



# Quality of life after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: a narrative review

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**Abstract:** Treatment of peritoneal carcinomatosis utilizing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) has become increasingly common over the past 20–30 years. Significant improvements in survival have been achieved for multiple pathologies with commensurate decreases in peri-operative morbidity and mortality. Despite these improvements, CRS/HIPEC continues to have a notable impact on patients' post-operative quality of life (QOL). To characterize the effect that CRS/HIPEC has on patient QOL, this review identifies and discusses 27 published articles on the topic. Reviewed papers included prospective cohort studies examining the acute post-operative period as well as cross-sectional studies of long-term survivors, with populations as large as 598 patients. Results were heterogenous, yet several trends emerged. Global, physical, and functional QOL tend to decrease significantly post-operatively before returning to baseline at 6–12 months, with long-term survivors showing durable improvement. Social QOL was often diminished as well, though less consistently. Emotional QOL, conversely, tends to improve as early as 3 months post-operatively. Depression, gastrointestinal symptoms, and constitutional symptoms were noted to be prevalent at multiple post-operative timepoints. QOL in both the immediate post-operative period (0–3 months) and longitudinally beyond 12 months were relatively less well-studied.

**Keywords:** Quality of life (QOL); cytoreductive surgery (CRS); hyperthermic intraperitoneal chemotherapy (HIPEC); peritoneal carcinomatosis

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## Introduction

The treatment of peritoneal metastases from intra-abdominal cancers has improved significantly over the past three decades due to the advent of cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC). Without treatment, peritoneal carcinomatosis is a universally fatal diagnosis with a median survival of approximately 6 months (1). This dismal prognosis is improved by treatment with systemic chemotherapy,

but with limited effectiveness possibly due in part to limited uptake across the peritoneum (2). HIPEC has gained popularity as a regional therapy allowing for direct application of chemotherapy to peritoneal disease intra-operatively; combined with the removal of all macroscopic tumor deposits, termed a complete cytoreduction, HIPEC can significantly improve long-term outcomes. Increases in survival after CRS/HIPEC have been observed in patients with peritoneal carcinomatosis from a wide variety

of primary neoplasms including appendiceal neoplasms causing pseudomyxoma peritonei (PMP), colorectal cancer, ovarian cancer, mesothelioma, and gastric cancer (3-7).

Despite these survival benefits in well-selected patient populations, initial experiences with CRS/HIPEC were marred by high rates of peri-operative morbidity and mortality. Complete cytoreduction may involve a complete peritonectomy as well as the removal of involved segments of bowel or other intra-abdominal organs; this extensive resection can lead to prolonged operative times and elevated intra-operative risk (8). Early peri-operative mortality rates were observed to be as high as 5%, while the rates of significant morbidity in initial reports ranged from 25–45% (9-11). Toxicity from the HIPEC portion of the operation was similarly frequent with rates as high as 55–65% (12,13). Since these early studies were reported, there have been substantial improvements with increased experience at specialized centers, however, there has been a persistent misperception that CRS/HIPEC is an unusually morbid procedure. As shown by Foster *et al.* in a recent study of NSQIP data, CRS/HIPEC is a safe procedure with comparable morbidity rates to similarly high-risk intra-abdominal procedures such as an esophagectomy or Whipple procedure (14). Multiple other studies have similarly demonstrated the safety of CRS/HIPEC with acceptable morbidity and mortality rates, even at moderate volume centers (15-18).

Despite this improvement in overall morbidity and mortality, there remains significant concern that these major operations will adversely impact patients' quality of life (QOL) post-operatively. A key factor in improving the patient experience with CRS/HIPEC has been careful patient selection. A patient's disease burden is thoroughly assessed with diagnostic laparoscopy to determine the likelihood of a complete cytoreduction at the time of CRS/HIPEC (19). This prognostication is critically important as the completeness of cytoreduction is a leading factor in post-operative patient outcomes (20,21). As with other high-risk operations, overall patient health and performance status are also predictive of post-operative outcomes and should be weighed thoughtfully before offering surgery (22). Patients are evaluated by a multi-disciplinary team, and it is estimated that less than half of those referred for CRS/HIPEC ultimately undergo cytoreduction (23,24). By following this rigorous selection process, optimizing outcomes can be achieved across all age groups (25).

