ARTICLE TITLE: Looking Up: Recent Advances in Understanding and Treating Peritoneal Carcinomatosis

CONTINUING MEDICAL EDUCATION ACCREDITATION AND DESIGNATION STATEMENT:
Blackwell Futura Media Services is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education (CME) for physicians.
Blackwell Futura Media Services designates this enduring material for a maximum of 1.5 AMA PRA Category 1 Credit™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

CONTINUING NURSING EDUCATION ACCREDITATION AND DESIGNATION STATEMENT:
The American Cancer Society (ACS) is accredited as a provider of continuing nursing education (CNE) by the American Nurses Credentialing Center’s Commission on Accreditation.
Accredited status does not imply endorsement by the ACS or the American Nurses Credentialing Center of any commercial products displayed or discussed in conjunction with an educational activity. The ACS gratefully acknowledges the sponsorship provided by Wiley for hosting these CNE activities.

EDUCATIONAL OBJECTIVES:
After reading the article “Looking Up: Recent Advances in Understanding and Treating Peritoneal Carcinomatosis” the learner should be able to:
1. Describe the role of cytoreductive surgery and hyperthermic intraperitoneal chemoperfusion in the treatment of peritoneal carcinomatosis.
2. Discuss common complications of peritoneal carcinomatosis and recommendations for palliative care of this condition.

ACTIVITY DISCLOSURES
No commercial support has been accepted related to the development or publication of this activity.

ACS CONTINUING PROFESSIONAL EDUCATION COMMITTEE DISCLOSURES
Editor, Director of Continuing Professional Education, and ACS Director of Medical Content
Ted Gansler, MD, MBA, MPH, has no financial relationships or interests to disclose.
Deputy Editor and ACS Director of Prostate and Colorectal Cancers
Durado Brooks, MD, MPH, has no financial relationships or interests to disclose.
Lead Nurse Planner and Associate Editor
Marcia Grant, RN, PhD, FAAN, has no financial relationships or interests to disclose.
Associate Editor and Chief Cancer Control Officer
Richard C. Wender, MD, has no financial relationships or interests to disclose.

AUTHOR DISCLOSURES
Laura A. Lambert, MD, FACS, FICS reports no conflicts of interest.

SCORING
A score of 70% or better is needed to pass a quiz containing 10 questions (7 correct answers), or 80% or better for 5 questions (4 correct answers).

CME INSTRUCTIONS ON RECEIVING CME CREDIT
This activity is intended for physicians. For information concerning the applicability and acceptance of CME credit for this activity, please consult your professional licensing board.
This activity is designed to be completed within 1.5 hours; physicians should claim only those credits that reflect the time actually spent in the activity. To successfully earn credit, participants must complete the activity during the valid credit period, which is up to 2 years from the time of initial publication.

CNE INSTRUCTIONS ON RECEIVING CNE CREDIT
This activity is intended for nurses. For information concerning the applicability and acceptance of CNE credit for this activity, please consult your professional licensing board.
This activity is designed to be completed within 1.5 hours; nurses should claim only those credits that reflect the time actually spent in the activity. To successfully earn credit, participants must complete the activity during the valid credit period, which is up to 2 years from the time of initial publication.

FOLLOW THESE STEPS TO EARN CREDIT
- Log on to acsjournals.com/ce.
- Read the target audience, educational objectives, and activity disclosures.
- Read the activity contents in print or online format.
- Reflect on the activity contents.
- Access the examination, and choose the best answer to each question.
- Complete the required evaluation component of the activity.
- Claim your certificate.

This activity will be available for CME/CNE credit for 1 year following its launch date. At that time, it will be reviewed and potentially updated and extended for an additional 12 months.

All CME/CNE quizzes are offered online FREE OF CHARGE. Please log in at acsjournals.com/ce. New users can register for a FREE account. Registration will allow you to track your past and ongoing activities. After successfully completing each quiz, you may instantly print a certificate, and your online record of completed courses will be updated automatically.
Looking Up: Recent Advances in Understanding and Treating Peritoneal Carcinomatosis

Laura A. Lambert, MD*

Until recently, a diagnosis of peritoneal carcinomatosis was uniformly accompanied by a grim prognosis that was typically measured in weeks to months. Consequently, the management of carcinomatosis revolves largely around palliation of symptoms such as bowel obstruction, nausea, pain, fatigue, and cachexia. A prior lack of effective treatment options created the nihilistic view that currently exists and persists despite improvements in the efficacy of systemic therapy and the evolution of multimodality approaches including surgery and intraperitoneal chemotherapy. This article reviews the evolution and current state of treatment options for patients with peritoneal carcinomatosis. In addition, it highlights recent advances in understanding the molecular biology of carcinomatosis and the focus of current and future clinical trials. Finally, this article provides practical management options for the palliation of common complications of carcinomatosis. It is hoped that the reader will recognize that carcinomatosis is no longer an imminent death sentence and that through continued research and therapeutic innovation, clinicians can make an even greater impact on this form of metastatic cancer. CA Cancer J Clin 2015;65:283-298. © 2015 American Cancer Society.

