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ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Impact of Major Complications on Patients' Quality of Life After Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy

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ABSTRACT

Introduction. Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is an effective treatment for selected patients with peritoneal surface malignancies (PSM). Although it can have significant morbidity, perioperative mortality is low. Little is known about whether major complications after CRS/HIPEC have a lasting impact on patients' quality of life (QOL).

Methods. We retrospectively reviewed data from a prospectively collected database on patients treated with CRS/HIPEC for PSM (2011–2014). Patients with CRS/HIPEC and 6-month QOL evaluation were included. Major perioperative complications (Clavien–Dindo grade 3/4) were the primary independent variable. QOL was evaluated using the validated EORTC QLQ-C30 score. The primary outcome was 6-month global health score. Secondary outcomes were individual functional and symptom domains.

Results. Forty-two patients were analyzed. Median age was 57.5; 64 % were female. Origin of PSM was appendix (55 %), colorectal (38 %), mesothelioma (5 %), and small bowel (2 %). Fourteen patients (33 %) had major (grade 3/4) complications. Median length of stay was 16 days; patients experiencing major complications had significantly increased length of stay (35.5 vs. 13 days, $p < 0.01$). Major complications included intra-abdominal abscess (9.5 %), bleeding (9.5 %), symptomatic pleural effusion (7.1 %), anastomotic leaks (7.1 %), and renal failure (2.4 %). The average global health score at 6 months was 68.1. The worst-rated symptom scores at 6 months were diarrhea (39.8) and fatigue (35.4). There were no significant differences in 6-month QOL scores between patients with and without major complications, globally or in specific domains.

Conclusions. Although major complications are common after CRS/HIPEC, QOL at 6 months recovers and is similar to those without major complications.

Peritoneal surface malignancy (PSM) from primary peritoneal or gastrointestinal origin traditionally has had traditionally a poor prognosis. Whereas primary peritoneal malignancies (e.g., peritoneal mesothelioma) are rare, PSM from gastrointestinal origin is common; 8–13 % of patients with colorectal cancer (CRC) develop peritoneal carcinomatosis at some point during their disease.[1,2] Aggressive surgical treatment, including cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC), has been shown to improve disease-free and overall survival in selected patients with PSM.[3–6] A few studies have evaluated patients' quality of life (QOL) after CRS/HIPEC and have demonstrated decreased QOL and functional status after CRS/HIPEC in the short-term with progressive improvement toward baseline over time.[7–13]

CRS/HIPEC can require extensive surgery, especially for those with considerable disease burden, and can be associated with significant morbidity. Major complication rates of 24–42 % have been reported in the literature, but most patients are rescued from their complications and perioperative mortality is 2–4 % when performed at experienced

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centers.[4–6,14] Perioperative complications may have a significant and lasting effect on a patient's QOL beyond the perioperative period. Although many studies have evaluated QOL after CRS/HIPEC, to our knowledge, no studies have directly compared patients with and without major complications to determine whether this may contribute to a lasting impact on patient's long-term QOL.[7–13]

The objective of this study was to determine if patients with major complications following treatment with CRS/HIPEC recover their QOL similar to those patients without major complications.

METHODS

Study Design

We conducted a retrospective, cohort study using data from a prospectively collected database on patients treated with CRS/HIPEC for PSM at a single institution (Mount Sinai Hospital, Toronto, Canada) between September 2011 and October 2014. All patients who were treated with CRS/HIPEC were eligible for inclusion. Patients were excluded from analysis if they did not complete a 6-month QOL evaluation. The 6-month time point was chosen because the purpose of the study was to evaluate QOL beyond the short-term perioperative period to determine if there was a lasting adverse impact of complications on QOL. Clinical, pathologic, demographic, and QOL data were obtained from the PSM database and used for analysis. This study was approved by the Research Ethics Board at Mount Sinai Hospital.

