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Effect of Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy on Quality of Life in Patients with Peritoneal Mesothelioma

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Abstract

Introduction.—Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) is an accepted treatment for peritoneal mesothelioma. In this study, we evaluated QOL after HIPEC for peritoneal mesothelioma.

Methods.—This was a prospective study performed after HIPEC for peritoneal mesothelioma between 2002 and 2015. Patients completed QOL surveys, including the Short Form-36 (SF-36), Functional Assessment of Cancer Therapy + Colon (FACT-C), Brief Pain Inventory (BPI), and Center for Epidemiologic Studies Depression Scale (CES-D) preoperatively and at 3, 6, 12, and 24 months postoperatively.

Results.—Overall, 46 patients underwent HIPEC for peritoneal mesothelioma and completed QOL surveys. Mean age was 52.8 ± 13.8 years and 52% were male. Good preoperative functional status was 70%. Median survival was 3.4 years, and 1, 3, and 5-year survivals were 77.4, 55.2, and 36.5%, respectively. CES-D score decreased at 3 months postoperatively, but increased at 24 months ($p = 0.014$); SF-36 physical functioning scale decreased at 3 months but returned to baseline at 12 months ($p = 0.0045$); and the general health scale decreased at 3 months, then improved by 6 months ($p = 0.0034$). Emotional well-being ($p = 0.0051$), role limitations due to emotional problems ($p = 0.0006$), social functioning ($p = 0.0022$), BPI ($p = 0.025$), least pain ($p = 0.045$), and worst pain ($p < 0.0001$) improved. FACT-C physical well-being decreased at 3 months but returned to baseline at 6 months ($p = 0.020$), and total FACT-C score improved at 6 months ($p = 0.052$).

Conclusion.—QOL returned to baseline or improved from baseline between 3 months and 1 year following surgery. Despite the risks associated with this operation, patients may tolerate HIPEC well and have good overall QOL postoperatively.

Malignant peritoneal mesothelioma (MPM) is a rare neoplasm, typically diagnosed after extensive peritoneal dissemination.¹ Peritoneal mesothelioma arises from the mesothelial

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lining of the peritoneum.² There are approximately 800 newly diagnosed cases per year in the US, and, without intervention, survival is estimated to be approximately 1 year.³ There is no screening program and patients most commonly present with nonspecific symptoms such as weight loss, dyspnea, chest pain, ascites, and palpable abdominal mass.² MPM has been treated effectively by cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS/HIPEC), which was declared the standard of care for this disease in 2008 by the Peritoneal Surface Oncology Group International (PSOGI).⁴

However, HIPEC is associated with significant morbidity and mortality (major morbidity 12%, operative mortality 0.9%, 30-day mortality 3–14%).^{5,6} These complications include anastomotic leaks, intestinal perforations, fever, abdominal bleeds, sepsis, pulmonary embolism, and fistula formation.⁵ Our previous work on QOL after HIPEC from all primary sites has shown that less morbid, although still life-altering, long-term complications affect QOL and include anxiety, sleep disturbances, and depressive symptoms.⁷

The overall success of HIPEC in this population of patients is related to physical recovery and overall QOL following the procedure. We define quality of life as the extent to which one's usual or expected physical, functional, emotional, and social/family well-being are affected by a medical condition or its treatment. In a large cohort of HIPEC patients, we have previously shown that quality of life declines for 3–6 months postoperatively, returns to baseline at approximately 6 months, and increases at future time points.^{7,8} Given the similar disease process and comparable operative course, it was hypothesized that QOL in peritoneal mesothelioma following CRS/HIPEC would follow a similar trend in recovery and overall QOL;⁹ however, there is a paucity of data available on QOL after HIPEC for patients with peritoneal mesothelioma.

The aim of this study was to examine the impact of HIPEC on QOL in patients with MPM by comparing pre-operative and postoperative QOL using multiple verified QOL surveys over the first 2 years after the procedure.

