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# More Synchronous Peritoneal Disease but Longer Survival in Younger Patients with Carcinomatosis from Colorectal Cancer Undergoing Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy

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## ABSTRACT

**Background.** Colonoscopy to detect colorectal cancer (CRC) is recommended starting at age 50 years; however, CRC rates are increasing in the prescreening population. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) has been proven effective in select patients with peritoneal carcinomatosis (PC) from CRC, although it has not been evaluated specifically in patients $< 50$ years.

**Methods.** CRC patients aged $< 50$ years at diagnosis undergoing CRS/HIPEC 2007–2017 were compared with those aged $\geq 50$ years. Age distribution was analyzed in patients undergoing colectomy alone versus CRS/HIPEC for CRC 1993–2013.

**Results.** A total of 98 patients underwent CRS/HIPEC, of which 44% were $< 50$ years. Younger patients were more likely to present with synchronous peritoneal metastases ($p = 0.050$). Receipt of perioperative chemotherapy was comparable ($p$ = not significant [NS]). Charlson Comorbidity Index and ECOG score were similar ($p$ = NS). Tumor grade was similar ($p$ = NS). Peritoneal Carcinomatosis Index, total organs resected, and anastomoses created were comparable ($p$ = NS). Major Clavien-Dindo morbidity and LOS were similar ($p$ = NS). Younger patients survived longer after CRS/HIPEC ($p = 0.011$). Demographic data from patients undergoing colectomy ($n = 225$) and CRS/HIPEC ($n = 98$) showed that age $< 50$ years was increasingly common with the more aggressive procedure (9% and 44% respectively, $p < 0.001$).

**Conclusions.** Younger patients with PC from CRC presented more often with peritoneal metastases at the time of diagnosis. Yet despite similar perioperative features at CRS/HIPEC, they survived longer than older patients. Patients undergoing CRS/HIPEC are overall younger than those undergoing index colectomy.

During the past few decades, the incidence of colorectal cancer (CRC) has been declining steadily.[1] This improvement has been attributed to both a reduction in risk factors and improved success in the removal of premalignant lesions during screening colonoscopy, which is recommended by the National Comprehensive Cancer Network (NCCN) starting at 50 years of age.[2,3] Despite this decrease in overall incidence, the rates of colorectal cancer specifically in the young population have paradoxically increased: while only 5–10% of colon and rectal cancers are currently diagnosed in this younger age group, it is estimated that people born in 1990 are at twice the risk of developing colon cancer compared with those born in 1950 and have four times the risk of developing rectal cancer.[1,4–6] Furthermore, because younger patients are not screened unless they have predisposing risk factors, more than 80% of patients are diagnosed when they are symptomatic, and therefore the majority of patients present with stage III or IV disease.[7] There is controversy as to whether CRC diagnosed in young age has a poorer prognosis, with contrasting results reported in previous studies.[8–12]



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Peritoneal carcinomatosis (PC) of CRC origin is generally considered end-stage disease. Given the higher rates of stage IV presentation in patients $< 50$ years, the development of PC in this population is of particular concern. Survival in patients with isolated PC has been reported to be approximately 16 months when treated with systemic chemotherapy and 17 months with the addition of at least one targeted agent.[13] However, over the past decades, a combination of systemic chemotherapy with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) has achieved longer term survival in select patients.[14–18] This treatment approach has been recently included in the updated NCCN guidelines for the treatment of select patients with resectable PC of CRC origin and is now considered the standard of care in appropriately selected patients.[19]

While the clinical benefit of CRS-HIPEC in patients with colorectal cancer has been demonstrated in both retrospective studies and a randomized clinical trial, to the best of our knowledge no studies have been conducted evaluating its efficacy specifically in patients aged $< 50$ years.[14–18] Moreover, it has been suggested that younger patients are likely to be offered more aggressive cancer care, thus confounding the assessment of the contribution of CRS/HIPEC to outcomes.[20,21] Therefore, the primary purpose of this study was to analyze the perioperative and long-term outcomes of patients $< 50$ years treated with CRS-HIPEC for colorectal cancer and to compare them to their older counterparts. The secondary goal of our analysis was to examine the age distribution of patients undergoing surgical procedures for primary and metastatic CRC.

