

## Research Article

# Does Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy Lead to Worse Quality of Life?

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## Abstract

**Background:** Cytoreductive surgery with Hyperthermic Intraperitoneal Chemotherapy (CRS+HIPEC) is being utilized more frequently to treat peritoneal surface malignancies. However, extensive surgery is associated with significant postoperative morbidity and prolonged recovery. This study evaluates whether patients undergoing CRS+HIPEC experience decreased short-term quality of life (QoL).

**Methods:** Patients scheduled for CRS+HIPEC for peritoneal malignancy were prospectively enrolled and completed the 26 item World Health Organization (WHOQOL-BREF) QoL questionnaire preoperatively and 3 months postoperatively. Questions assessed physical, psychological, social and environmental functioning. Patient demographics, treatment characteristics and morbidity were analyzed in conjunction with QoL scores.

**Results:** 28 patients consented to participate. Of these, 17 patients completed both the preoperative and postoperative questionnaires, and 14 or 82% of these underwent CRS+HIPEC. Median age of participants was 53 years, and most was Caucasian, non-Hispanic, and privately insured. Most patients had an ECOG status of 1. 53% of patients had an appendiceal primary tumor and 24% had comorbidities. 53% experienced R0 resection. Median ICU and hospital stay were 4 and 9 days respectively. Postoperative complications occurred in 35%, most frequently pleural effusion (18%), fistula formation (12%) and postoperative ileus (12%). Physical health scores increased postoperatively whereas psychological scores increased slightly. Increased time between questionnaires was associated with improved physical well-being scores and R2 resection with worse scores.

**Conclusions:** Despite significant morbidity, patients who undergo CRS+HIPEC maintain QoL and satisfaction with their health. Patients may be counseled that in addition to potential prolongation of survival, postoperative QoL is generally preserved or improved after CRS+HIPEC.

**Keywords:** Cytoreductive surgery; Hyperthermic intraperitoneal chemotherapy; HIPEC; Quality of Life; Peritoneal carcinomatosis

## Introduction

Peritoneal surface malignancies compose an oncologic entity with dismal survival rates and guarded prognosis despite ongoing investigations searching for curative treatment. Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS+HIPEC) has of late been acquiring acceptance as a standard of care treatment modality for peritoneal surface malignancies [1]. However, this extensive procedure is associated with significant postoperative morbidity and prolonged recovery [2]. Due to the ever-increasing necessity to determine health-related quality of life in cancer patients, particularly relating to the approval of treatments and patient care decisions, quality of life (QoL) studies are now routinely required to validate cancer clinical findings [3]. In particular, studies of treatment modalities for malignant diseases with limited survival improvements,

which CRS+HIPEC was considered until more recently, utilize quality of life measurements as primary or secondary endpoints [4]. Prior publications of case series and cohort studies have examined the health-related quality of life rated before CRS+HIPEC compared to the postoperative period. Many QoL studies of CRS+HIPEC have demonstrated that patients return to baseline functionality by six months to one year postoperatively [5-8]. Some studies have reported decreased physical functioning in the immediate postoperative period up to three months and increased psychological or emotional well-being in the distant postoperative period at approximately one year [8,9]. Nonetheless these evaluations are taken at different time points and lack a uniform short-term postoperative assessment of QoL after CRS+HIPEC. This study aims to evaluate whether patients with peritoneal surface malignancies who undergo CRS+HIPEC experience a detriment to their perceived short-term quality of life.

**Table 1:** Definition of Domain scores calculated from Items in the Quality of Life Questionnaire.

<b>Domain 1: Physical Health</b>	Includes questions on ADLs, medical dependence, energy levels, mobility, pain levels, sleep and work capacity.
<b>Domain 2: Psychological Health</b>	Includes questions on perceptions of body image, positive and negative feelings, self-esteem, personal beliefs, memory and concentration.
<b>Domain 3: Social relationships</b>	Includes questions on personal relationships, social support, and sexual activity.
<b>Domain 4: Environment</b>	Includes questions on financial resources, physical safety, healthcare accessibility and quality, home environment, opportunities to acquire new skills or participate in leisure activities, and transportation.