METHODS

The data used for this study were obtained from a prospectively maintained, ongoing HIPEC QOL clinical trial of patients enrolled from 2002 to 2015. Our study was approved by the Wake Forest Baptist Health Institutional Review Board. Patients completed QOL surveys preoperatively and then 3, 6, 12, and 24 months following HIPEC. All patients had biopsy-proven peritoneal mesothelioma. We did not include sarcomatoid variant cases in light of the poor outcomes, although biphasic cases were included.¹⁰ This QOL survey consisted of the Short Form-36 (SF-36), the Functional Assessment of Cancer Therapy + Colon (FACT-C), the Brief Pain Inventory (BPI), and the Center for Epidemiologic Studies Depression Scale (CES-D). Eastern Cooperative Oncology Group (ECOG) performance status rating, Peritoneal Cancer Index (PCI), resection status, morbidity, and mortality were also analyzed. The PCI is used to assess the extent of cancer throughout the peritoneal cavity. It is determined by dividing the peritoneal cavity into 13 regions (central, right upper, epigastrium, left upper, left flank, left lower, pelvis, right lower, right flank, upper jejunum, lower jejunum, upper ileum, and lower ileum) and using a score of 0–3 for each region (0 is

no tumor seen, 1 is largest tumor is smaller than 0.5 cm, 2 is largest tumor is between 0.5 and 5 cm, and 3 is largest tumor is > 5 cm).^{18,19}

Quality-of-Life (QOL) Instruments

The FACT-C questionnaire 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 components: physical well-being (PWB), social well-being (SWB), emotional well-being (EWB), and functional well-being (FWB). This survey uses a 5-point Likert scale to rate patient's symptoms for the prior week. The Trial Outcome Index (TOI) is used as a summary index of physical and functional outcomes, and is calculated by adding PWB + FWB + CCS. Higher scores reflect higher QOL at the time of questionnaire administration.¹¹

The SF-36 survey is a 36-item questionnaire consisting of eight areas of evaluation: physical functioning (PF), role physical (RP), role emotional (RE), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), and mental health (MH).^{12,13} The Mental Component Summary (MCS) and Physical Component Scales (PCS) are calculated from these eight subgroups. Higher scores indicate higher functioning with less psychological or functional limitations.

The CES-D scale is a 20-item questionnaire that assesses how often a person had depressive symptoms in sleep, appetite, or mood during the past week.¹⁴ It utilizes a Likert scale of 0 (none), 1 (some), 2 (occasional), or 3 (most of the time).¹⁵ This further uses scores 16, 23, and 28 to screen for possible, probable, and case depression, respectively.

The BPI survey 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. It examines whether pain interfered with activity, mood, normal work, relationships, and sleep.¹⁶ 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).¹⁷

Surgical Data

All procedures were performed at a single center using uniform techniques;^{18,19} our techniques have been described elsewhere.^{18,20} Briefly, patients underwent resection of macroscopically visible disease via a midline laparotomy incision with the goal of removing all visible peritoneal disease. Via a closed technique perfusion circuit, HIPEC was perfused for 90–120 min, with a target flow of 1 L/min and a target outflow temperature of 40 °C. Cisplatin was the preferred agent, but mitomycin C was also utilized in select cases. After perfusion, the abdomen was reopened, inspected, and then definitively closed. The operative variables included length of surgery, estimated blood loss, chemotherapy agent, PCI, and completeness of CRS. Completeness of cytoreduction was defined as R0/1 (no gross disease with negative or positive microscopic margins), R2a (< 5 mm of residual disease), R2b (5–20 mm of residual disease), or R2c (> 20 mm of residual disease).

Complications were evaluated in the first 90 days postoperatively and were graded according to 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, e.g. 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)²². In situations where more than one complication occurred, the most severe complication was recorded.

Statistical Analysis

Frequencies and proportions were calculated for all categorical measures, while mean and standard deviations were calculated for continuous data. The Kaplan-Meier method was used to estimate overall survival. To assess the change in quality-of-life measures over time, repeated measures analysis of variance was used to test for the significance of change across all visits. The relationship between survival and QOL measures was assessed using Cox proportional hazards regression. For all tests, a p value < 0.05 was considered statistically significant. SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA) was used for all statistical analyses.

