

Midwest Surgical Association

Life after hyperthermic intraperitoneal chemotherapy; measuring quality of life and performance status after cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy



Jennifer Ford, M.D.^a, Michael Hanna, B.S.^b, Anna Boston, A.N.P.B.C.^c,
Richard Berri, M.D.^{c,*}

^aDepartment of Surgery, St. John Hospital and Medical Center, Detroit, MI, USA; ^bDepartment of Human Biology, Michigan State University, East Lansing, MI, USA; ^cDepartment of Surgery, Section of Surgical Oncology, 22101 Moross Road, Professional Building 1, Suite 212, St. John Hospital and Medical Center, Detroit, MI, 48236, USA

KEYWORDS:

Cytoreductive surgery;
Hyperthermic
intraperitoneal
chemotherapy;
Quality of life;
Performance status

Abstract

BACKGROUND: Patients who undergo cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) can return to an acceptable performance status (PS) and quality of life 3 months postoperative.

METHODS: An HIPEC specific questionnaire was developed based on the validated Functional Assessment of Cancer Therapy Questionnaire. Each patient was contacted and questionnaire completed. An averaged score was calculated and stratified to an Eastern Cooperative Oncology Group PS. A retrospective chart review gathered patient characteristics and correlated to the patient's 3 months postoperative PS.

RESULTS: Between October 2011 and July 2014, 43 patients underwent complete CRS with HIPEC. The most common indications for surgery were colorectal (35%) and appendiceal malignancy (47%). Average scores were: physical well-being 15.4 of 20, social well-being 17.5 of 20, recovery 15 of 20, mental well-being 13.4 of 20, and functional well-being 18.1 of 24. These correlated to an Eastern Cooperative Oncology Group PS of 1, 0, 1, 1, and 1. Patient's age ($P = .235$), operative length ($P = .181$), hospital duration ($P = .43$), complications or peritoneal carcinomatosis index ($P = .815$) demonstrated no significance relative to postoperative PS.

CONCLUSIONS: Patients can recovery well from CRS with HIPEC. It is possible to return to an acceptable functional status within 3 months postoperative. Age, operative time, length of hospital stay, or peritoneal carcinomatosis index have no prohibitive effects on a long-term recovery.

© 2016 Elsevier Inc. All rights reserved.

There were no relevant financial relationships or any sources of support in the form of grants, equipment, or drugs.

The authors declare no conflicts of interest.

* Corresponding author. Tel.: +1-313-644-3252; fax: +1-313-343-7091.

E-mail address: richard.berri@stjohn.org

Manuscript received July 13, 2015; revised manuscript December 10, 2015

Patients with gastrointestinal or gynecologic malignancies with peritoneal carcinomatosis have dismal survival with significant morbidity and mortality because of a high disease burden within the abdominal cavity.¹ Average survival for peritoneal carcinomatosis of colorectal origin is 18 to 48 months, high-grade appendiceal adenocarcinoma

12 to 36 months and low-grade appendiceal adenocarcinoma greater than 60 months.¹ Until recently, most clinicians focused on comfort measures and palliation treatments for this subset of patients.

Cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) can be used for peritoneal carcinomatosis of gastrointestinal or gynecologic malignancies and demonstrates improved long-term survival over traditional chemotherapy alone.^{1,2} Current indications for CRS with HIPEC include: large volume of noninvasive peritoneal carcinomatosis or sarcomatosis, peritoneal mesothelioma, low volume peritoneal seeding, perforated gastrointestinal cancers, gastrointestinal cancer adherent to adjacent organs or structures, gastrointestinal cancer with positive peritoneal cytology, gastrointestinal cancer with ovarian involvement, tumor spill intraoperatively, recurrent ovarian cancer after a long disease-free interval, and palliation of patients with malignant ascites.³ With CRS + HIPEC, reported mean survival can be increased 18 to 44 months over mean survival when chemotherapy alone is implemented.¹

The Consensus Guidelines from the American Society of Peritoneal Surface Malignancies is the followed protocol by many institutions in an attempt to delivery standardized care.³ The intent of treatment is to perform complete removal of all gross disease. If possible, HIPEC is initiated by placement of perfusion cannulas and temperature probes within the abdomen. The perfusate is heated to 42°C with the addition of a chemotherapeutic agent to the perfusate for a perfusion time of 90 minutes.

