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Quality-of-Life Evaluation After Cytoreductive Surgery with Hyperthermic Intraperitoneal Chemotherapy

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Abstract

Background—Cytoreductive surgery (CS) with hyperthermic intraperitoneal chemotherapy (HIPEC) for peritoneal metastases can alleviate symptoms and prolong survival at the expense of morbidity and quality of life (QoL). This study aimed to monitor QoL and outcomes before and after HIPEC.

Methods—A prospective QoL trial of patients who underwent HIPEC for peritoneal metastases from 2000 to 2015 was conducted. The patients completed the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), the Functional Assessment of Cancer Therapy + Colon Subscale (FACT-C), the Brief Pain Inventory, the Center for Epidemiologic Studies Depression scale, and the Eastern Cooperative Oncology Group (ECOG) performance status at baseline, then 3, 6, 12, and 24 months after HIPEC. The trial outcome index (TOI) was analyzed. Proportional hazards modeled the effect of baseline QoL on survival.

Results—The 598 patients (53.8 % female) in the study had a mean age of 53.3 years. The overall 1-year survival rate was 76.8 %, and the median survival period was 2.9 years. The findings showed a minor morbidity rate of 29.3 %, a major morbidity rate of 21.7 %, and a 30-day mortality rate of 3.5 %. The BPI ($p < 0.0001$) and worst pain ($p = 0.004$) increased at 3 months but returned to baseline at 6 months. After CS + HIPEC, FACT-C emotional well-being, SF-36 mental component score, and emotional health improved (all $p < 0.001$). Higher baseline FACT-General (hazard ratio [HR], 0.92; 95 % confidence interval [CI], 0.09–0.96), FACT-C (HR, 0.73; 95 % CI 0.65–0.83), physical well-being (HR, 0.71; 95 % CI 0.64–0.78), TOI (HR, 0.87; 95 % CI 0.84–0.91), and SF-36 vitality (HR, 0.88; 95 % CI 0.83–0.92) were associated with improved survival (all $p < 0.001$). Higher baseline BPI (HR, 1.1; 95 % CI 1.05–1.14; $p < 0.0001$), worst pain (HR,

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1.06; 95 % CI 1.01–1.10; $p = 0.01$), and ECOG (HR, 1.74; 95 % CI 1.50–2.01; $p < 0.0001$) were associated with worse survival.

Conclusions—Although HIPEC is associated with morbidity and detriments to QoL, recovery with good overall QoL typically occurs at or before 6 months. Baseline QoL is associated with morbidity, mortality, and survival after HIPEC.

Cytoreductive surgery (CS) with heated intraperitoneal chemotherapy (HIPEC) has been used to treat peritoneal metastases or “carcinomatosis” from varying primary sites including the appendix, stomach, small bowel, ovary, mesothelium, and colon.^{1–7} Although HIPEC can be associated with high morbidity (minor 20 %, major 20 %) and mortality (1–8 %), it provides an opportunity for long-term survival, tumor control, and improvement of symptoms not achievable with other therapies for select patients.^{8–11} The high rates of morbidity are related to the extent of the procedure, comorbidities, and the effects of intraperitoneal chemotherapy on the bowel and its systemic hematologic effects.^{12–14} Studies have associated HIPEC with a wide variety of complications that are predominantly infectious, with extended hospital stays, prolonged recovery with anxiety, sleep disturbances, and depressive symptoms.^{13,15–21}

Peritoneal carcinomatosis represents stage 4 disease and is associated with substantial impairments to quality of life (QoL) due to abdominal distention, pain, early satiety, decreased energy, malnutrition, ascites, cachexia, and bowel obstruction. Although some patients are long-term disease-free survivors after HIPEC, most succumb to their disease. Health-related QoL is defined as the patient's assessment of the impact that their illness and its medical treatment has on their function including physical, psychological, social, and somatic, as well as on their general well-being.²² Therefore, careful evaluation of QoL after HIPEC is important to an evaluation of its impact on patients.

After HIPEC, QoL typically declines, but recovery typically occurs 3–6 months later. After this initial period of significant physical recovery, the benefits of extended survival and improved QoL emerge. Short-term morbidity and mortality have been reduced secondary to improved surgical techniques and patient selection. Therefore, it is important to determine the success of a palliative treatment such as HIPEC in terms of both survival and QoL. Higher baseline QoL predicts perioperative morbidity, treatment benefit, and overall survival for patients with metastatic and localized disease.^{23,24}

The current study had a twofold aim: (1) to examine the impact of HIPEC on QoL and (2) to examine the predictive value of preoperative QoL assessments on postoperative morbidity and mortality.