RESULTS

Of the 57 patients who underwent HIPEC for peritoneal mesothelioma during the time period of this study, 46 completed QOL surveys pre- and postoperatively. The clinical characteristics of the group of studied patients are listed in Table 1. The mean age was 53.0 ± 13.8 years (range 27–72 years), males represented 52.2% of the cohort, and the average body mass index (BMI) was 26.9 ± 5.4 . Median follow-up was 5.1 years, and median survival was 3.4 years. The baseline data for QOL measures are shown in Table 2. One-, 3- and 5-year survival was $77.4\% \pm 5.7\%$, $55.2\% \pm 7.2\%$, and $36.5\% \pm 7.9\%$, respectively. Preoperative functional status was defined as follows: 33%, 37%, 20%, and 11% of patients with an ECOG of 0, 1, 2, or 3, respectively. Overall survival was estimated using the Kaplan-Meier method (see Fig. 1).

With regard to complication rates, 30% of patients had no complications (Clavien-Dindo grade 0), 37% had 30-day minor morbidity (grades I and II), and 24% had 30-day major morbidity (grades III and IV). Mortality was 9% at 5 years postoperatively. The mean PCI was ± 11.0 , and the average length of stay (LOS) was ± 14.8 days. Results of the multiple QOL studies (FACT-C,¹¹ SF-36, CES-D,¹⁵ and BPI¹⁶) are delineated below.

Functional Assessment of Cancer Therapy + Colon (FACT-C)

PWB decreased at 3 months postoperatively, returned to baseline at 6 months postoperatively ($p = 0.020$ over the course of 2 years), and continued to improve, with the estimated mean above the baseline mean at 12 months postoperatively. There was an overall improvement in the total FACT-C score beginning at 6 months, which continued during the subsequent time points ($p = 0.052$). In those who received a complete resection, a higher social/family well-being score was observed in the FACT-C scale ($p = 0.021$). There was also a trend towards better overall FACT-C score ($p = 0.055$) in those who received a complete resection compared with those who had an incomplete resection.

Short Form-36 (SF-36)

Physical function decreased at 3 months, began to increase at 6 months ($p = 0.0045$), and improved past baseline at 12 months. The GH scale decreased slightly at 3 months, returned to baseline by 6 months, but then decreased again at 24 months ($p = 0.0034$). The EWB scale was increased at 3 months postoperatively, continued to increase at 6 and 12 months postoperatively ($p = 0.0051$), and returned to baseline at 24 months post-operatively. Role limitations due to emotional problems scores increased at 3 months postoperatively, decreased below baseline at 6 months postoperatively, and then increased past baseline at 12 and 24 months postoperatively ($p = 0.0006$). Low scores on the RE scale indicate a patient who has many problems with daily activities secondary to emotional health, and high scores indicate a patient with no problems with daily activities secondary to emotional health.²⁵ The SF scale improved following HIPEC at 3, 6, and 12 months postoperatively, but then decreased at 24 months postoperatively ($p = 0.0022$).

Center for Epidemiologic Studies Depression Scale (CES-D)

At baseline, mean CES-D was 13.6 ± 1.6 . It decreased starting at 3 months postoperatively and was lowest at 12 months postoperatively ($p = 0.014$), but increased again at 24 months postoperatively to just above baseline. A higher CES-D score was noted in those who received a complete resection ($p = 0.05$). Using a threshold score of > 16 (indicating depression) and ≤ 16 (indicating no depression), the baseline rate of depression was 31%, then 17% at 3 months, 21% at 6 months, 16% at 1 year, and 37% at 2 years. An improved CES-D score was also noted in those who were perfused with mitomycin C compared with those who were perfused with cisplatin ($p = 0.0051$).

Brief Pain Inventory (BPI)

BPI ($p = 0.025$), least pain ($p = 0.045$), and worst pain ($p < 0.0001$) improved following HIPEC, and continued to improve at each time point. Compared with baseline, BPI was significantly improved following HIPEC.