Keywords: peritoneal, carcinomatosis, hyperthermic intraperitoneal chemoperfusion (HIPEC), cytoreduction, ascites, hyperthermic, chemoperfusion

Introduction

Intraperitoneal carcinoma (carcinomatosis) remains one of the greatest oncologic challenges. Despite significant recent advances in cancer treatment, for most patients with carcinomatosis, it will be the ultimate cause of death and many providers still view all forms of carcinomatosis as a terminal condition. Unavoidably, this nihilistic view informs our approach to the treatment of patients with carcinomatosis. A grim prognosis is routinely administered with limited, if any, hope of effective treatment. For patients who present with a reasonable performance status, treatments offered are frequently limited to palliative systemic therapy, hopefully with an early referral to palliative care for supportive management and assistance with goals of care. For patients who present with an acute complication of carcinomatosis, hospice is often the only option offered. However, recent advances in our understanding of carcinomatosis demonstrate that it is not a single entity with a uniformly lethal behavior. Likewise, due to advances in surgical techniques and regional therapies, palliative systemic therapy is no longer the only treatment option available. Thus, as with most other forms of cancer, the treatment of carcinomatosis can and should be approached on an individual basis with respect to the patient, the tumor biology, and the variety of therapeutic options available. This article reviews current therapeutic and palliative treatment options, the focus of recent and ongoing research and clinical trials, and potential future directions for the treatment of carcinomatosis from various cancers.

The Evolution and Current Management of Peritoneal Carcinomatosis

Not all peritoneal “carcinomatoses” are created equal, neither across tumor types nor within a single tumor type. The prognosis associated with peritoneal dissemination of an indolent mucinous neoplasm of the appendix is typically measured in years, whereas the prognosis for peritoneal carcinomatosis from gastric cancer may be measured in weeks.1,2 Similarly, the expected prognosis of a patient with T4 signet ring cell cancer of the colon with diffuse miliary seeding of the peritoneum is much less than that of a patient with T4, lymph node-negative, low-grade colon cancer with a limited number of discrete, resectable tumor nodules within the peritoneum.3 However, once the diagnosis of carcinomatosis is made, patients are...
often informed that they have only months to live, and that there is no effective treatment. The notable exception to this generalization is AJCC TNM and FIGO stage III (peritoneally disseminated) ovarian cancer.

Currently, the average 5-year survival rate for all patients with stage III invasive epithelial ovarian cancer is 39%.4 For patients with stage III, optimally resected, epithelial ovarian cancer who receive intraperitoneal chemotherapy, the 5-year survival rate increases to 45% to 54%, with a median survival of 49 to 66 months.5–7 Over the course of the past 3 decades, 7 randomized clinical trials have demonstrated the efficacy of intraperitoneal chemotherapy in combination with intravenous chemotherapy.8 Current recommendations for the management of advanced ovarian, fallopian tube, and primary peritoneal cancers include a combined approach of optimal tumor debulking surgery (defined as not leaving any residual tumor nodules measuring greater than 1 cm), platinum-based combination intravenous chemotherapy, and intraperitoneal chemotherapy.9 It is my opinion that the uniqueness of subspecialty physicians (gynecologic oncologists) providing both the surgical and medical aspects of cancer treatment, compared with the general medical and surgical oncology communities, has allowed so much progress to be made for gynecologic oncology patients, whereas patients with carcinomatosis from nongynecologic malignancies have not fared as well.

Since the 1980s, surgical oncologists have developed and refined a combined approach of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemoperfusion (HIPEC) for patients with isolated peritoneal carcinomatosis. The initial report of the use of CRS/HIPEC in the United States was by Spratt et al from the University of Kentucky in Louisville in 1980.10 In this report, the authors described the technique of cytoreduction and HIPEC used to treat a young man with peritoneal dissemination of a mucinous neoplasm of the appendix. The authors also reviewed the efforts leading up to the understanding of peritoneal surface malignancies and the rationale for the regional approach, as well as the device used for HIPEC. Subsequently, in the late 1980s and early 1990s, a number of reports on the safety and efficacy of HIPEC in patients with advanced gastric cancer came out of Japan, mostly by Fujimoto et al.11,12 This was the beginning of what has become a global effort to discover better treatment options for carcinomatosis. In the United States, this effort was initially driven largely by the work of Sugarbaker, after whom this combined approach is often referred.13–15

The rationale behind this approach is to achieve a macroscopically complete cytoreduction of the carcinomatosis (no residual tumor measuring greater than 0.25-cm thick) and then treat any residual microscopic disease with high-concentration, hyperthermic chemotherapy applied directly into the peritoneal cavity. Achieving a complete cytoreduction involves major abdominal surgery. Based on the volume and distribution of the carcinomatosis, as well as the “invasiveness” of the peritoneal implants, achieving a complete cytoreduction may involve major peritoneal stripping, multivisceral resections (including the omentum, large and small bowel, stomach, spleen, gallbladder, uterus and ovaries, pancreas, ureters, and bladder), and the creation of temporary or permanent stomas.