Methods

The data for this study were obtained from a review of a prospectively maintained, ongoing HIPEC QoL clinical trial of patients enrolled from 2000 to 2015. This study was approved by the Wake Forest Baptist Health Institutional Review Board. Patients completed a self-administered QoL survey before HIPEC, then 3, 6, 12, and 24 months after HIPEC. The survey consisted of the Short Form-36 (SF-36), the Functional Assessment of Cancer

Therapy + Colon (FACT-C), the Brief Pain Inventory (BPI), the Center for Epidemiologic Studies Depression (CES-D) scale, and the Eastern Cooperative Oncology Group (ECOG) performance status rating. Clinicopathologic factors including tumor origin, peritoneal carcinomatosis index (PCI), resection status, morbidity, and mortality were analyzed.

QoL Instruments

The Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) is a 36-item questionnaire composed of eight areas: physical functioning (PF), role physical (RP), role emotional (RE), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), and mental health (MH).^{25,26} The Mental Component Summary (MCS) and the Physical Component Scales (PCS) are derived from the eight areas. Higher scores indicate better function, with either less psychological stress or functional limitations.

In this study, FACT-C was used to address symptoms related to peritoneal carcinomatosis. The FACT-C is a combination of the 27-item FACT-General FACT-G with a 9-item colon cancer subscale (CCS). The FACT-G is composed of four subscales: physical well-being (PWB), social well-being (SWB), emotional well-being (EWB), and functional well-being (FWB).²⁴ The survey uses a 5-point Likert scale to rate patient symptoms for the previous week. The trial outcome index (TOI) is used as a summery index of physical and functional outcomes. Higher scores indicate higher QoL. Calculation of TOI is determined by adding PWB + FWB + CCS.²⁴

The BPI is a 10-item questionnaire that uses a Likert scale of 0 (no pain) to 10 (worst pain imaginable) to assess pain during the past week and examines whether pain interfered with activity, mood, normal work, relationships, and sleep.²⁷ The CES-D is a 20-item questionnaire that assesses how often a person has depressive symptoms in sleep, appetite, or mood during the past week.⁴ It uses a Likert scale of 0 (none), 1 (some), 2 (occasional), and 3 (most of the time).²⁸ The CES-D uses scores of 16, 23, and 28 to screen respectively for possible, probable, and case depression. The ECOG is graded as 0 (normal), 1 (ambulatory with symptoms), 2 (bed rest < 50 % of daytime hours), 3 (bed rest > 50 % of daytime hours), and 4 (completely bedridden).²⁹

Surgical Data

Procedures were performed at a single center using uniform techniques.^{7,13,17} Briefly, patients underwent resection via laparotomy (in a few of the more recent cases of laparoscopy) with a goal of removing all apparent peritoneal disease. Via closed technique and a perfusion circuit, hyperthermic intraperitoneal chemotherapy was perfused for 120 min, with a target flow of 1 L/min and an outflow temperature of 40 °C. After perfusion, the abdomen was definitively closed.

The operative variables included length of surgery, estimated blood loss, chemotherapy agent, PCI index, and completeness of cytoreductive surgery. Completeness of cytoreduction was defined as R0/1 (no gross disease with negative or with positive microscopic margins), R2a (< 5 mm of residual disease), R2b (5–20 mm of residual disease), and R2c (> 20 mm of residual disease).

Complications were scored for the first 90 days after surgery and graded according the Clavien-Dindo criteria as follows: 0 (no complications), 1 (deviation from the normal course without a need for intervention), 2 (complication requiring pharmacologic intervention [blood transfusion, total parenteral nutrition]), 3a (complication requiring endoscopic or radiologic intervention), 3b (complication requiring surgical intervention), 4 (any life-threatening complication requiring intensive care unit care), and 5 (death).³⁰ If more than one complication occurred, the most severe complication was analyzed.

Statistical Analysis

Categorical variables are described as totals and frequencies, and continuous data are expressed as median or mean. One-way analysis of variance (ANOVA) was used for the mean of continuous variables and χ^2 tests for nominal variables. Univariate analysis was used to determine the relationships of preoperative variables and QoL measurements to the occurrence of adverse events. Pre-operative variables significantly associated with morbidity and mortality in the univariate analysis and those that achieved a *p* value lower than 0.2 were used to construct multivariable models. The logistic regression coefficient was used to estimate odds ratios for each of the independent variables in the model. Proportional hazards were used to model the effect of baseline QoL on overall survival. Overall survival was evaluated using the Kaplan–Meier method. A *p* value lower than 0.05 was considered statistically significant. The statistical analyses were performed using SAS (version 9.3; SAS, Cary, NC, USA).

Results

The participants in the study were 598 (71.5 %) of 836 patients who underwent HIPEC. The clinical characteristics of the QoL cohort are presented in Table 1. The mean age of the patients was 53.3 years, and 53.8 % were female. The mean PCI was 14.4. The majority of the patients had an appendiceal (58 %) or colorectal (21.8 %) primary tumor, and 88.3 % had an ECOG score of 0 or 1. The 30-day minor morbidity (grade 1 or 2) rate was 29.3 %. The major morbidity (grade 3 or 4) rate was 21.7 %, and the mortality was 3.5 %. The 30-day read-mission rate was 16.4 %. The hospital stay was significantly longer for the patients who had morbidity or mortality (median, 10 vs. 7 days; *p* = 0.0001).