Surgical Technique

All patients had a histologic diagnosis confirming either a colorectal, small intestinal, appendiceal, or mesothelioma primary. Patients were evaluated with a thorough history, physical examination, laboratory investigations, and cross-sectional imaging. All cases were reviewed at a multidisciplinary cancer conference. Surgical technique involved exploratory laparotomy, determination of peritoneal carcinomatosis index (PCI) and evaluation for resectability, and cytoreduction.[15] In our center, no patients underwent laparoscopic CRS/HIPEC. HIPEC was perfused using a closed technique. For PSM of low-grade mucinous appendiceal origin, chemoperfusion was administered with intraperitoneal mitomycin C 40 mg (MMC) for 90 min. For other high-grade GI primaries, chemoperfusion was administered with intraperitoneal oxaliplatin (460 mg/m^2) for 30 min with concurrent intravenous fluorouracil (5FU) and leucovorin. For peritoneal mesothelioma, chemoperfusion was administered with intraperitoneal oxaliplatin for 30 min.

Measurement of Quality of Life

QOL data were determined using the European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30).[16] The EORTC QLQ-C30 instrument is readily available, widely used, and validated in cancer patients.[17–19] The multiattribute questionnaire comprises 30 questions incorporating 5 functional scales (physical, role, cognitive, emotional, social), 3 symptom scales (fatigue, pain, nausea/vomiting), and a global health/QOL scale. Single-item scales factor other symptoms commonly reported by cancer patients (dyspnea, insomnia, appetite loss, constipation, diarrhea, finances). Both the function and symptom scores are scaled from 0 to 100. Higher scores in function reflect better performance with 100 being optimal; in contrast, lower scores in symptom reflect less severity with 0 being optimal. On the EORTC QLQ-C30 instrument, an absolute difference of 10 points has been considered to be clinically meaningful.[20] Patients completed questionnaires 6 months after CRS/HIPEC at routine follow-up surveillance assessments.

Analysis

Complications were graded from 1–5 using the Clavien–Dindo classification system.[21] Major complications were defined as grade 3 or 4 occurring within 30 days or in-hospital. The presence of a major complication was the primary independent variable. The 6-month QOL global health score was the primary dependent variable. Patient characteristics between the two groups (major complication vs. no major complication) were compared using the Student t test for continuous variables and Chi square test for categorical variables. Associations between the primary independent variable (major complication) and 6-month QOL were examined using the nonparametric Wilcoxon rank-sum test. A sensitivity analysis was conducted extending the time window for major complications to 90 days. A secondary analysis was conducted to determine the association between major complications and individual functional domains. All statistical analyses were performed using SPSS v22.0. All tests were two-sided with a $p < 0.05$ set as the level of statistical significance.

RESULTS

A total of 87 patients underwent CRS/HIPEC during the study period. Of these patients, 42 completed the 6-month QOL questionnaire and were included in this study. Clinical and pathologic characteristics of patients with and without major complications are summarized in Table 1. The median age was 57.5 years, and there was a female predominance (64.3 %). The most common disease site

TABLE 1 Clinical and pathologic characteristics of patients with and without major perioperative complications following CRS/HIPEC