Upon completion of the cytoreduction, HIPEC is typically administered for 30 to 120 minutes (depending on the preference of the surgical oncologist and the type of chemotherapy used). Jacquet and Sugarbaker described the peritoneal-blood barrier, which allows high concentrations of high molecular weight chemotherapy agents to be administered intraperitoneally with limited systemic absorption and toxicity.16 Hyperthermia was added to the treatment for 3 reasons. First, cancer cells are more sensitive to heat (typically at greater than 43°C for 1 hour) than normal cells.17–19 Second, there is a synergistic increase in cytotoxicity between hyperthermia and many chemotherapy agents.20,21 Third, it is theorized that hyperthermia may help the chemotherapy penetrate deeper into the peritoneal tissues. The whole treatment takes an average of 8 to 10 hours. Most centers admit patients to the intensive care unit immediately after surgery. The average length of stay in the hospital ranges from 8 to 22 days.22–25

Despite some negative press in the lay community and a paucity of level I evidence, the use of CRS/HIPEC has continued to expand in the United States and around the globe.26,27 Today, it is largely accepted as the standard-of-care treatment for the management of low-grade mucinous tumors of the appendix.28 It is gaining acceptance as part of the treatment of isolated carcinomatosis from colorectal cancer and peritoneal mesothelioma.29,30 Recent reports of long-term outcomes in patients with appendiceal cancer demonstrated a significant improvement in 5-year and 10-year survival rates (81% and 70%, respectively) in patients with low-grade mucinous tumors of the appendix compared with the use of CRS alone.1,31 For patients with peritoneal mesotheliomas who undergo complete cytoreduction and HIPEC, mean survival of 38 to more than 90 months are reported compared with 12 months for those who receive systemic therapy alone.30,32,33 For patients with isolated peritoneal carcinomatosis from colon cancer who undergo a complete cytoreduction and HIPEC, reported median survival of 32 to 63 months and 5-year survival rates of 44% to 58% compare favorably with an expected median survival of 5.2 to 23.9 months and a 5-year survival rate of 0% to 19% with systemic therapy alone (Table 1).1,7,32–36 Recently, the American Society of Peritoneal Surface Malignancies put forth an opinion statement establishing an expectation of a median survival of 30 months after CRS/HIPEC for patients with colorectal cancer.36 In addition, clinical trials
Recent Advances in Understanding and Treating Peritoneal Carcinomatosis

are currently ongoing to determine whether there is a role for HIPEC in the management of gynecologic malignancies, as well as other cancers such as gastric and pancreatic. However, for a number of reasons, based on patterns of care, the combination of CRS and HIPEC is still not considered by many to be in the mainstream of the management of carcinomatosis. The lack of randomized controlled trials, the magnitude of the intervention, a history of significant morbidity and mortality, technical variations (eg, open vs closed HIPEC, length of HIPEC, and choice of chemotherapy) in the approach across centers, and the undetermined independent efficacies of CRS and HIPEC have all contributed to the current controversy surrounding its use.

As with any new major surgical technique, over time seemingly unacceptable rates of morbidity and mortality improve. A comprehensive review of reported results from more than 20 CRS/HIPEC centers since 2003 shows major morbidity rates of 0% to 50% and mortality rates ranging between 0% to 6% at high-volume centers. These rates are now consistent with other major abdominal cancer operations such as pancreaticoduodenectomy and esophagectomy.

A number of recent reports also describe a learning curve for CRS/HIPEC that improves not only the morbidity and mortality but also the oncologic outcomes from the procedure. These studies have consistently suggested a need for 100 to 150 cases to be performed for a surgeon to become proficient. In addition, these studies have also demonstrated the benefits of experienced surgical mentors guiding less experienced CRS surgeons and of high-volume centers with comprehensive carcinomatosis programs.

Essential knowledge with regard to prognostic factors for carcinomatosis has also been gained through the experience of the past 30 years. CRS/HIPEC studies have repeatedly shown that the most important prognostic factor is the completeness of the cytoreduction. A complete cytoreduction is typically considered to be achieved if there is no gross residual disease (CC-0 or R0-R1) or if there is a minimal amount (measuring less than 0.25-cm in thickness) of residual disease (CC-1 or R2a). For the gynecologic malignancies, a cytoreduction is considered optimal if there is no residual disease measuring greater than 1.0 cm. Regardless of the scoring system used, it has been repeatedly demonstrated that HIPEC in the setting of an incomplete cytoreduction (leaving macroscopic disease measuring greater than 0.25 cm) offers no significant survival advantage over systemic chemotherapy alone. Similarly, within the gynecologic oncology literature, it has been demonstrated that a macroscopically complete cytoreduction (no macroscopic residual disease) plus intraperitoneal chemotherapy afford a significantly better oncologic outcome compared with an optimal (residual disease measuring <1 cm) cytoreduction (median survival of 128 months vs 48 months).