Table 2 shows the clinicopathologic factors of the patient as a function of 30-day morbidity and mortality. The factors associated with morbidity included resection status (*p* < 0.0001), lung disease (*p* = 0.0091), PCI (*p* = 0.01), length of surgery (*p* = 0.0003), and ECOG (0.019). In the analysis of QoL measurements, only SF-36 GH was associated with morbidity (*p* = 0.015). The QoL measures associated with major morbidity included the SF-36 physical QoL measures (PCS: *p* = 0.020; PF: *p* = 0.0025; RP: *p* = 0.038; and VT: *p* = 0.025), as well as the FACT-C measures (CSS: *p* = 0.0008; TOI: *p* = 0.27).

Mortality was associated with age (*p* = 0.0002), complication (*p* = 0.0004), DM (*p* = 0.0029), PCI (*p* = 0.028), and ECOG (*p* = 0.027). Differences were seen in baseline QoL scores and 30-day mortality for CSS and worst pain. The CSS score for 30-day survivors was 23.4 ± 4.9 compared with 20.1 ± 3.9 for those who died (*p* = 0.0034). The worst pain score for survivors was 3.4 ± 2.7 compared with 4.6 ± 2.6 for those who died within 30 days

($p = 0.0459$). There was a trend of better BPI scores for those who survived 30 days and those who did not ($p = 0.0706$).

Attrition over time was significant. Survey completion was 67.4 % at 3 months, 61.8 % at 6 months, 51.9 % at 12 months, and 33.4 % at 24 months. Attrition due to death was 8 % at 3 months, 12 % at 6 months, 20 % at 12 months, and 38 % at 24 months. Most attrition was due to causes other than death, which occurred between 0 and 3 months and was relatively stable thereafter at 26–28 %. Analysis of the 253 patients who did not participate in the QoL trial versus the participants showed no difference in median survival (37 vs. 34 months; $p = 0.22$), overall morbidity (72.3 vs. 67.9 %; $p = 0.22$), or mortality (3.9 vs. 3.5 %; $p = 0.84$).

FACT-C

Whereas EWB improved at 3 months postoperatively and remained above baseline ($p < 0.0001$), SWB declined postoperatively and remained lower ($p = 0.041$). Initially, FWB, CSS, and FACT-C dropped at 3 months and then rebounded to baseline or above by 6 months (both $p < 0.0001$). At 3 months, PWB, FACT-G, and TOI dropped significantly, then returned to baseline for months 6 through 12, but dropped again by 24 months (all $p < 0.0001$) (Fig. 1a).

SF-36

Similar to EWB from FACT-C, MCS and EH improved after CS + HIPEC (both $p < 0.001$). Although RE, SF, RP, BP, PCS, PF, GH, and VT all initially dropped at 3 months, then rebounded by 6 months, only RE and SF remained above baseline. Both RP and BP remained near baseline, whereas all the others drifted below baseline (all $p < 0.0001$) (Fig. 1b).

CES-D

At baseline, 29.7 % of the patients had a CES-D score of 16 or higher. The incidence of possible, probable, and case depression decreased over time (Fig. 1c). The baseline CES-D was 12.7, then increased slightly at 3 months, but showed significant improvement above baseline at 6 and 12 months ($p = 0.001$). By 24 months, CES-D scores had returned to baseline.

BPI

Worst pain and brief pain increased significantly at 3 months and returned to baseline by 6 months (Fig. 1d). Pain that interfered with ability to walk was significant between baseline and 3 months ($p = 0.0005$).

Overall Survival and Baseline QoL

Overall 1-year survival was 76.8 % (Fig. 2a). Median survival was 2.9 years. Survival was stratified by tumor type, PCI, and resection status (Fig. 2b–d). The SF-36 physical measures (PWB, FWB, FACT-G, FACT-C, TOI, PCS, PF, RP, BP, GH, SF, and VT) were associated with better survival, as was a higher baseline FACT-C (Table 3). Baseline mental QoL measures were not associated with survival. Higher baseline BPI (HR, 1.1 for 1 unit; 95 % CI 1.05–1.14; $p < 0.0001$), worst pain (HR, 1.1 for 1 unit; 95 % CI 1.01–1.10; $p = 0.01$), and

ECOG (HR, 1.74 for 1 unit; 95 % CI 1.50–2.01; $p < 0.0001$) were associated with worse survival.