Perioperative morbidity is classified according to the Clavien–Dindo scale. Grade III complication rates occur in 26% to 33% of cases; grade IV complications occur in 12% to 26% of cases.⁴ Average length of operation ranges from 433 to 470 minutes.⁴

To date, few studies have explored Quality of Life (QoL) in the postoperative period. The majority of these studies were single-center reviews that used validated questionnaires administered (retrospectively or prospectively) at the time of surgery, 3, 6, 9, or 12 months postoperatively. Most patients demonstrated a return to an acceptable functional status 4 to 24 months, with a return to baseline at 6 to 24 months postoperatively.^{1,4-6}

Studies are unable to provide a common consensus on which aspect of health was the most difficult to recover. McQuellon et al⁵ reported mental health had greatest difficulty recovering: depressive symptoms had a prevalence of 32% of patients at surgery and 24% 1-year postoperatively. A German study performed by Tsilimparis et al⁴ demonstrated that emotional well-being followed the slowest recovery path, a return to an acceptable status by 12 months post-operatively. Physical recovery returned to an acceptable status at 6 months, improving to slightly below baseline at 24 months postoperatively.⁴ Interestingly, at 36 months postoperatively, patients demonstrated a better than baseline physical function.⁴

Many validated modalities exist to measure functional and performance status (PS). The Eastern Cooperative Oncology Group (ECOG) PS is widely used across North America.⁷ This validated scale divides patients into 6 groups with a score of 0 being unlimited in performance capabilities.

We are unaware of any studies that have stratified postoperative QoL questionnaires to ECOG PS (or other functionality scale). The primary outcome of our study is to obtain a measure of patient's postoperative PS at 3 months. The secondary outcome is to determine if any significant relationships between age, length of operation, and duration of hospital stay or peritoneal carcinomatosis index (PCI) exist with PS.

Patient who undergoes complete CRS with HIPEC can return to an acceptable PS and QoL 3 months postoperatively regardless of age, PCI, duration of hospital stay, or length of operative time.

Methods

The inclusion criteria included patients who received complete CRS + HIPEC between October 2011 to July 2014, alive in July 2014, communicable by telephone, able to independently answer questions or choose to have their closest caregiver or relative respond and not currently residing in a rehabilitation program. The exclusion criteria were any patient who did not receive maximal CRS with subsequent HIPEC, patients who had since died (disease or nondisease related), those unreachable by telephone and those in a rehabilitation program or in-patient facility.

An institutional review board application was submitted and approved. Participants were assigned a random "participant number" to ensure Health Insurance Portability and Accountability Act compliance.

The questionnaire used was the general specific Functional Assessment of Cancer Therapy questionnaire validated and published by Ward et al.⁸ This questionnaire groups the questions together to address physical well-being, social well-being, recovery, mental well-being, and functional well-being. A few minor modifications were made. These modifications involved wording alteration and omission of certain questions to better address specific HIPEC-related morbidities. Each question has 5 possible answers; we assigned each answer a score: not at all (score of 0), a little bit (score of 1), somewhat (score of 2), quite a bit (score of 3), and very much.⁷ The higher score was assigned to the answers correlating to a higher level of function.

Patients were contacted by telephone and gave verbal consent. If the participant was unable to directly answer questions their closest caregiver or relative was allowed to answer on their behalf. Patients were asked to respond to the question with "not at all," "a little bit," "somewhat," "quite a bit," or "very much." The correlating numerical

score (0 to 4) for the patient's answer was circled. The scores for each section were added and converted into a percentage. A perfect score, 100%, indicates the patient had no functional deficits.

The maximum score a patient could obtain for a section was 20, except "functional well-being" that had a maximal score of 24. We stratified the results of the questionnaire to an ECOG PS. ECOG PS 0 to 4 were included; ECOG PS 5 was excluded for this study investigated only living patients. Questionnaire scores and/or percentages were evenly divided into 5 groups. The highest scores (80% and above) were assigned an ECOG PS of 0, 60% to 79% an ECOG PS of 1, 40% to 59% an ECOG PS of 2, 20% to 39% an ECOG PS of 3, and 0% to 19% an ECOG PS of 4. See [Table 1](#).

A retrospective chart review was performed for each participant. Demographic data were collected including patients' age, operative time, length of hospital stay, and PCI.