## METHODS

Data from March 2007 to December 2016 were retrospectively obtained from a prospectively maintained, institutional-review board-approved database. All patients diagnosed with PC of CRC origin who underwent CRS/HIPEC with curative intent at The Mount Sinai Hospital were included. Two cohorts were created: $< 50$ years and $\geq 50$ years at the time of original CRC diagnosis. Preoperative demographic and clinical data, as well as perioperative characteristics and postoperative outcomes were compared.

Preoperative workup and surgical technique have been previously described.[22] At our institution, diagnostic laparoscopy is routinely performed first and, if complete cytoreduction is deemed achievable, converted to laparotomy. Upon further open exploration of the abdomen, the peritoneal disease burden is evaluated using the peritoneal cancer index (PCI) according to the Sugarbaker/Jacquet classification.[23] Cytoreduction follows and completeness of cytoreduction (CC) score is recorded.[23] We deliver HIPEC in a closed fashion, with mitomycin C as the most commonly used chemotherapeutic drug, administered at a fixed dose of 40 mg for 90 min at an intraperitoneal temperature of 41–43 °C, as recommended by the consensus guidelines from the American Society of Peritoneal Surface Malignancies.[24] When necessary, anastomoses are created at HIPEC completion.

For the secondary aim of comparing the age distribution for CRC operations, demographic data were retrospectively collected from a surgical and pathologic database of specimens using the keywords "colorectal cancer" and "rectal cancer," including all consecutive patients undergoing index colectomy for a CRC primary from January 1993 to August 2013.

Data were analyzed with the Statistical Program of Social Sciences (SPSS 22, released 2013; SPSS Statistics for Windows, version 22.0; IBM Corporation, Armonk, NY). Categorical data were expressed as percentages and continuous data were expressed as medians. The Student *t*-test and Mann–Whitney test were used to compare continuous variables. Categorical variables were compared by the $\chi^2$ test or Fisher's exact test. Survival analyses were calculated using the Kaplan-Meier method; subgroups were compared with the log-rank test. Disease-free survival (DFS) was calculated as time from CRS/HIPEC to first evidence of recurrence, and CC score $> 1$ was regarded as immediate disease recurrence. Multivariate Cox regression was performed using all variables whose univariate analysis yielded a $p$ value $< 0.05$ as predictors. A $p$ value $< 0.05$ was considered statistically significant; all $p$ values were two-sided.

## RESULTS

### *Baseline and Perioperative Characteristics*

A total of 98 patients who underwent CRS/HIPEC for PC of CRC origin were included, of whom $n = 43$ (44%) were less than 50 years old. Demographic variables were comparable between the age cohorts (Table 1), including comorbidities and functional status scores ($p$ = NS). Patients $< 50$ years old were more likely to present with synchronous metastasis at diagnosis than those from the older group ($n = 27$, 63% vs. $n = 23$, 42%; $p = 0.050$). Among African American individuals, all younger patients (7/7, 100%), and two of three (67%) older patients presented with synchronous peritoneal metastases. Rates of preoperative chemotherapy administration were similar ($n = 29$, 67% vs. $n = 41$, 75%, $p$ = NS), and median time