## Methods

All patients enrolled in a prospective study who was scheduled to undergo cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS+HIPEC) for peritoneal surface malignancies between January 2011 and August 2015 at our tertiary center were eligible to participate in this health-related quality of life assessment. Participants who consented to this aspect of the study completed an itemized questionnaire modeled after the 26-item World Health Organization Quality of Life (WHOQOL-BREF) instrument [10]. The domains assessed in this questionnaire comprise physical (7 questions), psychological (6 questions), social functioning (3 questions) and environmental factors (8 questions) and are further defined in Table 1. Higher scores indicate higher quality of life. The selection of this questionnaire was based on the desire to utilize an international tool applicable to multicultural settings due to the notable diversity of our patient population as well as previous experience using this questionnaire by our study personnel. As this tool investigates self-evaluation of behaviors, health status, capacities and personal satisfaction [11], we felt this would appropriately reflect our patients' perspective of the short-term outcomes of surgical treatment. The objective of this study was thus to report patients' subjective experiences CRS+HIPEC to holistically assess therapy-related well-being in the short term postoperative period.

The health-related quality of life questionnaire was completed in both the preoperative period and three months postoperatively by participants during a follow-up appointment. Each question had five possible responses which were assigned numerical scores according to intensity of feeling as per a five-point Likert scale. The data was collected prospectively and patient demographics, Eastern Cooperative Oncology Group (ECOG) performance status, characteristics of treatment and postoperative morbidity were considered in conjunction with the quality of life data. Domain scores for each of the four aforementioned categories were calculated for both the preoperative and postoperative period as raw and transformed scores. Raw scores denote the use of all patient actual scores to comprise a single mean score per the WHOQOL-BREF manual formulas. Transformed scores are scaled from 0 to 100 and are calculated using the corresponding table in the WHOQOL-BREF manual for use to objectively compare different studies. Mean score differences between preoperative and postoperative questionnaires were calculated for each patient, for the entire cohort, and per domain. Univariate regression analysis was conducted to evaluate factors associated with domain score differences using R version 3.1.3 (Vienna, Austria). A *p* value less than 0.05 was considered statistically significant. The study protocol was approved by the local Institutional Review Board at the University of Miami.

## Results

Of the 85 patients whom were scheduled cytoreductive surgery

**Table 2:** Characteristics of patients who completed Quality of Life questionnaires.

	Preoperative QOL only (n=28)	Both QOL (n=17)
Median age (y) and range	52 (23-74)	53 (23-70)
Sex		
Male	9 (32%)	4 (24%)
Female	19 (68%)	13 (76%)
Race		
White	23 (82%)	12 (71%)
Black	4 (14%)	4 (24%)
Other	1 (4%)	2 (12%)
Ethnicity		
Non-Hispanic	17 (61%)	13 (76%)
Hispanic	11 (39%)	4 (24%)
Insurance status		
Private	20 (71%)	12 (71%)
Other	8 (29%)	5 (29%)
Primary tumor		
Colonic	6 (21%)	3 (18%)
Appendiceal	13 (46%)	9 (53%)
Ovarian	1 (4%)	1 (6%)
Other	8 (29%)	4 (24%)
Comorbidities Present	6 (21%)	4 (24%)
ECOG PS	1 (0-2)	1 (0-2)
Preoperative chemotherapy	18 (64%)	12 (71%)
CRS+ HIPEC	24 (86%)	14 (83%)
R0 resection	17 (61%)	9 (53%)
Postoperative PCI	0 (0-37)	0 (0-22)
Cytoreductive score	0 (0-3)	0 (0-3)
ICU LOS (d)	4 (0-52)	4 (0-52)
Hospital LOS (d)	9 (1-88)	9 (1-62)
Postop. complication(s)	7 (25%)	6 (35%)
Median time between q (d)	-	102 (82-154)

Y: years; ECOG: Eastern Cooperative Oncology Group; PS: Performance Status; CRS: Cytoreductive Surgery; HIPEC: Hyperthermic Intraperitoneal Chemotherapy; ICU: Intensive Care Unit; LOS: Length of Stay; PCI: Peritoneal Carcinomatosis Index; d: days; postop: postoperative; q: questionnaires. Data expressed as n (%) for categorical variables and median (range) for continuous variables.

and hyperthermic intraperitoneal chemotherapy, 28 (33%) patients of the entire cohort consented to participate in completion of the preoperative quality of life questionnaire. A total 17(20%) patients of the entire cohort completed both preoperative and postoperative

questionnaires. Of these participants, 14 underwent CRS+HIPEC while 3 underwent de bulking surgery only based on intraoperative findings.