Results

From the eligible study population ($n = 63$), 33 patients consented to participate in the study. Average age was 54.9 years; 12.2% were between the ages of 30 and 39, 15.2% between 40 and 49 years, 27.3% between 50 and 59 years, 39.3% between 60 and 69 years, 3% between 70 and 79%, and 3% were 80+ years.

The most common malignancy was appendiceal (47%) followed by colorectal (35%). The remainder (18%) included small bowel and gastric malignancies. The average PCI score was 12.5. Average length of stay was 9.8 hospital days, and average length of operation was 594.2 minutes.

The average scores for physical well-being was 15.4 of 20, social well-being 17.5 of 20, recovery 15 of 20, mental well-being 13.4 of 20, and functional well-being 18.1 of 24. This produced an overall score of 72.6 of 106. These score were stratified to an ECOG-performance scale value. See [Table 2](#) for average scores and correlation to ECOG PS.

Using one-way analysis of variances test, patient demographics were compared with ECOG PS at 3 months. Patient's age ($P = .235$), operative length ($P = .181$), hospital duration ($P = .43$), complications or PCI ($P = .815$) demonstrated no significance to postoperative PS.

Table 1 Stratification of raw scores to ECOG PS

Raw score for physical health	Percentage	ECOG PS
16–20	80–100	0
12–15	60–79	1
8–12	40–59	2
4–8	20–39	3
0–3	0–19	4

ECOG = Eastern Cooperative Oncology Group; PS = performance status.

Table 2 Average scores, percentile and ECOG PS stratification

Area of health	Average score ($n = 33$)	Percentage	ECOG PS
Physical well-being	15.4/20	77	1
Social well-being	17.5/20	87.5	0
Recovery	15/20	75	1
Mental well-being	13.4/20	67	1
Functional well-being	18.1/24	75.4	1

ECOG = Eastern Cooperative Oncology Group; PS = performance status.

Comments

Patients with peritoneal carcinomatosis from a gastrointestinal or gynecologic malignancy should be evaluated for HIPEC. Complete CRS + HIPEC may prolong survival time for appropriate candidates who undergo surgery.

In comparison to similar studies, our facility demonstrates a lower morbidity rate (as measured by the Clavien–Dindo scale): grade I/II 35%, grade III/IV 11%. Also improved from previous studies was our mortality rate: 0% at 30 or 60 or 90 days. This demonstrates that a single facility, community-based HIPEC center can deliver reliable results with improved outcomes.

The ECOG PS scale is a widely accepted and validated measurement of PS. We recognize there are many validated scales and methods to assess functional and/or PS. The ECOG PS is regularly used at our institution and was continued during the study due to its ease of use.

Stratification of our questionnaire data to a PS score is, to our knowledge, not reported elsewhere. This approach requires ongoing data collection to allow researchers to validate this questionnaire and stratification method. Future models should involved administration of the questionnaire 3 months postoperatively by the method described in our study. An office visit should be conducted within the same 3 month postoperative time frame with same clinician performing a thorough history and physical examination to assign a PS. This would then allow for correlation and validation of our stratification method. Until this is establish, our current model demonstrates to be a reliable, easily calculated, and relatively quick assessment of functional status for use in both outpatient clinic and inpatient ward settings.

Two trained clinicians were responsible for data gathering: 1 assessed all preoperative PS and the other contacted all participants for questionnaire completion. This ensured minimal internal variation within data collection. Inherent to the study design (retrospective) is recall bias. To minimize this bias, researchers gave patients reference points and asked for their response at 3 months postoperative. Patients were asked to provide answers based on the surgery alone; they were asked to

exclude any chemotherapy or neoadjuvant therapy experiences.

Investigators points of future development include administration the questionnaire preoperatively and various times postoperatively (3, 6, and 9 months) to allow for a more consistent method of data collection and stratification to PS and reduce any recall bias.

All patients returned to an acceptable functional status at 3 months postoperative. This is improved from multiple studies that quote a return to an acceptable functional status at 4 to 24 months.⁴⁻⁶ Consistent with other studies, mental well-being showed the greatest dealt in recovery. Social functioning returned to a baseline at 3 months (ECOG PS score 0) for our population but lagged in recovery in other studies.⁴ One may extrapolate, that patients continue to improve and may experience a better than baseline functional status at 6, 9, or 12 months postoperatively. Clinicians should focus postoperative counseling on the area(s) that which the questionnaire identified to have the greatest lag in recovery. Extra time counseling, referrals, and resource material should be made available to all patients in their area of need.