Two other important prognostic factors are the origin of the cancer and the cancer histology. In addition to contributing to the cancer’s potential aggressiveness and sensitivity to chemotherapy, these factors also contribute to a cancer’s resectability. A surgical concept that is often difficult to convey is the “stickiness” or “invasiveness” of a peritoneal surface malignancy, with more “sticky” or invasive tumors being harder to completely cytoreduce. An excellent example of the potential extremes of peritoneal “stickiness” is demonstrated by the spectrum of appendiceal cancers. Due to the thin wall of the appendix, perforation (either through cancer invasion or appendiceal overdistention due to luminal obstruction) and peritoneal dissemination are common presentations. Low-grade mucinous neoplasms of the appendix are frequently associated with a gelatinous mucinous ascites referred to as pseudomyxoma peritonei (Fig. 1A). These tumors tend not to invade either the parietal or visceral peritoneum and can often be adequately cytoreduced by simply evacuating the mucin and removing the appendix. There is still significant debate regarding whether these neoplasms should be considered true cancers. Well-differentiated mucinous adenocarcinomas of the appendix often behave similarly but may have a solid component of the peritoneal implants and a more invasive character requiring surgical

TABLE 1. Best Reported Survival With Peritoneal-Directed Therapy Compared With Systemic Therapy

| CANCER           | IP THERAPY         | MEDIAN SURVIVAL, MONTHS | STUDIES                        |
|------------------|--------------------|-------------------------|-------------------------------|
|                  | IP THERAPY         | SYSTEMIC THERAPY         | STUDIES                        |
| Appendix         | CRS/HIPEC ± EPIC   | 196                     | 117.6a                        | Chua 2012,1 Vogelzang 200332 |
| Colorectal       | CRS/HIPEC ± EPIC   | 62.7                    | 23.9                          | Esquivel 201416            |
| Mesothelioma     | CRS/HIPEC ± EPIC   | 92                      | 12.1                          | Feldman 2003,33 Baratti 201434 |
| Ovarian          | CRS/IPC            | 65.6                    | 49.7                          | Armstrong 200617          |

CRS, cytoreductive surgery; EPIC, early postoperative chemoperfusion; HIPEC, hyperthermic intraperitoneal chemoperfusion; IP, intraperitoneal; IPC, intraperitoneal chemotherapy. *Iterative CRS alone.
resection of viscera to achieve a complete cytoreduction. Although treatment guidelines for appendiceal cancer specify that a right hemicolectomy should be performed, recent studies have demonstrated that there is a low incidence of lymph node metastases with well-differentiated appendiceal cancers and that a right hemicolectomy does not appear to improve the oncologic outcome.49–51 Moderately or poorly differentiated and signet ring cell cancers of the appendix tend to produce less extracellular mucin, tend to be more invasive, and have a higher incidence of lymph node metastases. Right hemicolectomy is still recommended as part of the management of these tumors.52 Given their more aggressive nature and faster rate of growth, CRS/HIPEC is often preceded by systemic chemotherapy. Achieving a complete cytoreduction with these more aggressive tumors is challenging due to the diffuse miliary nature of dissemination, which often extensively involves the serosa and mesentery of the small bowel (Fig 1B). Unfortunately, neither computed tomography (CT) nor magnetic resonance imaging are perfect predictors of tumor “stickiness” or overwhelming small bowel or mesenteric involvement. Although there are some defined radiologic findings that suggest that peritoneal carcinomatosis cannot be completely cytoreduced (biliary obstruction, cauliflowering of the small bowel, multilevel bowel obstructions), because these higher grade tumors tend to grow in thin, plaque-like lesions, they are often undetectable on imaging. Better classification and understanding of the spectrum of appendiceal tumors and cancers is the topic of ongoing study and investigation.53,54

The impact of tumor volume also appears to be determined by the cancer’s site of origin. For low-grade appendiceal tumors, if a complete cytoreduction can be achieved, the actual volume of the tumor does not appear to have a prognostic impact.55,56 However, this is not true for colon cancer. A number of studies have demonstrated that even if a complete cytoreduction is achieved, patients with colon cancer with a higher burden of disease do not benefit as much from CRS/HIPEC.57,58 In an effort to provide a way of quantifying carcinomatosis, several scoring systems have been developed (Table 2).59–64 Some simply divide the abdomen into defined regions and ask the surgical oncologist to rate the volume of disease in each defined region based on the prescribed rating system. The scores for each region are tallied and an overall score is created. One of the most frequently used scoring systems is the Peritoneal Cancer Index (PCI) (Fig. 2).61 This system divides the peritoneal cavity and small bowel into 13 different sections. Each section is then given a score of 0 to 3 based on how much tumor is present in that region (0 indicates none, whereas 3 indicates confluent tumor or that measuring greater than 2.5 cm). Although still somewhat subjective, these systems allow surgical oncologists to better compare outcomes, including oncologic outcomes, morbidity, and mortality, based on the extent of tumor burden. Consequently, some centers restrict HIPEC in patients with colorectal cancer to a limited burden of disease (PCI of <15-20).53 Identifying prognostic factors such as tumor histology and PCI are essential to improving patient selection for these procedures.