**TABLE 1** Demographic and operative characteristics of study population

| Variable | Total | < 50 y/o | ≥ 50 y/o | *p* value |
|---|---|---|---|---|
| N | 98 | 43 (44) | 55 (56) | |
| Age at diagnosis (IQR) | 51 (42–59.2) | 40 (34–45) | 57 (53–65) | |
| Gender, F | 57 (58.2) | 25 (58.1) | 32 (58.2) | NS |
| Race, African-American | 10 (10.2) | 7 (16.3) | 3 (5.5) | NS |
| Charlson Comorbidity Index (IQR) | 8 (7–9) | 7 (6–7) | 9 (8–10) | |
| ECOG (IQR) | 1 (0–1) | 1 (0–1) | 1 (0–1) | NS |
| Time to CRS/HIPEC, months (IQR) | 14 (7–27) | 15 (6–29) | 14 (7–23) | NS |
| Preoperative chemotherapy | 70 (71.4) | 29 (67.4) | 41 (74.5) | NS |
| Histological differentiation | | | | NS |
| Good | 3 (3.1) | 1 (2.3) | 2 (3.6) | |
| Moderate | 58 (59.2) | 28 (65.1) | 30 (54.5) | |
| Poor | 24 (24.5) | 11 (25.6) | 13 (23.6) | |
| Signet | 13 (13.3) | 3 (7) | 10 (18.2) | |
| High grade | 37 (37.8) | 14 (32.6) | 23 (41.8) | NS |
| Synchronous peritoneal metastases | 50 (51) | 27 (62.8) | 23 (41.8) | .050 |
| PCI (IQR) | 9 (5–18.2) | 9 (4–17) | 10 (6–21) | NS |
| Organ resections (IQR) | 3 (2–5) | 3 (2–5) | 3 (2–5) | NS |
| No. anastomosis (IQR) | 1 (0–1) | 1 (0–1) | 1 (0–1) | NS |
| CC | | | | NS |
| 0 | 55 (56.1) | 27 (62.8) | 28 (50.9) | |
| 1 | 36 (36.7) | 16 (37.2) | 20 (36.4) | |
| 2 | 7 (7.1) | 0 | 7 (12.7) | |
| EBL, mL (IQR) | 200 (100–500) | 200 (100–425) | 200 (100–500) | NS |
| LOS (IQR) | 7 (5–10) | 7 (5–11) | 7 (6–9) | NS |
| Clavien-Dindo 30 days | | | | NS |
| 0 | 46 (46.9) | 22 (51.2) | 24 (43.6) | |
| 1–2 | 30 (30.6) | 9 (20.9) | 21 (38.2) | |
| 3–4 | 21 (21.4) | 12 (27.9) | 9 (16.4) | |
| 5 | 1 (1) | 0 | 1 (1.8) | |
| Abdominal reoperation 90 days | 10 (10.2) | 5 (11.6) | 5 (9.1) | NS |

Result is considered significant when $p < 0.05$

*IQR* interquartile range; *CRS/HIPEC* cytoreductive surgery and hyperthermic intraperitoneal chemotherapy; *PCI* peritoneal carcinomatosis index; *CC* completeness of cytoreduction; *EBL* estimated blood loss; *LOS* length of stay

from diagnosis to CRS/HIPEC was comparable (15 vs. 14 months, $p$ = NS).

At CRS/HIPEC, both cohorts were similar in all perioperative measures (Table 1). The two groups had similar median PCI scores (9 vs. 10, $p$ = NS). Median number of organs resected also were equal (3 vs. 3, $p$ = NS), as was the median number of anastomoses performed (1 vs. 1, $p$ = NS). Comparison of other perioperative variables, such as estimated blood loss, length of stay, postoperative complication rates, and abdominal reoperation, were all similar ($p$ = NS). Histological differentiation was also comparable among the groups ($p$ = NS).

*Survival Analysis*

At a median follow-up of 42 months (interquartile range [IQR] 1–3: 22.25–64.5), patients < 50 years survived significantly longer than older controls, both from time of initial diagnosis (median survival not reached vs. 52 months, $p = 0.015$; Fig. 1a) and from CRS/HIPEC (median survival not reached vs. 28 months, $p = 0.011$; Fig. 1b). Following CRS/HIPEC, no significant difference in disease-free survival (DFS) was detected between the two age groups (12 vs. 14 months, $p$ = NS; Fig. 1c). Moreover, patients who were diagnosed synchronously with PC had similar survival from initial