With CRS/HIPEC now recognized as a safe and

effective procedure in well-selected populations, there has been an increasing focus on patients' post-operative QOL. Short-term impairment of QOL is to be expected following CRS/HIPEC, as with any other major operation; however, the wide distribution of life expectancy across histologies illustrates the importance of optimizing QOL at varying time points. This recovery of QOL is multifactorial and depends on improvement in a patient's symptoms as well as physical, functional, emotional, and social well-being. Evaluation of these factors begins in the pre-operative clinic, where it has been noted that depression, low emotional well-being, poor nutrition, and decreased overall QOL are all associated with worsened post-operative outcomes (26-28). Following surgery, each dimension of QOL requires specific attention from the multidisciplinary team. To design post-operative protocols and programs that address QOL, it is essential to understand how CRS/HIPEC affects each domain of QOL. In this narrative review, we explore the growing body of literature on post-operative QOL in CRS/HIPEC patients and identify where gaps in our knowledge remain. We present the following article in accordance with the narrative review checklist (available at <http://dx.doi.org/10.21037/dmr-20-153>).

## Methods

### *Inclusion criteria*

Published studies included in this review were required to meet a set of criteria pertaining to both patient populations and study design. Reviewed studies were required to include adult patients ( $\geq 18$  years of age) undergoing CRS/HIPEC for peritoneal carcinomatosis from any intra-abdominal primary pathology. Only original randomized controlled, prospective cohort, or cross-sectional studies were eligible for inclusion. Lastly, only studies employing validated instruments for the measurement of healthcare-related QOL were included. Studies published in the English language at any time prior to our literature review in October 2020 were eligible for inclusion.

### *Study identification*

The studies included in this review were initially identified by querying PubMed (MEDLINE) using search terms including "Cytoreductive Surgery", "Heated Intraperitoneal Chemotherapy", "Peritoneal Carcinomatosis", "Post-Operative", "Quality of Life", "Well-Being", and

“Functional Status”. Potentially relevant studies from this search were included if they met the above-described criteria. The references from these studies and previous review articles in this initial search were reviewed as well; ultimately, 27 original articles were identified that met our criteria for review.

### *Narrative review*

Results and conclusions from each of the 27 articles included in this review were examined and summarized. Study design, year of publication, number of patients, primary pathologies, QOL instruments used, and the timing of post-operative assessments were collected in order to characterize each study. Whether or not a baseline, pre-operative assessment was performed was recorded as well. For cross-sectional studies, the median or mean time to follow-up was reported based on available published data. The main conclusions from each article were recorded and summarized as well.

## **Discussion**

### *Assessment of QOL*

Multiple factors can impact patients' QOL following CRS/HIPEC. Patients are often hampered by symptoms from either their disease or the operation, the most frequent of which are pain, diarrhea, constipation, dyspnea, and insomnia (29,30). Anorexia is a common symptom as well, and some patients may even require parenteral nutrition temporarily (31). Beyond somatic symptoms, patients may experience mood dysregulation with many suffering from persistent depression (32). Patients' return to their home life can be complicated by decreases in their social well-being as well, and many experience temporary impairments in their functional well-being or performance status. Taken together, all of these factors lead to limitations in patients' QOL immediately following CRS/HIPEC.

Efforts to mitigate this decrease in QOL depend on accurate measurement and evaluation in each separate domain of well-being. To this end, there are several validated instruments to measure QOL in cancer patients. The most commonly used general QOL questionnaires include the Short Form 36 (SF-36), the Functional Assessment of Cancer Therapy scale (FACT), and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ) (33-37).

The SF-36 is a 36-item questionnaire that assesses eight health domains and can be divided into broader physical and mental components; it is an effective tool for measuring general health perception as well as limitations due to physical, social, emotional, or functional issues (33). The FACT scale similarly measures physical, functional, social, and emotional well-being; the FACT-General (FACT-G) scale contains 28 items to assess QOL broadly, while the FACT-Colorectal (FACT-C) contains an additional colorectal cancer subscale with disease-specific items (34,35). The EORTC-QLQ similarly measures physical, role, emotional, cognitive, and social functioning over a 30-item general scale (EORTC-QLQ C30); as with the FACT-C scale, an additional eight-item colorectal cancer-specific subscale may be added (EORTC-QLQ CR38) (36,37). Overall functional and performance status is also assessed with the Eastern Cooperative Oncology Group (ECOG) scale in many CRS/HIPEC patients (38).

Many studies on QOL following CRS/HIPEC also employ more focused or disease-specific questionnaires. Pain is often evaluated using the Brief Pain Inventory (BPI), designed to assess both the intensity of pain and the interference pain creates in the patient's life (39). Assessment of depression is validated using the Center for Epidemiological Studies Depression scale (CES-D), and sleep quality was assessed in one study on CRS/HIPEC patients using the Pittsburgh Sleep Quality Index (40,41). Less frequently used questionnaires include the Gastro-Intestinal Quality of Life Index, the Psychosocial Concerns questionnaire, and the Life Appreciation scale (42,43). While the SF-36, FACT-G, and EORTC-QLQ C30 were the most commonly encountered instruments in this review, each of these questionnaires has been used in the evaluation of post-operative CRS/HIPEC patients.