Because of the morbidity and mortality associated with CRS/HIPEC, significant effort has gone into developing methods of identifying those patients who are most likely to benefit from the procedure. Three different scoring systems have been developed to incorporate a number of prognostic factors and better identify the patients who will
benefit from CRS/HIPEC. The Prognostic Score was created by Verwaal et al for patients with colon and rectal cancer.64 This score is calculated by the following equation:

\[
\text{Prognostic Score} = 0.592C + 1.875R + 0.448D + 0.487H + 0.343Re
\]

in which C indicates colon cancer (C = 1 if colon cancer, otherwise 0) and R indicates rectal cancer (R = 1 if rectal cancer, otherwise 0). D is 1 if the tumor is moderately/well differentiated or 2 if it is poorly differentiated. H is either 1 if the cancer does not have signet ring cells or 2 if there are occurrences of signet ring cells. The last variable, Re, refers to the number of affected regions in the abdomen (1–7), defined as follows: pelvis, right lower abdomen, omentum and transverse colon, small bowel and mesentery, subhepatic space and stomach, right subphrenic space, and left subphrenic space. Unlike other studies, the authors concluded from this study that it was not necessarily the volume of disease that mattered but rather the distribution and ability to achieve a complete cytoreduction. They also found that patients with signet ring cell or poorly differentiated histology, rectal cancer, or more than 5 regions involved with tumor had a poorer overall survival.

More recently, Esquivel et al65 and Pelz et al66 developed the Peritoneal Surface Disease Severity Score (PSDSS) for both colon and appendiceal cancer. These scores are composed of 3 elements: tumor histology, symptomatology, and PCI as determined from a preoperative CT scan. The scores are then divided into 4 (colon) or 5 (appendiceal) stages of disease severity. In their initial investigations of the usefulness of the PSDSS in patients with colon cancer, the authors found that all patients with a PSDSS stage IV (the worst stage) had a median survival of 5 months, with a median survival of only 7 months reported for those who had a complete CRS and HIPEC.66 More recently, in a multiinstitutional retrospective study of more than 1000 patients with carcinomatosis from colon cancer, the median survival for patients with a PSDSS of IV was 28 months for patients who underwent CRS/HIPEC compared with only 6 months for patients with a PSDSS of IV who received systemic therapy alone.3 It is unclear to what the improved survival may be attributed, but it is presumed to be due to a lower volume of disease in the patients with a PSDSS of IV in the multiinstitutional study (J. Esquivel, written communication, July 2014). Interestingly, the authors also found that patients with a PSDSS of I who only received systemic chemotherapy had a median survival of 45 months and the median survival had not been reached in those who received CRS/HIPEC, again suggesting that not all patients with carcinomatosis have a prognosis of 6 to 7 months and each patient needs to be treated individually and according to the burden and histology of their disease.

Although the first 2 scoring systems produce nicely stratified groups, the studies in which they were presented included patients who survived more than 2 years in the

| CLASSIFICATION       | ABDOMINAL REGIONS | TUMOR MEASUREMENTS | SCORING/STAGING                                                                 | PROGNOSTIC IMPLICATIONS                                                                 | STUDIES                                      |
|----------------------|-------------------|--------------------|---------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|----------------------------------------------|
| PCI                  | 13                | 0: no tumor        | Each region is given a score of 0 to 3 and the scores are totaled; maximum score is 39 | Predictive of survival and cytoreducibility in colorectal cancer                       | van der Vange 2000,62 Verwaal 200464        |
| Gilly staging        | NA                | <0.5 cm            | Stage 0: no macroscopic diseaseStage 1: <0.5 cm, one part of the abdomen Stage 2: <0.5 cm, diffuse in the abdomenStage 3: 0.5 to 2 cm nodulesStage 4: >2 cm nodules | Significant survival differences between stages 1 and 2 and stages 3 and 4             | Jacquet & Sugarbaker 199661                |
| Japanese Research Society for Gastric Cancer | NA | NA | PO: no implantsP1: implants near stomachP2: scattered implants in distant peritoneum and ovaryP3: numerous implants in distant peritoneum | Significantly lower survival rates for P3                                                | Gilly 199460                                |
| Dutch SPCI           | 7                 | None               | Each region is given a score of 0 to 3 and the scores are totaled; maximum score is 21 | Higher SPCI predicts worse outcome from CRS/HIPEC                                       | Goere 201563                                |

CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemoperfusion; NA, not applicable; PCI, Peritoneal Cancer Index; SPCI, Simplified Peritoneal Cancer Index.
highest risk groups. Therefore, it is hard to determine whether to not recommend CRS/HIPEC solely on the basis of these scores. To address this issue, Cashin et al developed a third scoring system for COlon and REctal Peritoneal carcinomatosis (COREP) based primarily on laboratory studies. Using an elaborate scoring system based largely on elevations and changes in systemic tumor markers (including carcinoembryonic antigen, CA 125, CA 19.9, and CA 15.3), COREP identifies patients who will likely die of their disease in fewer than 12 months and who therefore are not likely to benefit from CRS/HIPEC. Although none of these scoring systems can perfectly predict which patients will benefit from CRS/HIPEC, they are stepping stones toward helping us identify important prognostic factors as well as provide a means of discussing prognosis with patients and their families.

Despite significant advances in the surgical technique of CRS and improving rates of morbidity and mortality, the majority of patients with peritoneal carcinomatosis are not candidates for CRS/HIPEC. This may be due to the presence of extraperitoneal metastases, extensive involvement of the small bowel and mesentery, a high burden of disease in the gastrohepatic region, or the performance status of the patient. In addition, it is not infrequent that even patients with isolated peritoneal carcinomatosis are referred to the surgical oncologist only after receiving multiple lines of systemic therapy with continued disease progression. Because the success of CRS/HIPEC is dependent on the completeness of the cytoreduction, for CRS/HIPEC to be a meaningful adjuvant therapy, it needs to be considered routinely and early as part of a multimodality approach to treating carcinomatosis.

Multiagent systemic therapy regimens have led to significant improvements in the response rate and survival for patients with advanced colorectal cancer. Prior to the use of the cytotoxic agents oxaliplatin and irinotecan in combination with fluorouracil, either with or without a biologic agent such as bevacizumab or cetuximab, the expected survival for patients with peritoneal carcinomatosis from colorectal cancer was no more than 12 months. There are no modern, systemic chemotherapy trials limited to patients with isolated peritoneal carcinomatosis and most clinical trials do not specifically report on the survival of patients with peritoneal carcinomatosis. Furthermore, the majority of patients with carcinomatosis also have other sites of metastatic disease, such as the liver and/or the lung, and therefore it is hard, if not impossible, to determine the true survival in patients with isolated peritoneal carcinomatosis. Franko et al recently characterized the clinical course of 2095 patients with peritoneal carcinomatosis from colorectal cancer who were enrolled in 2 cooperative group, prospective, randomized trials of systemic chemotherapy (North Central Cancer Treatment Group trials N9741 and N9841, respectively) and contrasted that with patients with metastatic colorectal cancer with a different pattern of spread. Peritoneal carcinomatosis was identified in 364 patients (17.4%), of whom only 37 (10.2%) had isolated peritoneal carcinomatosis. Not surprisingly, the authors found that patients with peritoneal carcinomatosis had a significantly shorter overall survival (12.7 months vs 17.6
months; \( P < .001 \) and progression-free survival (5.8 months vs 7.2 months; \( P < .001 \)) compared with patients who did not have carcinomatosis. Despite these relatively low rates of survival, this finding represents a meaningful improvement in this lethal condition compared with outcomes prior to the use of modern multimodal therapy, and there were even some patients with carcinomatosis who survived more than 5 years (4.1%). This was not significantly different from patients who did not have carcinomatosis (6%). Because of the low number of patients with isolated peritoneal carcinomatosis, it is impossible to determine how their survival compares with that of other patients with only a single site of metastatic disease.

One randomized controlled trial and 2 retrospective studies have compared survival outcomes after CRS/HIPEC versus systemic chemotherapy alone in patients with isolated peritoneal carcinomatosis from colorectal cancer.\(^{71–73}\) In 2003, Verwaal et al\(^73\) reported the results of a randomized controlled clinical trial of CRS/CRS/EPIC versus systemic chemotherapy followed by systemic chemotherapy with fluorouracil and leucovorin compared with systemic chemotherapy with fluorouracil and leucovorin with or without palliative surgery. A total of 105 patients were randomized (54 to CRS/EPIC and 51 to systemic chemotherapy). After a median follow-up of 26.2 months, the median survival in the CRS/HIPEC group was 22 months compared with 12.6 months in the systemic chemotherapy group. In an 8-year follow-up study, the 5-year survival rate was 20% for patients in the CRS/EPIC group and 10% for patients in the systemic chemotherapy group. For patients in the CRS/HIPEC group who achieved a complete cytoreduction at the time of surgery, the 5-year survival rate was 45%.\(^74\)

Although these results are encouraging, this trial has received its share of criticism. First, 17% of all the patients had appendiceal cancer, which is typically more indolent than colon cancer. Although some have claimed that this has biased the results in favor of the CRS/HIPEC arm, 21% of the patients in the systemic chemotherapy arm had appendiceal cancer compared with 13% in the experimental arm. Second, there was some crossover from the systemic chemotherapy arm to the experimental arm. Third, the chemotherapy used is no longer the standard of care, although it was at the time of the study. Furthermore, these survival improvements in the CRS/HIPEC arm came despite a surgical mortality rate of 8%. In addition, these patients were not preselected as “good” CRS/HIPEC candidates and then randomized. These were all patients with isolated peritoneal carcinomatosis who were randomized regardless of their candidacy for CRS/HIPEC.