Discussion

As an aggressive treatment option, HIPEC is associated with considerable morbidity and mortality. However, it can offer long-term disease-free survival, palliation of symptoms, and improvements in QoL for select patients. Subsequently, measurement of the improvement in symptoms or QoL is important. The importance of monitoring QoL has been highlighted by a consensus panel on peritoneal malignancies, which recommended it as a standard of care for patients undergoing HIPEC.³¹ Furthermore, QoL measures have been shown to have prognostic value for predicting perioperative complications and may be an additional practical and noninvasive means of identifying patients at risk for significant morbidity and mortality, as well as predicting overall survival.^{32–34}

This study with 598 participants is by far the largest prospective QoL trial of patients who underwent HIPEC for peritoneal cancers. The study evaluated the impact of HIPEC on QoL over time and whether preoperative baseline QoL can predict morbidity, mortality, and survival. It mirrors previous work demonstrating significant impairments of QoL during the first 3 postoperative months, with improvement at or above baseline occurring by 6 months.³⁵ However, for patients with longer-term survival, some of the benefits seen from HIPEC at 6 through 12 months deteriorated with respect to physical scales of QoL at 24 months. This deterioration in physical QoL may reflect disease recurrence.

Although health-related QoL is an important patient-measured outcome in oncologic care, we measured with several validated instruments in an attempt to quantify QoL after HIPEC. Systematically examining QoL measures before and after HIPEC allows clinicians to offer better counsel to their patients. Specifically, it enables physicians to give their patients clearer preoperative expectations about postoperative physical and emotional function.³⁶ Furthermore, monitoring QoL postoperatively can detect problems earlier, allowing for intervention before an adverse event occurs, and it is an excellent aid in survivorship planning.

The prediction of perioperative complications currently is based on comorbidities and disease burden, whereas more recently, QoL measures have shown prognostic value. Anthony et al.³² found that higher morbidity was associated with lower baseline EWB, FWB, SWB, CSS, FACT-G, and FACT-C for patients undergoing open colon surgery.³² We have previously shown that HIPEC patients with higher EWB and better ECOG were less likely to have a morbidity.³⁴ In the current study, we found resection status, length of surgery, PCI, ECOG, and general health shown by SF-36 to be predictive of morbidity. The analysis of baseline QoL measurements showed that colon-specific subscale scores and higher worst pain were associated with 30-day mortality.

Findings have shown morbidity and mortality for patients undergoing HIPEC to be significantly predicted by ECOG and a major criterion for patient selection.^{37–40} Our study confirms ECOG as a significant predictor of morbidity, mortality, and overall survival.

Specifically, each point increase in ECOG was associated with a 74 % decrease in overall survival. We also found that worst pain and CSS, possible surrogates for symptomatology and performance, were both associated with worse survival and higher 30-day mortality.

Our trial found that mental QoL and depressive symptoms improved and remained at or above baseline 24 months after HIPEC. However, mental components and CES-D were not predictive of outcomes. Conversely, higher baseline physical QoL measurements from both FACT-C and SF-36 were significantly associated with better survival. We also found that EWB demonstrated improvement during the 24-month postoperative period despite detriments in physical components. This paradox may be due to emotional growth after periods of distress, as patients have successfully managed both physical and emotional stressors after HIPEC, resulting in an improved outlook and hope for long-term survival.³⁶

The selection process for HIPEC is essential, with both oncologic factors and performance status weighing heavily. Factors including preoperative depressive symptoms and social support should also be included in the selection process. Despite improvement in depressive symptoms, SWB decreased below baseline in the postoperative period, highlighting the need to evaluate social support preoperatively. We also found that depressive symptoms and pain were common at baseline. Nearly 30 % of patients had baseline depressive symptoms that significantly improved, exceeding baseline after HIPEC.

The effects of depression should not be underestimated. Depressed mood can affect food intake, result in malnutrition, and exacerbate cancer cachexia.⁴¹ In a study of patients with head and neck cancer, the recurrence or treatment failure rate was 50 % for the patients with depression and 20 % for those without depression.⁴² Findings have shown depression to be a modifiable factor for cancer patients. Psychological support has been shown to prolong survival and to improve mood and the perception of pain in cancer.^{33,43–46} Treatment with antidepressants such as selective serotonin reuptake inhibitors also has been shown to improve depressive symptoms and QoL for patients with advanced cancer.^{47,48}

The current study had several limitations. First, it was a single-institution study composed of heterogeneous patients with respect to primary tumor type and PCI. Additionally, it had a significant attrition rate. Attrition for some may have been due to physical limitations associated with recurrent disease or questionnaire fatigue, which could have underestimated poor QoL. By 24 months, nearly 40 % of attrition could be attributed to patient death. Yet, comparison of QoL between participants and non-participants showed no significant difference in median survival, morbidity, or mortality, leading us to surmise that QoL measures are likely to be similar between participants and nonparticipants and therefore between responders and nonresponders.

The study suggests that ideal candidates for HIPEC have a favorable pathology, low PCI, high probability for complete resection, and a good performance status including an ECOG score of 0/1, higher scores for physical QoL, and lower scores for physical pain. In conclusion, patients and physicians must weigh significant short-term detriments in terms of physical QoL, morbidity, and mortality over benefits including long-term survival and improved mental QoL. This study highlights the trajectory of recovery after HIPEC, the

value of measuring QoL, and the need for preoperative evaluation and treatment of modifiable factors including depression and pain.