### *QOL studies in CRS/HIPEC patients (2001–2020)*

There have been two previous systematic reviews of QOL after CRS/HIPEC that we were able to identify, both published in 2014 (44,45). Shan *et al.*, in a review and meta-analysis of 15 studies, concluded that healthcare-related QOL declined post-operatively at the 3- to 4-month timepoint, but then improved to pre-operative levels at 12 months. Benefits beyond 12 months were less clear, but likely continued for multiple years in surviving patients (44). Seretis *et al.*, reviewing 20 studies, likewise found that QOL decreases significantly in the acute post-operative period with improvement to approximately baseline levels between

6 and 12 months. Furthermore, this group concluded that QOL actually improved from baseline in long-term survivors beyond 12 months (45). Multiple additional studies have been published since the publication of these reviews, including several with larger sample sizes than any study from prior to 2014, prompting this updated review.

In our review of the literature published prior to October 2020, we were able to identify 27 studies on QOL after CRS/HIPEC (Table 1). Seventeen of these manuscripts were generated from prospective cohort studies, with one other paper using a retrospective review of prospectively collected QOL data; these papers using prospectively collected data had the advantage of measuring baseline QOL prior to surgery (29,30,32,42,46-59). One of these studies, and an additional eight papers, employed cross-sectional surveys of post-operative patients that tended to capture longer-term survivors from CRS/HIPEC (30,38,41,43,60-64). Lastly, one paper utilized QOL data collected during a clinical trial (65).

Given the low overall volume of CRS/HIPEC patients even at specialized centers, most studies included patients with multiple different primary histologies. For those that focused on a single histology, PMP was the most common diagnosis (30,50,53,63). The majority of studies had less than 100 patients enrolled, though samples sizes ranged from 5 to 598 patients. Follow-up intervals were variable, with 3 months being the most common timing of the initial post-operative QOL assessment. Eight studies included data from earlier than 3 months post-operatively, with the shortest interval being 2 weeks post-operatively in two separate studies (42,46,53,55,57-59,65). Follow-up in prospective studies typically continued for 12–24 months at regular intervals, with two studies continuing follow-up to 36 or 48 months (30,55). Attrition due to survival and patient response rates substantially impacted sample sizes at later timepoints in all studies, potentially limiting the utility of data from longer-term surveys in prospective cohorts. Cross-sectional studies, conversely, had mean or median follow-up intervals ranging from 10 months to 5 years.

### Global QOL

Each study included in this review used metrics that allow us to examine post-operative QOL either globally or broken down into multiple domains. In aggregate, there was broad agreement that there is an acute worsening of QOL immediately following CRS/HIPEC. There were discrepancies, however, in the duration of this decline in

QOL before returning to baseline. The most optimistic timing for a return to baseline came from the earliest study, by McQuellon *et al.* in 2001, suggesting that QOL improves by 3 months post-operatively (46). Importantly, the patients in this study were evaluated at 2 weeks post-operatively, allowing for relative improvements to be observed at the 3-month timepoint. Ford *et al.*, in a cross-sectional study, similarly concluded that acceptable QOL can be achieved by 3 months, though pre-operative baseline QOL was not measured in this study (38).

The majority of studies, however, found that patients required between 6–12 months to recover to baseline QOL (Table 2). This group included the three largest studies by Dodson *et al.*, Passot *et al.*, and Stearns *et al.*, accounting for 851 patients between them with a broad range of pathologies (30,42,56). Each of these three studies employed different instruments to measure QOL as well, potentially strengthening the broader consensus that QOL returns to baseline at 6–12 months.

Cross-sectional studies suggest that this improved overall QOL at 6–12 months is sustained in long-term survivors. These studies are limited by the lack of a baseline measurement of QOL prior to CRS/HIPEC, but they each independently conclude that patients achieve acceptable long-term QOL after surgery. Kirby *et al.* found similar results even in patients undergoing re-do CRS/HIPEC for PMP (63). Comparisons to control populations were not uniformly made, though Tan *et al.* and Chia *et al.* separately found that long-term QOL is similar to reference populations of cancer patients not undergoing CRS/HIPEC (62,64). Despite this adequate recovery, specific functional deficits remained in several studies, necessitating closer inspection of recovery in each domain of QOL.