Variable	All patients $n = 42$	No major complication $n = 28$	Major complication $n = 14$	p
Age[a], years (range)	57.5 (35–73)	54.5 (35–73)	60.5 (25–73)	0.27
Gender				0.04
Male	15 (35.7)	13 (46.4)	2 (14.3)	
Female	27 (64.3)	15 (53.6)	12 (85.7)	
Primary disease site, no. (%)				0.06
Appendix	23 (54.8)	19 (67.9)	4 (28.6)	
Colon	16 (38.1)	8 (28.6)	8 (57.1)	
Mesothelioma	2 (4.8)	1 (3.6)	1 (7.1)	
Small bowel	1 (2.4)	0	1 (7.1)	
Intraperitoneal chemo, no. (%)				0.05
MMC	18 (42.9)	15 (53.6)	3 (21.4)	
Oxaliplatin	24 (57.1)	13 (46.4)	11 (78.6)	
PCI[a] (range)	16 (3–39)	15.5 (3–39)	16 (5–37)	0.53
OR time[a], h (range)	11 (6–20)	11.5 (7–20)	10 (6–18)	0.49
No. of anastamoses[a] (range)	1 (0–3)	1 (0–2)	1 (1–3)	0.38
Stoma, no. (%)	2 (4.8)	1 (3.6)	1 (7.1)	0.61
CC, no. (%)				0.50
0	32 (76.2)	20 (71.4)	12 (85.7)	
1	7 (16.7)	6 (21.4)	1 (7.1)	
2	3 (7.1)	2 (7.1)	1 (7.1)	
ICU LOS[a], days (range)	3 (1–19)	2 (1–5)	6 (2–19)	<0.01
Hospital LOS[a], days (range)	16 (8–114)	13 (8–45)	35.5 (9–114)	<0.01

MMC mitomycin C, *PCI* peritoneal carcinomatosis index, *OR* operating room, *CC* completeness of cytoreduction, *ICU* intensive care unit, *LOS* length of stay

[a] Median

was the appendix (54.8 %). The median PCI was 16, and median operating room time was 11 h. Two patients (4.8 %) received an ostomy. The vast majority of patients (92.9 %) had a CC score of 0–1 following cytoreduction. Median hospital length of stay (LOS) was 16 days. Characteristics between groups were similar except that there was a higher proportion of females in the major complication group ($p = 0.04$) and oxaliplatin was more frequently used in patients with major complications ($p = 0.05$). Additionally, median hospital LOS (35.5 vs. 13 days, $p < 0.01$) and ICU LOS (6 vs. 2 days, $p < 0.01$) were significantly longer in patients with major complications. Baseline characteristics of patients who did not complete the 6-month QOL questionnaire and were excluded were similar to those that did complete it (Table S1, supplementary appendix). Patients who did not complete the 6-month QOL questionnaire had fewer overall complications (51.1 vs. 69.0 %) and major complications than study patients (6.7 vs. 33.3 %). The most common complication in the excluded patients was ileus requiring total parenteral nutrition (42.5 %, Table S2, Supplementary Appendix).

Complications

All perioperative complications in study patients (grade 1–4) are shown in Table 2. Major complications occurred in 14 patients (33.3 %). Four patients (9.5 %) developed intra-abdominal abscesses requiring percutaneous drainage. Three patients (7.1 %) had anastomotic leaks requiring intervention (reoperation or percutaneous drainage). Four patients (9.5 %) had postoperative hemorrhage requiring intervention (reoperation or angioembolization). Three patients (7.1 %) developed symptomatic pleural effusions requiring percutaneous drainage. One patient (2.4 %) had acute renal failure requiring dialysis. No additional patients with grade 3–4 complications were identified by extending the complication time window to 90 days.

Quality of Life

The QOL scores for all patients at 6-months are depicted in Table 3. The average global health score was 68.1. In terms of functional status, physical score (83.3)

TABLE 2 Perioperative complications of patients treated with CRS/HIPEC

Complication[a]	All complications	Major complications
Infectious, no. patients (%)		
SSI	4 (9.5)	–
UTI	10 (23.8)	–
Abscess	6 (14.3)	4 (9.5)
Anastomotic leak	4 (9.5)	3 (7.1)
Sepsis	2 (4.8)	1 (2.4)
Hematologic, no. patients (%)		
PE	2 (4.8)	–
Bleeding	6 (14.3)	4 (9.5)
Respiratory, no. patients (%)		
Pleural effusion requiring drainage	3 (7.1)	3 (7.1)
Ventilator >48 h	1 (2.4)	1 (2.4)
Unplanned reintubation	2 (4.8)	2 (4.8)
Renal, no. patients (%)		
Urinary retention	3 (7.1)	–
Acute renal failure	3 (7.1)	1 (2.4)
Gastrointestinal, no. patients (%)		
Ileus requiring TPN	15 (35.7)	–
Unplanned reoperation	3 (7.1)	3 (7.1)

SSI surgical site infection, *UTI* urinary tract infection, *PE* pulmonary embolism, *TPN* total parenteral nutrition

[a] Patients may be in multiple categories if they developed more than one complication

and cognitive score (79.0) were rated the highest, whereas social score (71.8) was rated the lowest. The worst-rated symptom scores were diarrhea (39.8) and fatigue (35.4).