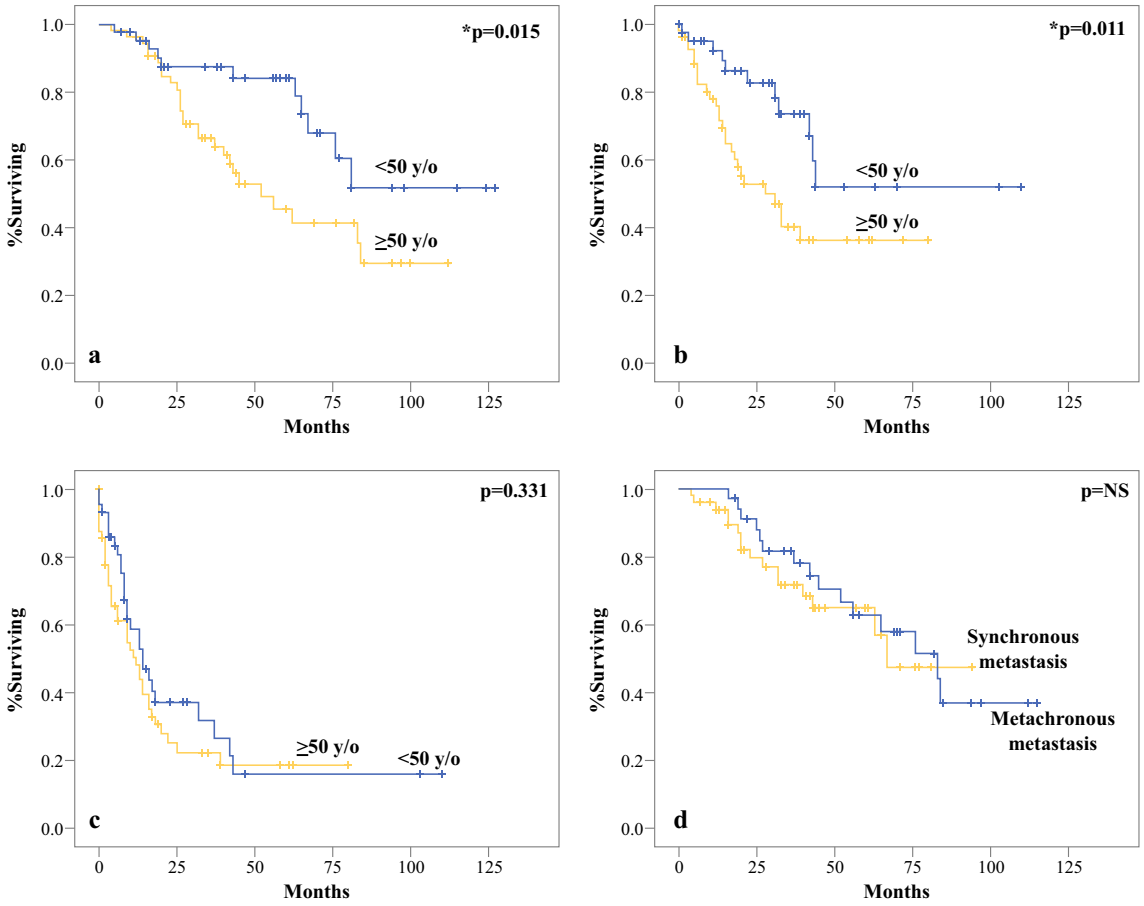


**FIG. 1** Survival analysis: overall survival from date of diagnosis (**a**), and following CRS/HIPEC (**b**); disease-free survival following CRS/HIPEC (**c**); overall survival in patients presenting with synchronous and metachronous disease at diagnosis (**d**)

diagnosis to those who developed metachronous peritoneal spread (median survival 83 vs. 67, $p$ = NS; Fig. 1d). On multivariate Cox regression, higher PCI score ($p < 0.001$), age ≥ 50 (0.026), and poor differentiation (0.033) were significant predictors of decreased survival (Table 2).