### Physical QOL

Trends in physical well-being mirrored those in global QOL in most studies. While a handful of studies stated that physical QOL improved to baseline levels by 3 to 4 months, the vast majority of prospective studies found that patients required at least 6–12 months to return to baseline levels. Thirteen separate studies independently identified somewhere between 6–12 months as the timepoint for recovery of baseline physical QOL (29,32,42,48-54,56-58). Three of these studies further stated that physical well-being on FACT-G can improve to above baseline levels at 12 months or later; however, results in survivors past 1 year are mixed (32,51,57). A recent paper by Stearns *et al.*

**Table 1** Characteristics of published studies on quality of life after CRS/HIPEC (2001–2020)

First author	Year	Design	N	Primary pathology	QOL metrics used	Baseline assessment	Post-operative assessment timing
McQuellon	2001	Prospective cohort	64	Multiple	SF-36, FACT-C, FACT-G, BPI, CES-D, ECOG	Yes	2 weeks, 3, 6, and 12 months
McQuellon	2003	Cross-sectional	17	Multiple	SF-36, FACT-C, CES-D, Life Appreciation Scale, Psychosocial Concerns Questionnaire, ECOG	No	Mean: 5.3±1.6 years (range, 3.1–8.0 years)
Schmidt	2005	Cross-sectional	20	Multiple	EORTC-QLQ C30	No	Mean: 4 years (range, 1–8 years)
Tuttle	2006	Prospective cohort	35	Multiple	FACT-C, FACT-G, TOI	Yes	4, 8, and 12 months
Knutsen	2006	Prospective cohort	5	Multiple	FACT-C, FACT-G, TOI	Yes	4 months
McQuellon	2007	Prospective cohort	96	Multiple	FACT-C, FACT-G, TOI, SF-36, CES-D, BPI, ECOG	Yes	3, 6, and 12 months
Lim	2007	Clinical trial	28	Sarcoma	FACT-G, SF-36	Yes	6–8 weeks and 3–6 months
McQuellon	2008	Prospective cohort	58	Appendiceal	FACT-C, FACT-G, TOI, SF-36, CES-D, ECOG	Yes	3, 6, 12, and 24 months
Jess	2008	Prospective cohort	23	PMP	SF-36, EORTC-QLQ CR38	Yes	3, 6, 12, 18, and 24 months
Zenasni	2009	Cross-sectional	68	Multiple	EORTC-QLQ CR38	No	Median: 2.4 years (range, 1.1–9.1)
Macri	2009	Prospective cohort	17	Multiple	FACT-G	Yes	3 and 6 months
Alves	2010	Prospective cohort	46	PMP	EORTC-QLQ C30	Yes	1, 3, 6, and 12 months
Lim	2010	Prospective cohort	32	Multiple	EORTC-QLQ C30	Yes	1, 3, 6, and 12 months
Hill	2011	Prospective cohort	62	Multiple	FACT-C, FACT-G, TOI, SF-36, CES-D, BPI, ECOG	Yes	3, 6, and 12 months
Duckworth	2012	Cross-sectional	102	Multiple	FACT-C, FACT-G, TOI, SF-36, Pittsburgh Sleep Quality Index	No	Mean: 4.2 years (range, 1.1–16.5 years)
Tsilimparis	2013	Prospective cohort	90	Multiple	EORTC-QLQ C30	Yes	1, 6, 12, 24, and 36 months
Kirby	2013	Cross-sectional	63	PMP	FACT-C, FACT-G	No	Median: 31 months (range, 6–161 months)
Tan	2013	Cross-sectional	27	Multiple	EORTC-QLQ C30	No	Mean: 10 months (range, 6–16 months)
Passot	2014	Prospective cohort	216	Multiple	GIQLI	Yes	1, 3, 6, and 12 months
Chia	2014	Cross-sectional	63	Multiple	EORTC-QLQ C30	No	Mean 1.3 years (range, 0.24–10.18 years)

Table 1 (continued)



Table 1 (continued)

First author	Year	Design	N	Primary pathology	QOL metrics used	Baseline assessment	Post-operative assessment timing
Albertsmeier	2014	Prospective cohort	40	Multiple	EORTC-QLQ C30	Yes	3, 9, and 18 months
Dodson	2016	Prospective cohort	598	Multiple	FACT-G, FACT-C, TOI, SF-36, BPI, CES-D, ECOG	Yes	3, 6, 12, and 24 months
Ford	2016	Cross-sectional	33	Multiple	FACT-G, ECOG	No	3 months
Hinkle	2017	Retrospective review	36	Multiple	FACT-C	Yes	2 weeks, 1, 3, 6, and 12 months.
Stearns	2018	Prospective cohort	137	PMP	EORTC-QLQ C30	Yes	3, 6, 9, 12, 18, 24, 36, 48, and 60 months (first period). Cross-sectional survey at mean of 8.11 years (second period)
Kopanakis	2018	Prospective cohort	80	Multiple	FACT-C	Yes	1, 3, 6, 12, 18, and 24 months
Ali	2020	Prospective cohort	46	Mesothelioma	FACT-G, FACT-C, TOI, SF-36, BPI, CES-D	Yes	3, 6, 12, and 24 months

BPI, Brief Pain Inventory; CES-D, Center for Epidemiological Studies Depression scale; ECOG, Eastern Cooperative Oncology Group; EORTC-QLQ, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; FACT-C, Functional Assessment of Cancer Therapy-Colorectal; FACT-G, Functional Assessment of Cancer Therapy-General; GIQLI, Gastrointestinal Quality of Life Index; SF-36, Short Form 36; TOI, Trial Outcome Index.

suggested that 18 months is needed to return to baseline physical status (30). The 90 patients included in a study by Tsilimparis *et al.* experienced an even more prolonged recovery, with decreased physical functioning scores on EORTC QLQ-C30 persisting for 24 months post-operatively; a return to baseline was only observed in the six patients who survived and responded to follow-up at 36 months (55).

