorectal	0.875	0.492–1.557	0.651			
OSH	0.890	0.471–1.682	0.719			
Synchronous metastases	0.075	1.725–3.147	0.075	1.194	0.570–2.502	0.639
Time to HIPEC	0.931	0.526–1.646	0.805			
Emergent surgery	0.573	0.277–1.188	0.135			
Poor differentiation	1.140	0.618–2.102	0.674			
Preoperative chemotherapy	2.169	1.058–4.446	0.034	2.059	0.937–4.526	0.072
PCI > 20	1.676	0.659–4.264	0.278			
CC = 1	2.040	1.154–3.608	0.014	1.968	1.030–3.760	0.040
Positive LN at 1st surgery	1.432	0.728–2.819	0.298			
Any complication	1.092	0.620–1.926	0.760			
Severe complication	1.368	0.660–2.833	0.399			

HR hazard ratio, *CI* confidence interval, *OSH* outside hospital, *HIPEC* hyperthermic intraperitoneal chemotherapy, *PCI* peritoneal carcinomatosis index, *CC* completeness of cytoreduction, *LN* lymph node

[a]Results are considered statistically significant at $p < 0.05$

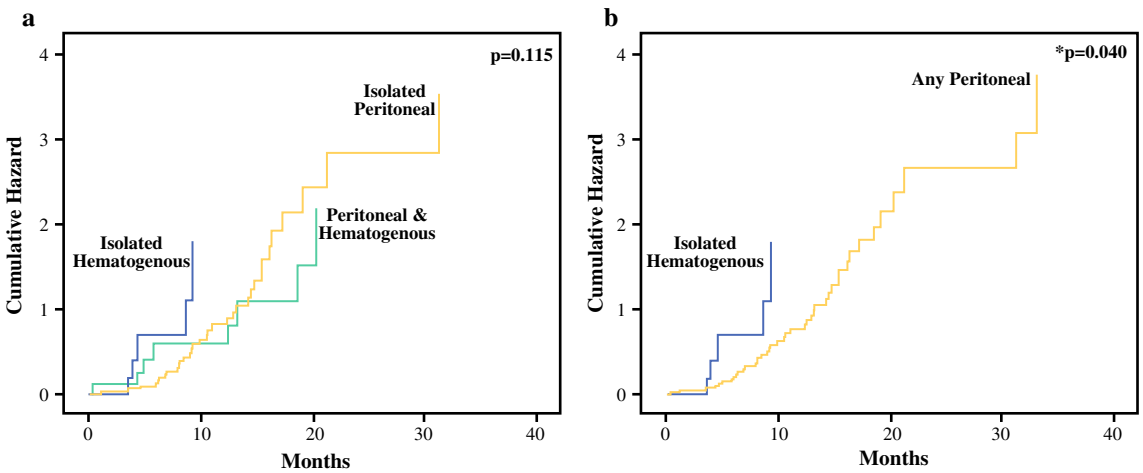

FIG. 2 Comparison of time to recurrence following CRS/HIPEC between: **a** isolated peritoneal, isolated hematogenous, and peritoneal and hematogenous recurrences combined; **b** isolated hematogenous and any peritoneal recurrence

Treatment of Recurrences and Survival

Among the 15 patients who experienced some form of hematogenous recurrence (6 with isolated and 9 with combined hematogenous and peritoneal recurrence), 13 (87%) received adjuvant therapy after surgery. Furthermore, all the patients were treated with systemic therapy after recurrence, and five patients (33%) underwent surgical resection of the metastasis (3 had repeat CRS/HIPEC and 2 had liver resection). During a median follow-up period of 32 months, the median survival after CRS/HIPEC was not reached by the patients receiving surgery, and their median DFS was 19 months. The patients who received systemic treatment alone had a median OS of 31 months and a median DFS of 5 months (OS, non-significant *p*; DFS, $p = 0.007$).

Moreover, of the 34 patients who experienced peritoneal-only recurrence after CRS/HIPEC, 11 (32%) underwent repeat debulking, with or without HIPEC, and survived significantly longer than those who received only systemic treatment (median survival, 25 vs 43 months; $p = 0.015$).

DISCUSSION

This retrospective analysis of 74 patients with PC secondary to CRC and AC was performed to identify clinical characteristics that may be associated with definite patterns of recurrence after complete CRS/HIPEC. To our knowledge, this is the first analysis to include and compare patients with colorectal and appendiceal carcinomas, and to use a fixed-dose protocol as per American Society of Peritoneal Surface Malignancies (ASPSM) guidelines. Our results indicate that the peritoneum is the most frequent site of failure after CRS/HIPEC in CRC and AC patients. Nevertheless, these patients with peritoneal-only recurrence demonstrated relatively long survival after CRS/HIPEC compared with the survival rates published in the literature for treatment with systemic chemotherapy alone.[3] In addition, we found that the patients with hematogenous-only recurrence tended to have recurrence earlier.