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Fig. 1. Quality of life parameters by time of measurement (**a**, **b**), depression score (**c**) and pain assessment (**d**)

Fig. 2. Overall survival for entire series (a), stratified by primary site (b), PCI score (c) and R score (d)

Table 1**Participant characteristics**

Characteristic	N ± SD	%
Age at HIPEC	53.3 ± 12.1	
Sex		
Female	322	53.9
Male	276	46.1
Race		
White	527	88.1
Black	54	9.1
Other	17	2.8
Primary tumor		
Appendix	346	58.0
Colorectal	120	21.8
Mesothelium	50	8.4
Ovary	22	3.7
Small bowel	12	2.0
Other	37	6.2
Resection status		
R0/R1	301	50.4
R2a	181	30.3
R2b	85	14.2
R2c	30	5.0
Albumin	3.8 ± 0.5	
BMI	27.9 ± 6.0	
Preop chemo		
Yes	190	33.6
No	375	66.4
Postop complication		
Yes	406	67.9
No	192	32.1
DM		
Yes	64	11.3
No	502	88.6
Heart disease		
Yes	44	7.8
No	521	92.2
Lung disease		
Yes	17	3.0
No	549	97.0
Smoking history		
Yes	192	35.5

Characteristic	N ± SD	%
No	367	64.5
PCI index	14.4 ± 9.1	
Length of surgery	8.2 ± 2.6	
ECOG		
0	316	53.8
1	202	34.4
2	54	9.2
3	15	2.6
QOL measures		
FACT-C	104.4 ± 18.2	
PWB	21.7 ± 5.5	
SWB	23.9 ± 3.9	
EWB	16.3 ± 4.9	
FWB	19.2 ± 5.9	
CSS	23.3 ± 4.9	
FACT-G	81.1 ± 15.0	
TOI	64.2 ± 13.9	
CESD	12.8 ± 10.2	
BPI	2.0 ± 2.5	
Least pain	1.8 ± 1.5	
Worst pain	3.4 ± 2.7	
SF-36 PCS	44.8 ± 10.8	
SF-36 MCS	48.3 ± 11.3	

BMI body mass index, *DM* diabetes mellitus, *PCI* peritoneal carcinomatosis index, *ECOG* eastern cooperative oncology group performance status, *CES-D* centers for epidemiologic studies depression, *PWB* physical well-being, *SWB* social well-being, *EWB* emotional well-being, *FWB* functional well-being, *CSS* colon specific subscale, *FACT-G* functional assessment of cancer therapy—General: *FACT-C* *FACT-G* + *CSS*, *TOI* trial outcome index, *SF-36* short form-36, *PCS* physical component score, *MCS* mental component score, *PF* physical function, *RP* role physical, *BP* bodily pain, *GH* general health, *EH* emotional health, *RE* role emotional, *SF* social function, *VT* vitality

Table 2
Clinicopathologic factors as a function of 30-day morbidity and mortality