Age, pathology, and prior intervention were not found to be significant related to PS at 3 months. This may prevent exclusion of potential candidates based on advanced age, pathology, and treatment history.

Conclusions

Patients can recovery well from HIPEC. It is possible to return to an acceptable functional status within 3 months postoperative. Age, operative time, length of hospital stay, or PCI may have no significant long-term effects on recovery for the well-selected patients who undergo complete CRS + HIPEC.

References

1. Zhu Y, Hanna N, Boutros C, et al. Assessment of clinical benefit and quality of life in patients undergoing cytoreduction and hyperthermic intraperitoneal chemotherapy (HIPEC) for management of peritoneal metastases. *J Gastrointest Oncol* 2013;4:62–71.
2. Ihemelandu C, McQuellon R, Shen P, et al. Predicting postoperative morbidity following cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CS + HIPEC) with preoperative fact-C (functional assessment of cancer therapy) and patient-related performance status. *Ann Surg Oncol* 2013;20:3519–26.
3. Turaga K, Levine E, Barone R, et al. Consensus guidelines from the American society of peritoneal surface malignancies on standardizing the delivery of hyperthermic intraperitoneal chemotherapy (HIPEC) in colorectal cancer patients in the United States. *Ann Surg Oncol* 2014; 21:1501–5.
4. Tsilimparis N, Bockelmann C, Raue W, et al. Quality of life in patients after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: is it worth the risk? *Ann Surg Oncol* 2013;20:226–32.
5. McQuellon R, Loggie B, Lehman A, et al. Long-term survivorship and quality of life after cytoreductive surgery plus intraperitoneal

hyperthermic chemotherapy for peritoneal carcinomatosis. *Ann Surg Oncol* 2003;10:155–62.

6. Tuttle TM, Zhang Y, Greeno E, et al. Toxicity and quality of life after cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy. *Ann Surg Oncol* 2006;13:1627–32.
7. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the eastern cooperative oncology group. *Am J Clin Oncol* 1982;5: 649–55.
8. Ward WL, Hahn EA, Mo F, et al. Reliability and validity of the functional assessment of Cancer therapy-colorectal (FACT-C) quality of life instrument. *Qual Life Res* 1999;8:181.

Discussion

Discussant

Dr. Mathew Chung (Grand Rapids, MI): Your complication rates of grade 3 and 4 complication rates are much better than our results and was published in most literature in this area. So maybe you guys do a better job there, but that was a little bit lower than was generally reported. The other comment is, if I read your article correctly, you had 63 patients who underwent this procedure; 43 cytoreduction, HIPEC, and then 33 were included in the study. So about half of the population were lost or did not consent, so I am not so sure if you can make meaningful conclusions based on that if you have lost half the patients that you operated on, although those half that did report their outcomes reported good results.

Second comment would be, these were results based on questionnaires, and there is some inherent problems with that methodology as well. Of course, most patients, especially if they like the surgeon, are going to say I did great, when, in fact, they may not be able to go up a flight of stairs.

Specific questions I have for you are, what chemotherapy did you use for all these HIPECs? Did that vary based on tumor pathology?

Second question, I know very small percentage of your patients have small bowel cancer. Usually HIPEC is not recommended for that in general. So why was it used, and what are your outcomes? And, third, do you have an age cutoff for HIPECs? I know functional status trumps everything, but one of the patients I think was 88 years old, and personally I would have a hard time recommending this aggressive procedure for an 88-year-old.

Dr. Berri: As far as the numbers enrolled within our study, the patients were not necessarily lost to follow-up. For example, the 33 patients of the 63 were those that were able to consent and actually connect with over the phone within the time constraints of our study. Postoperatively, we see the patients once they are released from the hospital at 1-week postoperative, 2 weeks postoperative, and then every 2 months for to next 2 years, at least if everything goes well, if not more frequently. So the patients are continued to be followed, and even if they, the remaining patients were able to be included within our study, we would expect it not to alter our results that much, for we are continuing to follow the patients. We have been able to

analyze their morbidities that they have developed, and they do not differ significantly from the ones that were included and this is also demonstrated in secondary study that we have being presented as a poster where we examined all the comorbidities of the rest of the HIPEC patients as well.