The results of average QOL scores for patients with and without major complications are depicted in Table 3. There was no statistically significant difference between the two groups in global health score (mean difference: 8.3; $p = 0.16$). Similarly, no significant difference was seen in the function or symptom-related domains.

DISCUSSION

In recent years, the number of centers treating patients with PSM with CRS/HIPEC has increased worldwide. It is well established that complications following CRS/HIPEC treatment are common, but most patients are rescued from their complications so perioperative mortality is low. However, it is unclear whether there is any lasting impact of this morbidity on patients' QOL. We report the QOL for patients with and without major perioperative complications. To our knowledge, this is the first report to examine this issue in patients treated with CRS/HIPEC.

Major perioperative complications (grade 3–4) occurred in 33.3 % of cases; this is consistent with previous reports.[4–6,14] The majority (11/14) were managed with radiological-guided interventions and three patients required reoperation. Despite this morbidity and the resultant significant increase in hospital LOS, QOL scores at 6 months across all domains were not statistically different from those without major complications. This suggests that QOL can be rescued notwithstanding major complications. The average global health score of 68.1 in the study cohort is consistent with previous reports at 6-months following CRS/HIPEC.[22–24] Emotional functioning scored well in both patients with and without major complications, which may reflect renewed hope following treatment regardless of perioperative complications.[25]

Social functioning score was the lowest in the functional domains, which may suggest that it is the slowest to recover following CRS/HIPEC or that it remains lower in this population of patients. The worst-rated symptom score was diarrhea, demonstrating that these patients may have significant impairments in long-term bowel function. There may be a number of factors contributing to this including exposure to hyperthermic chemoperfusion, bowel resection, and cholecystectomy.[26,27] Persistent fatigue also is a major symptom following CRS/HIPEC; it rated second worst in our cohort of patients, consistent with previous reports.[22–24] Despite the overall favorable QOL scores, the results also suggest that some domains and symptoms are impaired and warrant further research, because they are commonly reported in cancer patients and gains made could significantly improve overall health-related QOL in CRS/HIPEC patients.[28,29]

Interestingly, we noted that patients with major complications were more likely to be female (85.7 vs. 53.6 %, $p = 0.04$) and were more likely to have had intraperitoneal chemotherapy with oxaliplatin (78.6 vs. 46.4 %, $p = 0.05$) than MMC. Reasons for these differences are not entirely clear. However, a significant proportion of female patients treated at our center have undergone previous pelvic surgery for presumed gynecologic malignancy before CRS/HIPEC. This increase in adhesions from previous surgery and subsequent increase in prior surgical score (PSS) may have increased the risk of major complications.[30–32] Votanopoulos and colleagues have demonstrated previously that HIPEC with oxaliplatin can be associated with greater platelet and neutrophil toxicity compared with MMC, particularly in splenectomy patients.[33] This may place patients treated with oxaliplatin at higher risk for perioperative complications. However, in our study population, patients who received intraperitoneal oxaliplatin usually had underlying colorectal primaries and were more likely to have received concurrent IV fluorouracil and to have received a course of 3–6 months of neoadjuvant

TABLE 3 Summary of quality of life scores for patients with and without major complications 6 months following treatment with CRS/HIPEC