Characteristic	No morbidity (<i>n</i> = 192) <i>N</i> (%) or mean $\pm$ SD	Morbidity (<i>n</i> = 406) <i>N</i> (%) or mean $\pm$ SD	<i>p</i> value	No major morbidity (<i>n</i> = 428) <i>N</i> (%) or mean $\pm$ SD	Major morbidity (<i>n</i> = 170) <i>N</i> (%) or mean $\pm$ SD	<i>p</i> value	No mortality (<i>n</i> = 577) <i>N</i> (%) or mean $\pm$ SD	Mortality (<i>n</i> = 21) <i>N</i> (%) or mean $\pm$ SD	<i>p</i> value
Age	52.0 $\pm$ 11.1	54.0 $\pm$ 12.5	0.063	52.7 $\pm$ 11.8	54.9 (12.7)	0.049	53.0 $\pm$ 12.0	63.0 $\pm$ 10.9	0.0002
Sex									
Female	116 (60.4)	206 (50.7)	0.028	244 (57.0)	78 (45.9)	0.014	310 (53.7)	12 (54)	0.83
Male	76 (39.6)	200 (49.3)		184 (43.0)	92 (54.1)		267 (46.3)	9 (46)	
Race									
White	167 (87.8)	360 (89.1)	0.71	377 (88.3)	150 (88.8)	0.47	506 (88.0)	19 (90)	>0.99
Black	20 (9.1)	34 (8.4)		41 (9.6)	13 (7.7)		52 (9.0)	2 (10)	
Other	5 (3.1)	10 (2.5)		9 (2.1)	6 (3.5)		17 (3)	0 (0)	
Primary tumor			0.59			0.79			0.35
Appendix	112 (58.)	235 (57.9)		243 (56.8)	104 (61.2)		336 (58.3)	11 (52)	
Colorectal	35 (18.2)	82 (20.2)		83 (19.4)	34 (20.0)		113 (19.6)	4 (19)	
Mesothelioma	16 (8.3)	31 (7.6)		37 (8.6)	10 (5.9)		46 (8.0)	1 (5)	
Ovarian	9 (4.7)	13 (3.2)		17 (4.0)	5 (2.9)		22 (3.8)	0	
Small bowel	6 (3.1)	6 (1.5)		10 (2.3)	2 (1.2)		12 (2.1)	0	
Other	14 (7.3)	39 (9.6)		38 (8.9)	15 (8.8)		48 (8.3)	5 (23.8)	
Resection status			<0.0001			<0.0001			0.24
R0/R1	121 (63.0)	180 (44.4)		237 (55.5)	64 (37.7)		294 (51.0)	7 (33)	
R2a	46 (24.0)	135 (33.3)		127 (29.7)	54 (31.8)		172 (29.9)	9 (43)	
R2b	17 (8.9)	68 (16.8)		49 (11.5)	36 (21.2)		82 (14.2)	3 (14)	
R2c	8 (4.2)	22 (5.4)		14 (3.3)	16 (9.4)		28 (4.9)	2 (10)	
Albumin	3.9 $\pm$ 0.5	3.8 $\pm$ 0.5	0.30	3.9 $\pm$ 0.5	3.7 $\pm$ 0.6	0.0042	3.8 $\pm$ 0.5	3.7 $\pm$ 0.5	0.28
BMI	28.4 $\pm$ 6.0	27.7 $\pm$ 5.9	0.16	27.9 $\pm$ 5.8	28.1 $\pm$ 6.3	0.65	27.9 $\pm$ 6.0	27.9 $\pm$ 6.3	0.99
Preop chemo			0.22			0.77			0.62
Yes	58 (30.2)	132 (35.4)		133 (33.3)	57 (34.5)		185 (33.9)	5 (26)	
No	134 (69.8)	241 (64.6)		267 (66.7)	108 (65.5)		361 (66.1)	14 (74)	
DM			0.068			0.019			0.0029
Yes	15 (7.8)	49 (13.1)		37 (9.2)	27 (16.4)		57 (10.4)	7 (37)	