Overall Survival

In terms of baseline QOL data and relationship to overall survival, no QOL scales were associated with an increase in survival; however, two QOL categories approached statistically significant results. One was the SF-36 PF subscale, in which it was found that each additional 10 units in the score decreased the risk of death by 11% (hazard ratio [HR] 0.89, 95% confidence interval [CI] 0.78–1.01; $p = 0.079$). The second was the SF-36 energy/fatigue subscale, in which it was found that each additional 10 units in the score decreased the risk of death by 15% (HR 0.85, 95% CI 0.72–1.01; $p = 0.06$).

DISCUSSION

MPM is a life-threatening and highly morbid disease with few options for effective management and treatment. CRS/HIPEC is an effective means of reducing the disease burden, however it is not without complications or significant morbidity. This study sought to evaluate the effects of HIPEC on quality of life at various time points following surgery during recovery. Multiple surveys were utilized to provide a long-term evaluation of

physical, mental, and emotional well-being pre- and postoperatively. Previous quality-of-life data with regard to HIPEC in colorectal cancer showed that baseline QOL data predicted out-come^{14,23} and return to baseline quality of life after approximately 6 months.⁷ This study showed results similar to the colorectal cancer experience, i.e. improvement in overall QOL score from baseline as early as 3 months, but typically sustained from 6 through 24 months postoperatively.

The initial decrease in QOL was likely due to pain and limitations associated with a large laparotomy incision, as well as physiologic impact of complications. Deconditioning may also play a role in those who are hospitalized for a longer period of time. As time goes on, patients begin to heal from their incisions and their strength increases as they move more and return to their normal daily functions. The decrease in QOL measures after 24 months could be a result of disease recurrence. Unfortunately, this is only a hypothesis as we do not have sufficient data to correlate the two. In the future, we may consider specifically evaluating QOL measures in patients with recurrence of their disease compared with those without recurrence.

Early in the experience, we utilized mitomycin C, as the chemotherapeutic agent in HIPEC, for 120 min. However, later in the experience, we changed to cisplatin in the perfusate, for 90 min, based on a protocol from the surgery branch of the National Cancer Institute.^{21,24}

In an earlier study, while we found improved outcomes with the cisplatin regimen, we did not find a significant difference in QOL.²¹ In this study, we found that patients who were perfused with mitomycin C had improved CES-D scores compared with those who were perfused with cisplatin (10.2 vs. 12.6; $p = 0.0051$). This finding may be due to the adverse effects associated with the two chemotherapeutic agents. Some studies have shown that cisplatin may have greater adverse effects, specifically neutropenia, thrombocytopenia, gastrointestinal disturbances, metabolic disturbances, and nephrotoxicity.^{26,27}

In this trial, we included patients who underwent CRS/HIPEC for palliation of ascites (R2b and R2c) resections. Patients with incomplete cytoreductions are anticipated to have higher morbidity and mortality rates. In a study performed in 2009, it was shown that those who underwent a complete cytoreduction had a 5-year survival of 45%, whereas those with an incomplete cytoreduction had a median survival of < 1%.²⁸ The data show that complete resection has a salutatory effect on QOL. In those with a complete resection, there was a statistically significant improvement in CES-D score compared with baseline ($p = 0.05$). There was also a trend toward improvement in overall FACT-C score compared with baseline in patients who received a complete resection ($p = 0.055$). No other statistically significant differences in QOL were observed between those who received a complete cytoreduction and those with an incomplete cytoreduction, likely secondary to the small sizes of both groups. The importance of complete cytoreduction has long been known in terms of survival, and this study reflects its importance in terms of QOL.^{18,19}

There are limitations to this study. First, this was a single-institution study, with patients having a variety of baseline characteristics and a rare disease. Our study also had a modest sample size, although it represents one of the larger studies of peritoneal mesothelioma.

Another limitation is the significant attrition rate, with only 46 of the original 57 patients completing all of the QOL surveys. This may have affected the results since those who did not complete the QOL surveys may have had poorer outcomes, thus causing limitations. Our overall QOL results might not be reflective of these decrements; however, considering the rarity of peritoneal mesothelioma, this does represent the largest QOL study we are aware of.