*Age Distribution Analysis*

For the secondary purpose of analyzing age distribution of patients undergoing different procedures for CRC, we identified 225 patients who underwent colectomy during the designated time period. Among them, 9% ($n$ = 21) were < 50 years. There were 98 patients who underwent CRS/HIPEC, of whom 44% ($n$ = 43) were < 50 years. When comparing the age distribution, patients undergoing CRS/HIPEC were overall younger than those undergoing index colectomy ($p < 0.001$; Fig. 2).

## DISCUSSION

The incidence of CRC is increasing in patients < 50 years of age and the likelihood of presenting with advanced stages has been reported to be higher as well. Our study confirms that the young patients in our PC cohort more often presented with Stage IV disease at diagnosis, whereas older patients tended to develop PC metachronously. This finding is likely to be attributed to the lack of screening strategies in this younger age group. Thus, the impact of young age in patients undergoing CRS/HIPEC is of increasing clinical relevance. The relatively high morbidity associated with this procedure limits the adoption of CRS/HIPEC in comorbid, unfit patients, as demonstrated by a number of studies.[25–28] Older age also has been included among the predictors of poor perioperative outcome, including a recent prognostic nomogram specifically created on a CRC population.[25,29–31] These findings, together with the recent increase in CRC incidence in young adults, may explain the relatively high rates of patients < 50 years undergoing CRS/HIPEC.[4–6]

**TABLE 2** Cox regression, predictors of survival following CRS/HIPEC

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | *p* | HR | 95% CI | *p* |
| Age < 50 yr | 0.359 | 0.207, 0.843 | 0.015 | 0.434 | 0.208, 0.906 | 0.026 |
| Gender, female | 0.745 | 0.392, 1.415 | NS | | | |
| Charlson Comorbidity Index | 1.168 | 1.019, 1.339 | 0.026 | | | |
| ECOG | 1.317 | 0.729, 2.377 | NS | | | |
| Stage at Dg | 0.786 | 0.439, 1.407 | NS | | | |
| Grade | 1.708 | 1.134, 2.575 | 0.011 | 1.604 | 1.039, 2.475 | 0.033 |
| Synchronous metastasis | 0.677 | 0.333, 1.374 | NS | | | |
| Preoperative chemotherapy | 0.656 | 0.309, 1.395 | NS | | | |
| PCI score | 1.104 | 1.965, 1.145 | < 0.001 | 1.120 | 1.068, 1.174 | < 0.001 |
| Anastomosis | 1.164 | 0.857, 1.582 | NS | | | |
| CC score | 2.068 | 1.311, 3.261 | 0.002 | 0.697 | 0.351, 1.385 | NS |
| 30-day reoperation | 1.466 | 0.450, 4.781 | NS | | | |

Result is considered significant when $p < 0.05$

*HR* hazard ratio; *CI* confidence interval; *PCI* peritoneal carcinomatosis index; *CC* completeness of cytoreduction

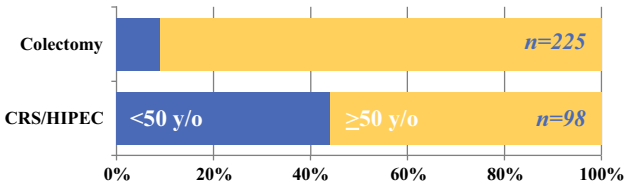


**FIG. 2** Age distribution of patients undergoing colectomy vs. CRS/HIPEC for CRC

To our knowledge, our study is the first to assess perioperative outcomes and survival in patients < 50 years with carcinomatosis undergoing CRS/HIPEC and to compare their results with a control group of older patients. Prior studies have suggested that younger patients with CRC tend to have an aggressive biological profile, due to higher incidence of mucinous histology, signet ring cells, and mutations in mismatch-repair genes.[32] Our subset of patients with carcinomatosis did not show this. In our cohort, prognostic indicators, such as PCI, grade, and comorbidities, were comparable between the groups; nevertheless younger patients survived longer after CRS/HIPEC. Being younger than 50 years was confirmed to be independently associated with improved survival on multivariate analysis. Although we found equal rates of chemotherapy administration between the two groups, our secondary analysis demonstrated that patients undergoing CRS/HIPEC are overall younger than those undergoing index colectomy. It is possible that the improved prognosis in younger patients may be partly a result of more aggressive cancer treatment.