Characteristic	No morbidity (<i>n</i> = 192) <i>N</i> (%) or mean $\pm$ SD	Morbidity (<i>n</i> = 406) <i>N</i> (%) or mean $\pm$ SD	<i>p</i> value	No major morbidity (<i>n</i> = 428) <i>N</i> (%) or mean $\pm$ SD	Major morbidity (<i>n</i> = 170) <i>N</i> (%) or mean $\pm$ SD	<i>p</i> value	No mortality (<i>n</i> = 577) <i>N</i> (%) or mean $\pm$ SD	Mortality (<i>n</i> = 21) <i>N</i> (%) or mean $\pm$ SD	<i>p</i> value
No	177 (92.2)	325 (86.9)		364 (90.8)	138 (83.6)		490 (89.6)	12 (63)	
Heart disease			0.25			0.085			0.052
Yes	11 (5.7)	33 (8.8)		26 (6.5)	18 (10.9)		40 (7.3)	4 (21)	
No	181 (94.3)	340 (91.2)		374 (93.5)	147 (89.1)		506 (92.7)	15 (79)	
Lung disease			0.0091			0.17			>0.99
Yes	11 (5.7)	6 (1.6)		15 (3.7)	2 (1.2)		17 (3.1)	0 (0)	
No	181 (94.3)	368 (98.4)		386 (96.3)	163 (98.8)		530 (96.9)	19 (100)	
Smoking history			0.22			0.24			0.21
Yes	58 (30.2)	134 (36.1)		130 (32.8)	62 (38.0)		183 (33.8)	9 (50)	
No	130 (69.1)	237 (63.9)		266 (67.2)	101 (62.0)		358 (66.2)	9 (50)	
PCI index	12.2 $\pm$ 9.2	15.2 $\pm$ 8.9	0.01	13.6 $\pm$ 8.6	17.0 $\pm$ 10.2	0.0094	14.2 $\pm$ 9.0	21.9 $\pm$ 8.3	0.028
Length of surgery	7.3 $\pm$ 2.7	8.3 $\pm$ 2.9	0.0003	8.0 $\pm$ 2.4	8.8 $\pm$ 2.9	0.0072	8.0 $\pm$ 2.9	8.8 $\pm$ 1.5	0.065
ECOG			0.019			<0.0001			0.027
0	120 (63.20)	196 (49.4)		252 (60.0)	64 (38.3)		311 (54.8)	5 (25)	
1	53 (27.9)	149 (37.5)		133 (31.7)	69 (41.3)		190 (33.5)	12 (50)	
2	14 (7.4)	40 (10.1)		31 (7.4)	23 (13.8)		42 (9.2)	2 (10)	
3	3 (1.6)	12 (3.0)		4 (0.9)	11 (6.6)		14 (2.5)	1 (5)	
QOL measures FACT-C									
PWB	22.0 $\pm$ 5.4	21.4 $\pm$ 5.6	0.39	22.0 $\pm$ 5.4	21.0 $\pm$ 5.7	0.059	21.7 $\pm$ 5.6	21.4 $\pm$ 5.0	0.81
SWB	24.1 $\pm$ 3.9	23.8 $\pm$ 3.9	0.34	24.0 $\pm$ 3.9	23.8 $\pm$ 4.0	0.64	23.9 $\pm$ 4.0	24.7 $\pm$ 2.8	0.36
EWB	16.4 $\pm$ 4.7	16.3 $\pm$ 5.0	0.76	16.1 $\pm$ 5.0	16.8 $\pm$ 4.8	0.16	16.3 $\pm$ 5.0	16.6 $\pm$ 4.0	0.79
FWB	19.7 $\pm$ 5.9	19.0 $\pm$ 6.0	0.22	19.3 $\pm$ 5.9	18.9 $\pm$ 6.0	0.49	19.2 $\pm$ 6.0	17.9 $\pm$ 5.5	0.33
CSS	23.6 $\pm$ 4.8	23.2 $\pm$ 4.9	0.41	23.8 $\pm$ 4.8	22.2 $\pm$ 5.0	0.0008	23.4 $\pm$ 4.9	20.1 $\pm$ 3.9	0.0034
FACT-G	82.2 $\pm$ 14.3	80.5 $\pm$ 15.3	0.23	81.3 $\pm$ 14.8	80.3 $\pm$ 15.5	0.48	81.1 $\pm$ 15.0	80.6 $\pm$ 13.6	0.89
TOI	65.2 $\pm$ 13.6	63.7 $\pm$ 14.1	0.25	65.1 $\pm$ 13.7	62.1 $\pm$ 14.3	0.027	64.4 $\pm$ 14.0	59.4 $\pm$ 12.1	0.13
FACT-C	105.8 $\pm$ 17.5	103.7 $\pm$ 18.5	0.23	105.2 $\pm$ 18.0	102.5 $\pm$ 18.7	0.13	104.5 $\pm$ 18.3	100.7 $\pm$ 16.1	0.37
CES-D	12.4 $\pm$ 8.7	12.9 $\pm$ 10.9	0.52	12.6 $\pm$ 10.0	13.3 $\pm$ 10.7	0.48	12.9 $\pm$ 10.3	10.4 $\pm$ 8.7	0.3
BPI	2.1 $\pm$ 2.6	2.0 $\pm$ 2.4	0.69	2.0 $\pm$ 2.5	2.1 $\pm$ 2.5	0.57	2.0 $\pm$ 2.5	2.4 $\pm$ 2.1	0.5
Least pain	1.8 $\pm$ 1.6	1.9 $\pm$ 1.5	0.48	1.8 $\pm$ 1.6	1.9 $\pm$ 1.4	0.70	1.8 $\pm$ 1.5	2.3 $\pm$ 1.6	0.22
Worst pain	3.6 $\pm$ 2.9	3.3 $\pm$ 2.5	0.26	3.4 $\pm$ 2.7	3.6 $\pm$ 2.6	0.46	3.4 $\pm$ 2.7	4.6 $\pm$ 2.6	0.046