The question regarding small bowel, there are very limited data based on small bowel malignancies and the use of HIPEC; however, there are some consensus or limited data that explores that, if there is a low tumor burden and a low disease burden, that HIPEC will still benefit these patients. The one that was included in the study and subsequently since then, a few more patients with small bowel malignancies have been included in our studies. But this specific one is approximately 2 and a half years, 30 months from the surgery and remains disease free with an excellent PS.

As far as chemotherapy, the ones included in this study at this time is, we included Mitomycin-C that was heated to 42°C, and there are different chemotherapeutic agents that can be used based on the primary pathology. Cisplatin is another one. Mitomycin-C is mentioned so it really depends on the primary pathology and the consensus guidelines as established by the American Society of Peritoneal Surface Malignancies that you can use as guidelines. But the short answer, it is Mitomycin-C used in this case.

As far as age goes, the generally accepted an age cutoff is approximately 70 years, however, at our institution, with the use of the multidisciplinary tumor board, we are able to evaluate the patients very comprehensively. We also use not only PS comorbidities, but we use an National Surgical Quality Improvement Program risk calculator quite extensively as well. And if the patient has a very low acceptable risks or development of postoperative complications and we feel they are appropriate candidate, we will still offer CRS and HIPEC to the patient.

Dr. Roderich Schwarz (Goshen, IN): I think you are doing a very important activity in measuring quality of life outcomes for a disease spectrum that is difficult to measure in terms of outcome intervention successes because it is a spectrum of diseases. And some patients present with strong symptoms and others actually do not. So I think having this quality of life assessment and symptom scale preoperatively and then comparing it to an early and perhaps more delayed 3-month postoperative time point would be more meaningful, and also you have patients who were evaluated and not considered candidates for this. It would be very helpful to have the same quality of life assessment for those so you can actually prove that your intervention made a difference. So I am curious if you are thinking about looking into that, as well.

Dr. Berri: Absolutely. That is an excellent comment and that is something that we have started to discuss and use within our program as well. We feel that this is kind of our starting project for it and are in complete agreement with you that this would be an excellent tool now to use in

preoperative assessment of the patients 1-week postoperative, 3 weeks postoperative and be able to use it longitudinally. It is not only trace and be able to track the patient's recovery but be able to compare it within the patients as well.

When we performed the study as well, it was a third party who called the patients and asked them about all the questions, so we tried to eliminate any surgeon bias or preferential bias as previously mentioned for the surgeon and direct nurse practitioners as well that were involved in the patients' primary care. And even if the patients do have an affinity to, we are blinded from actually asking the questionnaire.

Dr. Robert P. Sticca (Grand Forks, ND): As you know, many of these patients require sigmoid and upper rectal resections because of a bulky disease in the pelvis and they end-up with colostomies. Did you guys correlate when you had to do a colostomy whether that impacted the quality of life, their functional status, and their feelings of well being after the surgery?

Dr. Berri: We did not look at that specifically. That would be a great point to move forward from here, because, as you said, it does impair the quality or alter the quality of life or the PS is an adjustment for the patients.

Dr. Christopher R. Mchenry (Cleveland, OH): I was very impressed with your hospital readmission rate, which was only 3%. I mean, that is lower than our readmission rate for thyroidectomy. And it was so impressive in such a complex group of patients. And we know from Medicare data, that 25% to 33% of patients who are readmitted, are readmitted to other hospitals. So is this readmission rate just to your hospital? And then, finally, what transitions to care have you instituted that have resulted in such a low hospital readmission rate?

Dr. Berri: This is the readmission rate at our institution specifically. In our patient population, they are very involved with communication with the surgeon, with the nurse practitioner, and multiple other institutions that they may be living around. 20% of our patients do live over 200 miles away, so if they do go to their home institution, we found that communication and transfer back to our hospital has been excellent thus far. So this is just within our home institution.

As far as transitions to care, part of the reason why we believe that our readmission rate is so good, is we do a very extensive preoperative evaluation, including a prehab program, as well, making sure the patients are in their best functional status. Once they have been decided and once the surgery has been scheduled, they will undergo a prehab program to ensure that they are at their maximal strength, at their maximum PS to that point, as well.

Postoperatively, at our institution we have a very, again, multidisciplinary approach. We have physical therapy, occupational therapy, and social work. The nurse practitioner who works with the patients, they are very involved in the postoperative care. And so we are able to transition the patients most of the time back to their own home.