QOL evaluation	All patients $n = 42$	No major complication $n = 28$	Major complication $n = 14$	p
Global health score	68.1 (20.1)	70.8 (20.6)	62.5 (18.4)	0.16
Function				
Physical score	83.3 (18.9)	85.0 (17.0)	80.0 (22.5)	0.41
Role score	76.2 (25.8)	78.6 (23.9)	71.4 (29.5)	0.50
Emotional score	77.8 (18.5)	79.2 (18.8)	75.0 (18.2)	0.46
Cognitive score	79.0 (23.0)	80.4 (24.0)	76.2 (21.4)	0.36
Social score	71.8 (31.8)	75.0 (29.2)	65.5 (36.7)	0.44
Symptom				
Fatigue	35.4 (26.0)	32.9 (25.0)	40.5 (28.1)	0.44
Nausea/vomiting	7.3 (14.0)	4.8 (8.9)	12.8 (20.6)	0.32
Pain	23.0 (27.8)	23.8 (31.2)	21.4 (20.1)	0.75
Dyspnea	8.1 (17.9)	9.9 (20.3)	4.8 (12.1)	0.50
Insomnia	25.4 (27.4)	29.8 (29.2)	16.7 (21.7)	0.15
Appetite loss	14.3 (25.7)	10.7 (18.3)	21.4 (36.1)	0.50
Constipation	5.6 (14.6)	3.6 (10.5)	9.5 (20.4)	0.32
Diarrhea	39.8 (37.4)	42.0 (36.5)	35.7 (40.2)	0.54
Finances	26.2 (39.3)	32.1 (42.0)	14.3 (31.3)	0.16

QOL quality of life

Mean scores, standard deviation in parentheses

systemic chemotherapy. No patients received postoperative chemotherapy and postoperative management was similar in all patients, irrespective of their underlying disease. Therefore, although some preoperative factors may be causally related to the complication rate, they are not plausibly correlated with the study outcome (QOL at 6 months postoperatively) and should not confound the association between complications and 6-month QOL.

Our study has some limitations. It was a conducted in a single, tertiary care institution and the sample size was modest, which limits our ability to perform robust multivariable analyses and determine whether certain specific complications (e.g., anastomotic leak, fistula) lead to worse QOL than others. In addition, it is possible that with a larger sample size, we would be able to demonstrate smaller but statistically significant differences. However, based on the literature, a difference in score of 10 points is considered clinically meaningful and most of the domains (including global health score) in our study population showed differences smaller than this.[20] In this study, we examined the impact of 30-day complications. Although major complications theoretically could occur after this time point and affect the study outcome, in the present study, no additional patients with major complications were identified by extending the time window from 30 to 90 days. This study was not designed as a longitudinal study, and therefore, QOL was measured at one medium-term time point (6 months). It is possible, although unlikely, that at later time points, the QOL of patients with major complications will diverge from those without. In this study, patients did not complete a baseline (pre-CRS/HIPEC) QOL assessment. However, this is unlikely to be an unmeasured confounder, as baseline QOL is unlikely to be correlated to the exposure (major complication). Finally, although the completion rate of the 6-month QOL questionnaire could potentially introduce a selection bias (nonresponse bias), the baseline characteristics of patients who did not complete the QOL questionnaires were similar to those who did, and there were very few patients with major complications in this group. As a result, it is unlikely that there was a significant selection bias wherein patients with the worst QOL were excluded, because they were too debilitated to complete the study questionnaires.

CONCLUSIONS

In this evaluation of QOL in patients following treatment with CRS/HIPEC, major perioperative complications were associated with more interventions and significantly increased length of hospitalization but did not significantly impair patients' QOL at 6 months after surgery. Although common, the occurrence of major complications does not preclude patients from meaningful health-related QOL recovery following CRS/HIPEC. Nonetheless, further

study with a larger cohort and multiple time-point assessments is warranted. Additionally, specific symptom and functional domains that are particularly impaired may be avenues for further research and intervention.

Compliance with Ethical Standards

Disclosures The authors have no disclosures.

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