Characteristic	No morbidity (<i>n</i> = 192) <i>N</i> (%) or mean $\pm$ SD	Morbidity (<i>n</i> = 406) <i>N</i> (%) or mean $\pm$ SD	<i>p</i> value	No major morbidity (<i>n</i> = 428) <i>N</i> (%) or mean $\pm$ SD	Major morbidity (<i>n</i> = 170) <i>N</i> (%) or mean $\pm$ SD	<i>p</i> value	No mortality (<i>n</i> = 577) <i>N</i> (%) or mean $\pm$ SD	Mortality (<i>n</i> = 21) <i>N</i> (%) or mean $\pm$ SD	<i>p</i> value
SF-36									
PCS	45.6 $\pm$ 10.9	48.4 $\pm$ 10.2	0.28	45.5 $\pm$ 10.6	43.1 $\pm$ 11.2	0.020	45.0 $\pm$ 10.8	41.3 $\pm$ 11.2	0.16
MCS	44.5 $\pm$ 10.8	48.3 $\pm$ 11.9	0.87	48.4 $\pm$ 11.4	48.3 $\pm$ 11.3	0.93	48.3 $\pm$ 11.4	48.6 $\pm$ 8.8	0.92
PF	46.1 $\pm$ 10.4	44.8 $\pm$ 10.8	0.19	46.1 $\pm$ 10.3	43.0 $\pm$ 11.4	0.0025	45.3 $\pm$ 10.7	41.7 $\pm$ 10.4	0.15
RP	42.1 $\pm$ 12.5	40.8 $\pm$ 12.6	0.26	41.9 $\pm$ 12.5	39.5 $\pm$ 12.5	0.038	41.3 $\pm$ 12.6	39.1 $\pm$ 12.3	0.47
BP	48.4 $\pm$ 11.7	49.6 $\pm$ 10.8	0.25	49.3 $\pm$ 11.2	49.0 $\pm$ 10.8	0.77	49.4 $\pm$ 11.1	44.7 $\pm$ 10.0	0.071
GH	47.6 $\pm$ 9.7	45.3 $\pm$ 10.3	0.015	46.4 $\pm$ 10.3	45.4 $\pm$ 9.6	0.28	46.1 $\pm$ 10.2	44.8 $\pm$ 9.9	0.59
EH	49.5 $\pm$ 9.2	48.9 $\pm$ 10.9	0.48	49.1 $\pm$ 10.4	49.2 $\pm$ 10.5	0.90	49.2 $\pm$ 10.5	46.7 $\pm$ 8.6	0.31
RE	45.6 $\pm$ 12.9	45.3 $\pm$ 13.2	0.76	45.7 $\pm$ 13.0	44.7 $\pm$ 13.2	0.42	45.3 $\pm$ 13.1	47.6 $\pm$ 12.6	0.45
SF	44.7 $\pm$ 10.9	45.0 $\pm$ 11.3	0.78	45.2 $\pm$ 11.1	44.1 $\pm$ 11.3	0.33	44.9 $\pm$ 11.3	43.7 $\pm$ 7.5	0.51
VT	49.8 $\pm$ 11.6	48.8 $\pm$ 11.8	0.36	49.9 $\pm$ 11.7	47.4 $\pm$ 11.7	0.025	49.2 $\pm$ 11.7	46.8 $\pm$ 11.0	0.38

BM/body mass index, *DM* diabetes mellitus, *PC*/peritoneal carcinomatosis index, *ECOG* eastern cooperative oncology group performance status, *CES-D* centers for epidemiologic studies depression, *PWB* physical well-being, *SWB* social well-being, *EWB* emotional well-being, *FWB* functional well-being, *FACT-G* functional assessment of cancer therapy—General, *FACT-CFACT-G* + CSS, *TOI* trial outcome index, *SF-36* short form-36, *PCS* physical component score, *MCS* mental component score, *PF* physical function, *RP* role physical, *BP* bodily pain, *GH* general health, *EH* emotional health, *RE* role emotional, *SF* social function, *VT* vitality

Table 3
Effect of baseline quality of life (QOL) on overall survival using proportional hazard model

Index	Unit increase	HR	95 % CI	p value
Brief pain index (BPI)				
Worst	1	1.06	(1.01, 1.10)	0.01
Least	1	1.04	(0.96, 1.12)	0.33
BPI	1	1.1	(1.05, 1.14)	<0.0001
CES-D	1	1.01	(1, 1.02)	0.14
ECOG	1	1.74	(1.50, 2.01)	<0.0001
FACT-C				
PWB	5	0.71	(0.64, 0.78)	<0.0001
SWB	5	1.04	(0.90, 1.22)	0.58
EWB	5	1.02	(0.90, 1.15)	0.78
FWB	5	0.8	(0.72, 0.88)	<0.0001
CSS	5	0.73	(0.65, 0.83)	<0.0001
FACT-G	5	0.92	(0.89, 0.96)	<0.0001
FACT-C	5	0.93	(0.90, 0.96)	<0.0001
TOI	5	0.87	(0.84, 0.91)	<0.0001
SF-36				
PCS	5	0.82	(0.78, 0.87)	<0.0001
MCS	5	0.99	(0.94, 1.04)	0.68
PF	5	0.83	(0.79, 0.87)	<0.0001
RP	5	0.88	(0.84, 0.92)	<0.0001
BP	5	0.92	(0.87, 0.97)	0.0013
GH	5	0.88	(0.83, 0.93)	<0.0001
EH	5	0.99	(0.94, 1.05)	0.76
RE	5	0.97	(0.93, 1.02)	0.19
SF	5	0.91	(0.87, 0.96)	0.0002
VT	5	0.88	(0.83, 0.92)	<0.0001

CES-D centers for epidemiologic studies depression, *ECOG* eastern cooperative oncology group performance, *PWB* physical well-being, *SWB* social well-being, *EWB* emotional well-being, *FWB* functional well-being, *CSS* colon specific subscale, *FACT-G* functional assessment of cancer therapy—General: *FACT-C* *FACT-G* + *CSS*, *TOI* trial outcome index, *SF-36* short form-36, *PCS* physical component score, *MCS* mental component score, *PF* physical function, *RP* role physical, *BP* bodily pain, *GH* general health, *EH* emotional health, *RE* role emotional, *SF* social function, *VT* vitality