Few studies have been conducted on the outcomes of CRS/HIPEC in younger patients.[33–35] Only one paper from Dhir and colleagues included a specific analysis on the outcomes of young patients with PC of CRC origin undergoing CRS/HIPEC.[35] In their study, 37 patients aged 15–39 years with CRC underwent CRS/HIPEC, but no survival difference was detected compared with older controls.[32] In our study, survival (measured both from time of diagnosis and from CRS/HIPEC) was significantly longer in patients < 50 years, despite higher rates of peritoneal disease at presentation. This result was confirmed in our Cox multivariate regression analysis on overall survival following CRS/HIPEC, where even after adjusting for different demographic and perioperative covariates, age < 50 years was confirmed to be a significant prognostic factor for improved survival.

Interestingly, DFS was similar between the two cohorts, supporting the possibility that these younger patients receive more aggressive treatment, as others have hypothesized.[20,21] In an interesting paper from Quah and colleagues, patients < 40 years old with stage II CRC were more likely to receive adjuvant chemotherapy following resection and had a greater number of lymph nodes examined.[21] The authors pointed out that clinicians may perceive younger patients as more fit to tolerate aggressive chemotherapy regimens. In our study, we analyzed administration of perioperative chemotherapy and time from diagnosis to CRS/HIPEC in an attempt to address this. While these did not differ among the two groups, we could not perform an analysis on the number of cycles and different regimens used between the groups, which may be crucial in future studies focusing on this population. Beyond chemotherapy, it is possible that surgeons are more likely to offer aggressive surgical treatment to younger patients. Indeed, our secondary analysis demonstrated a

remarkably high rate (44%) of young patients undergoing CRS/HIPEC for PC of CRC origin. We propose that this aggressive approach may contribute to the improved survival that we report.

Lastly, it has been reported that by 2030, 10.9% of all colon and 22.9% of all rectal cancers will be diagnosed in patients younger than the screening age, doubling the current incidence.[4] This concerning trend led the American Cancer Society to lower the threshold for initiation of screening in average-risk subjects with either a high-sensitivity stool-based test or a structural (visual) exam.[36] A consideration of earlier screening also is discussed in the NCCN guidelines for high-risk populations, such as African Americans. Our analysis, although limited by the low number of African American patients, confirms the high incidence of synchronous peritoneal metastases in this population. While lowering the threshold age for initiating screening colonoscopies may sound appealing, the absolute number of young patients diagnosed with CRC is relatively low, and the costs and risk of implementation may outweigh the benefit.[37] It is therefore necessary to develop further multidisciplinary research efforts in this population of patients to identify those at risk. For example, our integrated health system has initiated data collection to a comprehensive database to allow future investigation in this direction.

Our study has several limitations, mostly due to its retrospective nature. Our relatively small cohort of highly selected patients undergoing CRS/HIPEC may not be representative of the entirety of patients with PC of CRC origin. Data on actual performance of colonoscopy in patients >50 year old could not be obtained, because we are a tertiary referral institution, and most of these patients were referred to us after diagnosis at an outside hospital. However, our study is the first to report the high incidence of the prescreening age group among patients with PC of CRC origin referred for CRS/HIPEC. This is of particular importance in the worrisome demographic trends of CRC epidemiology, which will likely lead to an increase in the number of young patients referred for this procedure.

## CONCLUSIONS

We report that (1) younger patients with PC of CRC origin presented more often with peritoneal metastases at diagnosis; (2) despite similar perioperative features at CRS/HIPEC younger patients demonstrated longer overall survival than older patients; and (3) patients < 50 years were more common in the group undergoing CRS/HIPEC than those undergoing index colectomy.

**CONFLICT OF INTEREST** The authors declare no potential conflicts of interest.

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