Despite the obvious desire for more prospective randomized controlled trials to provide evidence of the usefulness of this aggressive and often morbid treatment, accruing patients to a trial in which they may be randomized to a nonintraperitoneal arm has proved to be nearly impossible. In 2004, Elias et al had to close a trial that randomized patients to CRS and systemic chemotherapy versus CRS with early postoperative intraperitoneal chemoperfusion (EPIC) and systemic chemotherapy early due to poor accrual.\(^71\) Despite our lack of knowledge of the contribution of EPIC to CRS, patients would not risk being randomized to the non-EPIC arm. The results of the study, based on a total of 36 patients (of an anticipated 98), showed no difference in the 2-year survival rate (60% in each arm) between CRS and CRS/EPIC. (All patients achieved a complete cytoreduction and received 3 months of fluorouracil-and-leucovorin-based systemic chemotherapy.) This finding further begs the question regarding the benefit of EPIC in the setting of complete cytoreduction and modern systemic chemotherapy in patients with colon cancer.

More recently, Stojarinovic and Esquivel spent more than a decade putting together a multicenter phase 3 clinical trial comparing standard systemic chemotherapy (with the option for CRS/EPIC at the time of disease progression) with CRS/EPIC plus standard systemic chemotherapy for patients with isolated peritoneal carcinomatosis from colon cancer. After filing more than 25 versions, the trial (ClinicalTrials.gov NCT01167725), which was sponsored by the Walter Reed Army Medical Center in collaboration with the National Cancer Institute, opened in August 2010. The estimated enrollment was 340 patients. Because patients with stage IV colon cancer, including those with isolated peritoneal carcinomatosis, are typically referred to a medical oncologist up front (as opposed to a surgical oncologist), the responsibility for enrolling patients in this trial fell on the medical oncology community. During the first year, only one patient was enrolled and the study was closed.

In the absence of prospective data, Franko et al retrospectively compared outcomes between systemic chemotherapy and CRS/HIPEC versus systemic chemotherapy alone in patients with peritoneal carcinomatosis from colorectal cancer.\(^72\) The study included 105 patients: 67 who underwent CRS/HIPEC and 38 who received systemic chemotherapy alone. The groups were matched with regard to sex, site of tumor origin, tumor grade, and T and N categories. The control group was older (aged 59 years vs 51 years; \( P < .001 \)) and had a higher prevalence of liver metastases (35% vs 15%; \( P = .14 \)). Patients who underwent CRS/HIPEC had a median survival of 34.7 months compared with 16.8 months for those receiving systemic chemotherapy alone. The authors concluded that modern systemic chemotherapy does improve survival for patients with peritoneal carcinomatosis from colorectal cancer and that CRS/HIPEC can further prolong survival in selected patients. They also acknowledged that
these are not exclusive treatment modalities but are adjuncts to each other.\textsuperscript{72}

In a similar study, Elias et al compared patients who would have been candidates for CRS/HIPEC but only received systemic chemotherapy with a similar group of patients who received both systemic chemotherapy and CRS/HIPEC.\textsuperscript{35} Forty-eight patients underwent CRS/HIPEC and after screening 75 patients with isolated peritoneal carcinomatosis who did not undergo CRS/HIPEC, the authors identified 48 who they believed would have been appropriate candidates for CRS/HIPEC (the fact that there were 48 patients in each arm was coincidental). The groups were equivalent in all regards except that patients in the standard arm were older (aged 51 years vs 46 years; \(P = .01\)) and more of these patients had tumors with undetermined differentiation (7 patients vs 0 patients; \(P = .02\)). Both groups had similar chemotherapy regimens. The median follow-up was 95.7 months in the standard group versus 63 months in the CRS/HIPEC group. The 2-year and 5-year overall survival rates were 81\% and 51\%, respectively, for the CRS/HIPEC group and 65\% and 13\%, respectively, for the standard group. The median survival was 23.9 months in the standard group versus 62.7 months in the CRS/HIPEC group (\(P < .05\), log-rank test). All patients in the CRS/HIPEC group had a complete cytoreduction. Similar to the study by Franko et al,\textsuperscript{72} the study by Elias et al also suggested that there is a potential benefit of CRS/HIPEC in patients with isolated peritoneal carcinomatosis from colorectal cancer who achieve a complete cytoreduction and who receive modern systemic chemotherapy.\textsuperscript{35} What was surprising, and encouraging, from this study was the 5-year survival rate of 13\% for patients who only received systemic chemotherapy.