Long-term survivors assessed in cross-sectional studies also had mixed results for physical QOL, though they generally did not compare favorably with reference populations. Schmidt *et al.* and Duckworth *et al.* both found that physical QOL was below that of a general control population at a mean of 4 and 4.2 years, respectively (41,60). Tan *et al.* found no difference from a reference population of cancer patients, with Chia *et al.* finding similar results when comparing CRS/HIPEC patients to patients undergoing outpatient cancer treatment (62,64). The latter study compared CRS/HIPEC patients to metastatic or recurrent cancer patients as well, and in this instance CRS/HIPEC patients did have significantly higher physical functioning

scores on EORTC QLQ-C30.

When viewed independently of a reference population, however, long-term survivors from CRS/HIPEC demonstrated adequate physical well-being. Zenasni *et al.* found that 95.7% of patients had high scores for physical functioning on EORTC QLQ-CR38 at a median of 2.4 years (61). McQuellon *et al.*, in a 2003 study, similarly found high physical well-being scores in 17 patients at a mean of 5.3 years after surgery. Of these 17 patients, 10 had baseline QOL surveys completed at 6 months post-operatively, and over time they had shown significant improvement in physical QOL (43). While this is a small sample size, it is representative of a larger trend in the literature that physical QOL decreases in the first year after surgery before improvement to patients' approximate baseline.

### *Emotional QOL and mental health*

Relative to overall QOL, emotional QOL and mental health consistently took less time to recover to baseline

**Table 2** Main findings from published studies on quality of life after CRS/HIPEC (2001–2020)

First author	Year	Main findings
McQuellon	2001	QOL decreases considerably at 2 weeks post-operatively before improving to baseline or better over 3–12 months. Patients experience improvement in pain post-operatively, but depression is a persistent feature in 29% of patients
McQuellon	2003	Long-term survival with good QOL is possible for selected patients following CRS/HIPEC. Long-term survivors experience improvement in physical and functional QOL compared to surveys at 6 months post-operatively
Schmidt	2005	Long-term survivors achieve satisfactory QOL post-operatively, though long-term survivors have impairments in social QOL and functional status relative to the general population. Symptoms including diarrhea and constipation remain frequent
Tuttle	2006	Global QOL was similar to baseline levels at 4 months and was significantly improved at 8 and 12 months. Social well-being remained unchanged from baseline, while improvements were seen in all other domains
Knutsen	2006	Overall QOL based on all metrics returns to baseline at 4 months post-operatively
McQuellon	2007	Acceptable QOL and return of functional status can be achieved between 3 and 6 months post-operatively, though some deficits remain. Pain improves post-operatively, but 20–30% of patients continue to experience depressive symptoms
Lim	2007	QOL scores at 6–8 weeks following CRS/HIPEC were lower than baseline but returned to baseline on surveys collected between 3 and 6 months post-operatively
McQuellon	2008	Global, physical, and functional well-being declined at 3 months after surgery but improved to near baseline levels at 6 and 12 months. Emotional QOL improved significantly, yet 33% of patients experienced persistent depressive symptoms
Jess	2008	Patients experienced a significant decrease in global and physical QOL at 3 months after surgery, returning to normal at 6 months post-operatively. Social and emotional QOL were not significantly changed post-operatively
Zenasni	2009	Long-term survivors reported good to very good QOL in 19 out of 21 dimensions explored, with deficits remaining for future prospects and sexual functioning
Macri	2009	Global, physical, and functional well-being decrease initially after surgery before returning to baseline at 6 months post-operatively
Alves	2010	Global, physical, and social functioning decrease significantly at 1 month post-operatively but return to baseline by 12 months. Pain improves as well, though only in patients undergoing a complete cytoreduction
Lim	2010	QOL scores return to baseline at 3 months for 53% of patients, with 73% returning to baseline by 12 months
Hill	2011	Pain, physical, and social well-being are worsened at 3–6 months and recover by 12 months. Emotional well-being improves from baseline
Duckworth	2012	Long-term survivors from CRS/HIPEC achieve similar healthcare-related QOL as the general population, though pain is a persistent issue and some long-term physical and functional deficits remain
Tsilimparis	2013	Patients recovering from CRS/HIPEC have an initial decrease in QOL in almost all elements at 1 month post-operatively with most recovering by 6–12 months. Long-term survivors achieve similar QOL as a reference population
Kirby	2013	QOL was not greatly impacted in long-term survivors after repeat CRS/HIPEC for PMP. QOL was largely similar after both initial and redo procedures
Tan	2013	Global health and all domains of QOL are similar to a reference population of cancer patients not undergoing CRS/HIPEC
Passot	2014	Overall QOL is significantly decreased up to 6 months post-operatively but returns to baseline after 12 months. Emotional QOL improves above baseline
Chia	2014	Patients achieve good quality of life after CRS/HIPEC when compared to outpatient cancer patients and a reference population of patients with recurrent or metastatic cancer