Of the seventeen participants who completed both health-related quality of life questionnaires, the median time between surveys was 102 days or three months and two weeks. The characteristics of participants who completed QoL questionnaires are shown in Table 2.

The median age of patients who completed both questionnaires was 53 years. Most participants were female, namely 13 (76%) participants. Most patients were Caucasian and non-Hispanic, 12 and 13 respectively. The median and most frequent ECOG performance status of patients who completed the questionnaires was 1, with two patients scoring higher and lower respectively. The majority, 12 participants, had private insurance. Approximately half, 9 participants, had appendiceal primary tumors, whereas only one patient with ovarian cancer completed the quality of life questionnaires. Four of the participants had significant comorbidities, including hypertension in all 4, diabetes mellitus in 1, dyslipidemia in 1, and hypothyroidism in 2. Twelve patients underwent preoperative systemic chemotherapy. Approximately half 9 participant's experienced R0 margin-free resection. The median length of stay in the surgical intensive care unit and hospital postoperatively was 4 days and 9 days respectively. Postoperative complications occurred in 6 participants who completed both questionnaires. The most common postoperative complications were pleural effusion in 3 (18%) patients, fistula formation in 2 (12%) patients, postoperative ileus in 2 (12%) patients, and intra abdominal abscess and deep venous thrombosis which occurred in 1 (6%) patient each.

All participants completed all of the questions in the surveys, except for one participant who omitted one question related to physical health, specifically the degree of limitation in daily activities caused by physical pain. There was no difference in preoperative and postoperative domain 3 and 4 scores relating to social relationships and environment respectively. The domain 1 score relating to physical health increased in the postoperative quality of life questionnaires. The domain 2 score relating to psychological health increased slightly in the postoperative period. The domain scores and mean differences are listed in Table 3. Upon univariate regression analysis for patient, disease and treatment factors, and increased number of days between questionnaires was found to be associated with improved domain 1 physical well-being QoL scores. R2 resection with residual gross tumor burden was associated with worse domain 1 QoL scores (Table 4).

## Discussion

In addition to the traditional surgical morbidities associated with CRS+HIPEC, assessment of patient QoL in the immediate and short-term postoperative period is necessary to justify recommendations of this surgical treatment as standard of care. In the current study, patient health-related quality of life after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal surface malignancies was evaluated to determine whether patients experience worse QoL in the immediate postoperative period. Our results indicate that our patients generally have preserved or improved quality of

**Table 3:** Differences in Domain Scores for 14 CRS+HIPEC patients who completed both questionnaires.

	Pre RS	Pre TS	Post RS	Post TS	MD (RS)	MD (TS)
D1	13.1	19	15.4	31	1.16	12
D2	14	31	14.7	38	0.81	7
D3	18.7	100	16.7	100	-0.38	0
D4	15.8	25	14.5	25	-0.18	0

Pre: preoperative; post: postoperative; RS: Raw Score; TS: Transformed Score with maximum score of 100; MD: Mean Difference; D: Domain.

**Table 4:** Univariate regression coefficients and odds ratios for factors associated with Differences in Domain 1 scores.

Factor	$\beta$ value	OR (95% CI)	p value
Sex	-1.984	0.14 (0.01-7.25)	0.28
Age at diagnosis	-0.021	0.98 (0.87-1.10)	0.74
No. days pre-post	-0.081	0.92 (0.87- 0.98)	0.02*
Race			
White	1	--	--
Black	-0.95	0.39 (0.02-7.93)	0.55
Other	-0.307	0.74 (0.01-147.3)	0.91
No. comorbidities	0.29	1.34 (0.51-3.49)	0.57
Primary tumor			
Colon	1	--	--
Appendix	2.25	9.49 (0.22-41.2)	0.27
Other	2.55	12.8 (0.21-79.5)	0.25
ECOG PS	-0.14	0.87 (0.01-67.8)	0.95
Pre op chemo	-0.98	0.38 (0.02-6.21)	0.51
Postoperative PCI	0.07	1.08 (0.86-1.34)	0.53
Cytoreduction	0.83	2.29 (0.58-8.97)	0.26
Resection margin			
R0	1	--	--
R1	1.92	6.80 (0.25-18.4)	0.28
R2	2.96	19.4 (1.59-25.0)	0.04*
ICU LOS	0.05	1.05 (0.98-1.13)	0.19
Hospital LOS	0.05	1.05 (0.96-1.15)	0.33
Postop. Complic	0.2	1.22 (0.33-4.54)	0.78