CONCLUSIONS

It is important that patients and physicians understand the risks and benefits of undergoing HIPEC and the effects of recovery, both physically and emotionally. Immediately following surgery and up to 3 months afterwards, there is a decrease in overall QOL; however, from that time point up to 24 months postoperatively, there is an overall improvement in QOL on multiple measures of physical and emotional well-being, up to, and in some areas better than, baseline. These results may help guide us in determining which patients may benefit from interventions for psychological health and at which time points postoperatively these services should be offered. This study shows that the improvement in QOL can be very significant compared with the preoperative status, and this could be used in the counseling of patients on the likely trajectory of recovery following HIPEC for peritoneal mesothelioma.

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FIG. 1.
Kaplan-Meier curve for overall survival after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy of the entire cohort of studied patients

TABLE 1

Clinical characteristics of participants

Characteristic	Number $\pm$ standard deviation	Percentage
Age at HIPEC (years)	52.8 $\pm$ 13.8	
Sex		
Female	22	48
Male	24	52
Race		
White	39	85
Black	5	11
Other	2	4
Resection status		
R0/R1	16	35
R2a	20	43
R2b	7	15
R2c	3	7
Albumin	3.5 $\pm$ 0.7	
BMI	26.9 $\pm$ 5.4	
DM		
Yes	33	83
No	7	17
Heart disease		
Yes	0	0
No	40	100
Lung disease		
Yes	1	2
No	39	98
Smoking history		
Yes	9	23
No	22	56
Past	8	21
Preoperative chemotherapy		
Yes	37	90
No	4	10
PCI	17.5 $\pm$ 11.0	
Length of surgery (hours)	7.8 $\pm$ 2.2	
ECOG		
0	15	33
1	17	37
2	9	20
3	5	11

Characteristic	Number $\pm$ standard deviation	Percentage
Length of hospital stay (days)	14.6 $\pm$ 14.8	
Clavien-Dindo grade		
0	14	30
I	4	9
II	13	28
IIIa	5	11
IIIb	3	7
IVa	2	4
IVb	1	2
V	4	9

HIPEC hyperthermic intraperitoneal chemotherapy, *BMI* body mass index, *PCI* Peritoneal Cancer Index, *ECOG* Eastern Cooperative Oncology Group

TABLE 2

Effect of baseline quality of life on overall survival using a proportional hazard model

QOL survey	Measure	Unit increase for HR	HR	95% CI	p value
BPI	Worst pain	1	0.96	0.83–1.11	0.56
	Least pain	1	0.97	0.79–1.19	0.75
FACT	BPI	1	1.06	0.91–1.23	0.46
	Physical well-being	1	0.96	0.90–1.02	0.17
	Social well-being	1	0.98	0.85–1.12	0.71
	Emotional well-being	1	1.06	0.97–1.15	0.22
	Functional well-being	1	0.95	0.89–1.01	0.11
SF-36	Subscale	1	0.97	0.90–1.03	0.3
	FACT	10	0.91	0.72–1.15	0.42
	TOI	10	0.83	0.66–1.05	0.11
	FACT + subscale	10	0.91	0.76–1.10	0.34
	CES-D	1	1.00	0.95–1.05	0.99
	Physical functioning	10	0.89	0.78–1.01	0.079
	Role physical	10	0.95	0.86–1.06	0.37
	Pain	10	1.05	0.92–1.19	0.47
	General health	10	0.95	0.79–1.15	0.61
	Emotional health	10	1.04	0.80–1.36	0.76
SF-36	Role emotional	10	0.95	0.87–1.04	0.23
	Social functioning	10	0.89	0.76–1.04	0.13
	Energy/fatigue	10	0.85	0.72–1.01	0.06

QOL quality of life, HR hazard ratio, CI confidence interval, BPI Brief Pain Index, FACT Functional Assessment of Cancer Therapy, CES-D Center for Epidemiologic Studies Depression Scale, SF-36 Short Form-36, TOI Trial Outcome Index