Table 2 (continued)

Table 2 (continued)

First author	Year	Main findings
Albertsmeier	2014	Symptoms increase while physical and social functioning decrease at 3 months post-operatively before all recovering to baseline by 9 months
Ford	2016	Patients achieved an acceptable functional status within 3 months post-operatively
Dodson	2016	General and physical QOL decline post-operatively but improve to baseline at 6–12 months. Social QOL displays a longer recovery period, while emotional QOL actually improves from baseline. Poor scores on QOL metrics are associated with decreased survival
Hinkle	2017	All domains of QOL decreased initially post-operatively but improved to baseline at 6 months. Early recurrence within the first year post-operatively decreases QOL significantly at 6 and 12 months
Kopanakis	2018	Significant worsening of QOL was observed in all subscales with subsequent improvement at intervals between 3–12 months. Improvement in physical well-being is related to symptom eradication, whereas emotional well-being relates to prognosis
Stearns	2018	Physical, and social functioning decrease post-operatively before returning to baseline by 18 months. Emotional functioning improves post-operatively. Symptoms generally improve after 12 months, though some cognitive and gastrointestinal symptoms persist. Long-term QOL is comparable to a reference population
Ali	2020	Almost all measures of QOL significantly decreased at 3 months with subsequent improvement beginning at 6 months. Select subscales including global health and social functioning decreased again at 24 months

CRS/HIPEC, cytoreductive surgery with hyperthermic intraperitoneal chemotherapy; QOL, quality of life; PMP, pseudomyxoma peritonei.

levels or better. While overall QOL declines acutely post-operatively, there is no consensus across prospective studies that emotional health declines at all. Three separate studies found that emotional QOL did not change post-operatively, with Jess *et al.* showing a non-significant trend towards higher emotional functioning (29,50,52). Seven other studies did identify a significant increase in emotional QOL post-operatively; Stearns *et al.*, Dodson *et al.*, Hill *et al.*, and McQuellon *et al.* in a 2008 paper all independently observed this improvement in emotional health beginning at the first post-operative assessment, occurring at 3 months post-operatively in each study (30,42,51,53,54,56,57). This timing of the first post-operative survey may mask a transient decrease in emotional health prior to 3 months, as Kopanakis *et al.* showed that emotional well-being decreased at 1 month prior to improving to above baseline levels at 3 months (57). Any decrease from baseline does not appear to be sustained, however, and the longest recovery time for emotional QOL in any study was 6 months.

This rapid recovery of baseline emotional QOL may be related to a relatively low baseline as many patients experience depressive symptoms both before and after surgery. Multiple studies included in this review from Wake Forest have used the CES-D to evaluate levels of clinically significant depression in post-operative CRS/HIPEC patients. The most recent paper from this group, by Ali

*et al.*, found that 31% of patients had scores on CES-D consistent with depression at baseline; this rate decreased initially post-operatively before increasing again to 37% of patients at 24 months (32). Even if rates of depression decrease in survivors post-operatively, they are persistently measured at 24–33% at 12 months (46,49,51,56).

Whether these seemingly high rates of depression are significantly different than the general population is not clear. Schmidt *et al.*, Duckworth *et al.*, and Tan *et al.* all showed that emotional well-being in CRS/HIPEC patients is similar to a control general population; these studies utilized combinations of the EORTC QLQ-C30, FACT-C, and SF-36 scales without CES-D, however, limiting our ability for comparison (41,60,62). Chia *et al.* showed that CRS/HIPEC long-term survivors do have higher emotional functioning scores on EORTC QLQ-C30 than both outpatient cancer patients and those with metastatic disease, arguing against long-term emotional health issues relative to similar patients (64). In aggregate, the evidence suggests that CRS/HIPEC patients experience a fairly quick recovery of emotional QOL while still experiencing persistent depression.

### Social QOL

Various QOL instruments measure social well-being



or QOL within the context of how patients' illness and treatment affect their relationships with friends and family. Changes in social QOL tended to be subtle, with several papers identifying no significant change from baseline at any point post-operatively (48-52). Of these, two papers from McQuellon *et al.* did show a non-significant trend towards decreased social functioning on SF-36 at 12 months post-operatively (49,51).