OR: Odds Ratio; CI: Confidence Interval; No: number; pre-post: between preoperative and postoperative questionnaire completion; ECOG: Eastern Cooperative Oncology Group; PS: Performance Status; preop: Preoperative; PCI: Peritoneal Carcinomatosis Index; ICU: Intensive Care Unit; LOS: Length of Stay; postop: Postoperative; complic: complications.

life in the three-month postoperative period. In particular, physical health and psychological health demonstrate a modest increase in QoL ratings whereas social relationships and environmental factors are maintained at baseline.

The effect of CRS+HIPEC has been reported by several investigators using a variety of validated QoL tools. Many studies showed that patients who undergo CRS+HIPEC return to baseline health-related QoL in the long-term postoperative period [5-7,12]. However, short-term QoL has differed. A recent meta-analysis of fifteen CRS+HIPEC quality of life studies showed that physical well-

being declined in the early postoperative period but increased by six to twelve months. Intense physical pain decreased postoperatively in half of the patients while overall health-related QoL was preserved, with emotional health showing the greatest improvement [13]. A systematic review, in contrast, demonstrated that QoL scores return to 80-100% of baseline values at 3 months and improve up to 12 months postoperatively in survivors [14]. A recent study on CRS+HIPEC performed on twenty-three peritoneal carcinomatosis patients showed that physical functioning decreased at three months postoperatively. Factors associated with poorer QoL included a higher peritoneal carcinomatosis index (PCI), three month recurrence, and longer operative time [9]. In contrast, a study of forty-three patients who underwent CRS+HIPEC that measured QoL at three months found that functional status returned to acceptable levels and patient age, operative time, hospital length of stay, PCI and postoperative complications were not associated with these results [15]. Our patients experienced similar preservation of health-related quality of life as compared to other major centers with improvement in satisfaction with physical health at three months postoperatively. This may, in part, be related to the relatively low morbidity that our patients experienced. In our study, increased number of days between questionnaires was shown to be associated with improved QoL scores. This indicates that patient perceptions of their well-being will continue to improve as time increases postoperatively. Also in our study, R2 resection margin was associated with worse physical well-being at three months postoperatively, likely related to poorer perception of outcome as well as disease progression.

We elected to use the WHOQOL-BREF as it is a well validated and easily performed questionnaire which is a testament to its practical application. Other instruments that have been used in CRS+HIPEC quality of life studies include the EORTC and FACT-C forms. These forms are internationally accepted tools that also include assessment of overall health, physical well-being, emotional or psychological well-being, and social functioning. As these forms assess the same domains as the WHOQOL-BREF, we elected to use the latter in this study. Our study personnel have experience using the WHOQOL-BREF and we all find it simple to use.

Some of the limitations of this study include the small sample size of patients who consented to partake in the study, as well as the low compliance rate for completing both preoperative and postoperative questionnaires. Slightly more than half of the patients who completed the preoperative questionnaires ultimately completing the postoperative questionnaires and might be due to the variability in our patients backgrounds and unfamiliarity with quality of life studies. Due to the regency of our study data, longer-term postoperative QoL has yet to be assessed. Although QoL studies on CRS+HIPEC have been conducted previously, we wished to share our experience with short-term postoperative QoL as we represent a major urban area of referral with vast population variability.

## Conclusions

In conclusion, despite associated morbidity, patients who underwent CRS+HIPEC maintained their perceptions of their own

health and QoL at three months post-procedurally. Patients may be counseled that in addition to potential prolongation of survival, short-term postoperative health-related quality of life – including physical functioning - is generally preserved or improved after CRS+HIPEC.

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MM was responsible for the study conception and design. SL and PO performed the acquisition of data. RC did the analysis of data. RC and TG prepared the manuscript. YD, SH, BH, MF, and MM reviewed the manuscript.

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