For the patients treated with CRS/HIPEC for PC of CRC origin, peritoneal-only recurrence is reported for 30–60% of patients, hematogenous-only metastases for 18–47% of patients, and combined peritoneal and hematogenous recurrence for 13–30% of patients.[10,12–15] Possible explanations for the wide range of peritoneal-only recurrence rates may be related to the different HIPEC protocols in common practice. Most available studies examining patterns of recurrence after CRS/HIPEC are from institutions using variable methods of intraperitoneal chemotherapy dosing, as opposed to the more recent guidelines from the ASPSM followed at our institution,[19] which recommend a fixed dose of mitomycin C. Setting guidelines for HIPEC delivery in addition to standardizing treatment strategies may help to achieve more reliable comparisons between different analyses.

Similar to previous reports, we found a high overall recurrence rate, with 76% of patients experiencing recurrence during the follow-up period. Our median DFS periods of 14 months for CRC and 15 months for AC also were comparable with the published data on patients undergoing HIPEC.[10,12–15] Our findings demonstrate that after CRS/HIPEC, recurrences most often occur in the peritoneum only, even if complete cytoreduction is achieved during the initial CRS/HIPEC. These results contrast with recurrences after curative resection of primary CRC, in which the most frequently involved site is the liver, and the peritoneum is only the third most frequently involved site.[20–25]

A recent analysis of patients with moderately and poorly differentiated AC after hemicolectomy demonstrated that all recurrences were localized in the peritoneum.[26] Only one study examined recurrence rates for patients with AC undergoing CRS/HIPEC. In that series including only cases with poorly differentiated and signet ring features, DFS was 1.2 years.[27] In our study also, no patients with AC had hematogenous-only spread. Furthermore, these patients showed a tendency for peritoneal-only recurrence (84%) compared with the patients with primary CRC (60%). Importantly, our patients with peritoneal-only recurrences still demonstrated a long median survival after CRS/HIPEC (33 months).

Compared with the patients receiving systemic chemotherapy for peritoneal carcinomatosis of CRC origin, whose median survival was 16 months with the use of cytotoxic agents and 17.1 months with the use of at least one targeted agent according to a recent meta-analysis,[4] the results of our study showed a long survival and may suggest CRS/HIPEC effectiveness in providing control of peritoneal disease and prolonged survival. Moreover, the patients who underwent repeat cytoreduction, with or without CRS/HIPEC, survived significantly longer than those who did not receive surgery and were treated with systemic chemotherapy. Among our patients with peritoneal-only recurrence, no patterns of intraabdominal location of recurrence were found.

The Kaplan–Meier analysis showed that patients with hematogenous-only recurrence tend to have recurrence earlier, whereas patients with peritoneal-only spread or combined spread have a longer DFS. Although this cohort of patients with isolated distant recurrence is small, they likely represent occult micrometastatic disease already present during CRS/HIPEC. Among these patients, nonsignificant trends toward poor differentiation and synchronous metastasis at the primary resection also were noted. Because this cohort of patients did not clearly benefit from CRS/HIPEC, further studies are needed to identify and better address this population. Nonetheless, even for the patients with early distant recurrence, long-term survival was achieved, likely due to the administration of adjuvant chemotherapy and further aggressive systemic treatment at the time of recurrence.

In this analysis, the majority of the patients had a diagnosis of peritoneal recurrence within the first 18 months of follow-up evaluation. Although regarded as acceptable cytoreduction, CC-1 still predicted early recurrence. Early detection of the peritoneal recurrence may allow for a more complete cytoreduction to a CC of 0.

Our study had several limitations, mostly due to its retrospective nature and relatively small number of included patients, with the latter potentially limiting the generalization of the survival analysis for the CRC and AC subsets. Considering the advances with more effective systemic chemotherapy treatments for patients with PC, larger prospective trials are required for further validation of the advantage offered by CRS/HIPEC. Moreover, future directions of research may include a second-look laparoscopy for high-risk patients 6–12 months after primary CRS/HIPEC aimed at potential identification of occult

peritoneal recurrence. This would allow selected patients to undergo secondary treatment at a stage most amenable to repeat cytoreduction and HIPEC.

CONCLUSION

Recurrence in patients with PC from CRC and appendiceal adenocarcinoma is common, even after optimal CRS/HIPEC, most often involving the peritoneum. Our findings emphasize that isolated distant metastasis tends to recur sooner than peritoneal metastasis, highlighting the need for methods to identify occult metastatic disease and allow for better patient selection. Patients experiencing isolated peritoneal recurrence had long survival after CRS/HIPEC, suggesting its effectiveness at controlling peritoneal disease and prolonging survival.

DISCLOSURE There are no conflicts of interest.

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