Notably, each of these papers finding no change in social well-being were among the earliest studies on QOL after CRS/HIPEC. More recent, and often larger, studies consistently showed decreases in social QOL. For papers that did find a significant decrease in social QOL, recovery times were generally 12 months or longer, with larger cohorts from Stearns *et al.* and Tsilimparis *et al.* only achieving baseline levels at 18 or 24 months, respectively (30,42,53-55). Only one study found that patients never regained baseline social QOL, albeit the largest in this review; Dodson *et al.* showed that social well-being on FACT-C decreased at 3 months post-operatively and did not fully recover by 24 months (56). Ali *et al.* conversely found that social well-being increased post-operatively beginning at 3 months, though this finding was an outlier among all studies reviewed (32).

Results from cross-sectional studies were largely consistent with those from prospective studies. Zenasni *et al.* found that 88.4% of patients had high social functioning scores on EORTC QLQ-C30 at a median follow-up of 2.4 years, but other published data was more neutral with regard to social QOL in long-term survivors (61). Duckworth *et al.* found no difference between CRS/HIPEC patients and a general control population using multiple instruments, while Schmidt *et al.* found decreased scores on EORTC QLQ-C30 at a mean of 4 years when compared to a general population (41,60). Results were slightly more positive when comparing to populations of cancer patients; Tan *et al.* found no significant difference at a mean of 10 months post-operatively, whereas Chia *et al.* concluded that CRS/HIPEC patients had higher social functioning than other cancer patients on EORTC QLQ-C30 at a mean of 1.3 years post-operatively (62,64).

### ***Functional and performance status***

Assessment of a patient's functional status following surgery overlaps somewhat with physical QOL and is treated differently by various instruments. For example, the SF-36 questionnaire assesses limitations in common activities

and includes these in the score for patients' physical functioning. The FACT scale instead separates functional well-being into a category distinct from physical well-being, focusing on a patient's ability and satisfaction in their return to normal activities. Studies employing FACT or ECOG tended to report functional QOL separately from physical QOL, though with similar findings.

Using FACT-C, multiple groups showed that patients were able to regain baseline functional well-being by 6–12 months post-operatively (51,52,57,58). They each showed decreases in functional well-being on initial post-operative evaluations with McQuellon *et al.*, in a 2001 paper, notably showing severe limitations in functional well-being at 2 weeks after surgery (46). For survivors at 1 year post-operatively, there was evidence from both Tuttle *et al.* and McQuellon *et al.*, in a 2007 paper, that functional well-being increases above baseline levels (48,49).

Long-term survivors are not uniformly able to return to their normal activities, even up to several years after their operation. By example, Hill *et al.* found that only 47% of patients were able to return to normal activities at 12 months (54). Longer term cross-sectional analyses were slightly more positive; McQuellon *et al.*, in a 2003 paper including 17 patients, showed that 88% had a score of 0 on the ECOG scale, with functional well-being improved at a mean of 5.3 years post-operatively compared to baseline surveys at 6 months (43). Despite this high functional status based on ECOG and FACT, the same study found that only 47% of patients had returned to work with another 24% on disability. Kirby *et al.* showed a considerably higher percentage of patients returning to work with 90% returned at a median follow-up of 31 months, though this study only included patients with PMP (63). Studies including more aggressive pathologies suggested higher rates of long-term disability. Duckworth *et al.* notably found that 45% and 84% of patients were limited in moderate or vigorous activity, respectively, at a mean of 4.2 years post-operatively (41). While many patients recover to pre-operative performance status within a year after surgery, there is ample evidence that others experience enduring functional limitations.

### ***Pain and other somatic symptoms***

Post-operative CRS/HIPEC patients experience a constellation of frequent symptoms both prior to and after surgery. Abdominal pain and gastrointestinal symptoms such as anorexia, nausea, constipation, and diarrhea are frequent, as are constitutional symptoms like fatigue and insomnia.

The impact that surgery has on these symptoms is variable. Multiple prospective studies have shown that pain, typically assessed using the BPI, improves post-operatively after an initial worsening. Hill *et al.* and Tsilimparis *et al.* both found that pain increased initially after surgery before returning to baseline levels. McQuellon *et al.* concluded in 2007 that pain actually improves from baseline levels at 12 months, with only 8% of patients reporting intense pain compared to 17% pre-operatively (49,54,55). This improvement may be dependent on the success of the operation, as Alves *et al.* showed that only patients with a complete cytoreduction experienced improvement in pain; those undergoing debulking only experienced no relief (53).

Other somatic symptoms appeared to be more persistent in long-term survivors. Despite finding that pain improves to baseline levels, Tsilimparis *et al.* showed that fatigue, dyspnea, insomnia, and diarrhea all remain frequent in long-term survivors (55). This mirrors the findings of Schmidt *et al.* that patients have high rates of constipation and diarrhea relative to the general population despite having comparable pain levels (60). Fatigue and insomnia were particularly common in survivors. Tan *et al.* showed that CRS/HIPEC patients at a mean of 10 months post-operatively experience higher rates of fatigue than a reference population of cancer patients, and Kirby *et al.* estimate that 27% of CRS/HIPEC patients with PMP experience significant fatigue at a median of 31 months following surgery (62,63). This may be related to insomnia, as Duckworth *et al.* found that 56% of patients with multiple pathologies continue to experience insomnia at a mean follow-up of 4.2 years (41). Lastly, sexual dysfunction was infrequently evaluated but may be prevalent in long-term patients; Zenasni *et al.* found that 77% of patients reported issues with sexual function at a median follow-up of 2.4 years after surgery (61). Altogether, these findings show that multiple symptoms may decrease in the first year after surgery but remain prevalent in long-term survivors.

## Summary

In this review of 27 published articles on QOL after CRS/HIPEC, several trends in the literature became clear. In the majority of studies, global QOL decreases acutely post-operatively with an eventual return to baseline at approximately 6–12 months. This improvement appears to be sustained in long-term survivors. When examining the domains of QOL individually, both physical and functional QOL mirrored this trend in global QOL with

an acute decline post-operatively followed by recovery to baseline levels at 6–12 months. Some functional limitations persist, but many long-term survivors are able to return to normal activities. Social QOL was often diminished post-operatively as well, though less dramatically, and the time interval to regain baseline social QOL tended to be 12 months or longer. Emotional QOL was the least affected of all domains with many studies actually showing improvements from baseline emotional QOL post-operatively; persistent depression was an issue in long-term survivors, however. Regarding somatic symptoms, patients were generally observed to have less pain post-operatively, but other gastrointestinal and constitutional symptoms remained prevalent.

As utilization of CRS/HIPEC continues to increase across various histologies, the emphasis on post-operative QOL at different timepoints will only grow in importance. Early cohorts of CRS/HIPEC patients suffered from limited life expectancy, as evidenced by the significant attrition in the earliest studies reviewed here. However, there have been major improvements for several subsets of patients. By example, those with PMP secondary to low-grade appendiceal mucinous neoplasms (LAMNs) can expect a median survival of approximately 20 years after a successful cytoreduction (66). Survival benefits are more limited in the treatment of more aggressive, high-grade neoplasms; despite also arising from the appendix, appendiceal adenocarcinoma has a median overall survival of 91 months, decreasing to only 32 months with the presence of high-risk signet ring cells (67). Aggressive neoplasms from other sites in the abdomen have similar or shorter expected survival, but the overall trend in survival after CRS/HIPEC has been incremental improvement. Cross-sectional studies of long-term survivors offer some insight on longitudinal QOL concerns, but overall the existing literature on QOL after CRS/HIPEC is heavily weighted towards the first 12 months after surgery. As the number of long-term survivors following CRS/HIPEC continues to grow, further studies will be necessary to better characterize this population's QOL and identify their needs. Improved understanding of this population will be essential for the successful implementation of survivorship programs and resources at CRS/HIPEC centers.

To maintain improvements in QOL, these programs should focus on interventions that have been shown to improve QOL in post-operative cancer patients. Patient education, psychological counseling, exercise programs, and cognitive therapy have all been shown to be effective

in improving post-operative QOL in various cancer populations (68-70). Some somatic symptoms such as fatigue and insomnia may be improved by these programs, while others would likely benefit from pharmacologic interventions. Gastrointestinal symptoms are particularly prevalent and can be addressed with patient-tailored regimens of laxatives, pro-motility agents, and anti-diarrheal agents. Depression, a similarly prevalent symptom in post-operative patients, is often treated by a combination of anti-depressant therapy, neurostimulation, and psychiatric counseling (71). Pre-operative psychiatric “prehabilitation” programs may also play an important role in decreasing rates of depression in future patients (72).

Benefits from the development of these programs and resources would not be limited to long-term survivors. An equally important area for improvement is the first several months post-operatively, which remain less well understood despite significant fluctuations in QOL (73). This was the period associated with the most dramatic decrease in QOL across nearly all studies, yet it is the least well-studied. Of the 27 papers reviewed here, only eight assessed QOL prior to 3 months post-operatively. This lack of published data focusing on QOL in the immediate post-operative period potentially limits the ability of physicians to design protocols that treat and preempt frequent issues. It is not clear why there is a lack of data in the first 3 months after surgery, but to better address the symptoms that patients face following surgery, this critical period requires further attention. Continued study of the patient experience both in this acute post-operative period and in the period following 1 to 2 years post-operatively will ensure that increases in longevities are matched by improvements in QOL.

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