The Prodige 7 trial is a prospective, multicenter phase 3 trial being conducted in France that is randomizing patients who have a complete cytoreduction to HIPEC versus no HIPEC. In this study, all patients have a PCI of $\leq 25$. HIPEC is performed with oxaliplatin (at a dose of 460 mg/m$^2$) in 2 L/m$^2$ of dextrose 5\% over 30 minutes at a minimum temperature of 42\°C. The trial has enrolled the expected 280 patients. Although the final results are not yet available, the authors have reported that the overall survival is higher than expected in both arms.\textsuperscript{75} It is hoped that this trial will answer the question concerning the value added by HIPEC. One concern that will be raised if the results do not show any benefit of HIPEC will be the HIPEC chemotherapy regimen (short duration, high-dose oxaliplatin HIPEC).

Despite the lack of evidence of a direct benefit of HIPEC in addition to CRS, HIPEC is also being tested in a number of different settings. Several recent studies have suggested a potential benefit of adjuvant HIPEC for patients with colon and gastric cancer who are at high risk of developing peritoneal carcinomatosis.\textsuperscript{76–79} Currently, there are a few studies that are prospectively studying the role of second-look laparotomy and HIPEC among patients with high-risk colorectal cancers.\textsuperscript{80–84} The role of HIPEC is also being defined in pancreatic and ovarian cancer as well as sarcomas. Due to the difficulty in accruing patients to randomized controlled trials without a HIPEC arm, some HIPEC trials in the United States are focusing more on comparing different chemotherapy agents used at the time of HIPEC (ie, oxaliplatin vs mitomycin) or HIPEC versus EPIC (ClinicalTrials.gov identifiers NCT01580410 and NCT01815359, respectively) The rationale for such trials is that in the setting of a complete cytoreduction, a difference in survival based on the type of chemotherapy used or compared with EPIC would indicate a benefit attributable to the HIPEC itself.

**Current Research and Clinical Trials in Peritoneal Carcinomatosis**

As with most other types of cancer, there is growing interest in the genomic profiling of peritoneal carcinomatosis to gain insight into the biology of this form of metastatic disease. It is hoped that understanding the genetic mutations that drive cancer progression within the peritoneum will help to identify more specific targets for treatment. Indeed, it has been through this type of investigation that the debate about the origin of pseudomyxoma peritonei involving the appendix and ovaries was resolved, primarily demonstrating an appendiceal origin.\textsuperscript{85} It is also becoming recognized that different forms of metastasis, including peritoneal carcinomatoses, possess gene expression profiles that are unique from tumors that metastasize to other areas.\textsuperscript{86,87} Varghese et al compared the gene expression profiles of colon cancer metastases to the liver or peritoneum (n=20) with high-grade appendiceal cancer metastases to the peritoneum (n=8).\textsuperscript{88} Using microarray analysis, the authors found a site-specific segregation of liver and peritoneal metastases. The most commonly aberrant genes included those involved in metastasis, angiogenesis, cell cycle regulation, cell proliferation, and adhesion. Interestingly, they did not find a significant difference in the genomic profiles of the peritoneal metastases when comparing those of colorectal and appendiceal origin. These findings supported those published in 2 previous reports from Norway.\textsuperscript{87,89} In these studies, which were conducted in 2007 and 2004, respectively, the authors used comparative genomic hybridization and microarray analysis, respectively. In addition to comparing the genomic profiles of liver and peritoneal metastases, they also examined the primary tumor. The authors found that the metastatic lesions had significantly more mutations than the primary tumor.
and that the mutational pattern was different between the peritoneal and liver metastases.

In 2012, Levine et al used microarray analysis to investigate the differences between appendiceal and colorectal peritoneal carcinomatosis.90 Although these are clearly 2 clinically distinct cancers, advanced appendiceal cancer is routinely treated in a fashion similar to advanced colon cancer. Although there is some clinical evidence to show that the treatments for colon cancer have some efficacy for appendiceal cancer, there is little molecular evidence to support this approach.91–98 The study by Levine et al compared the gene expression profile of the peritoneal metastases from 26 appendiceal cancers (24 of which were low grade) with that of 15 colon cancers, as well as the survival of the patients.90 The initial unsupervised hierarchical clustering revealed 3 clusters: low-risk appendiceal (cluster 1), high-risk appendiceal (cluster 2), and colorectal (cluster 3) cancer. The median survival for clusters 1 to 3 was 39 months, 33 months, and 18 months, respectively. Thus, unlike the study by Varghese et al,88 Levine et al found a distinct genomic difference between the appendiceal and colon carcinomas, particularly when compared by survival risk.90 Although this finding is not surprising given the high number of low-grade appendiceal tumors used in the study compared with that of Varghese et al,88 who included only high-grade appendiceal cancers, an intriguing finding by the authors was a significant risk stratification within the low-grade appendiceal cancers based on the genomic profile. The expressed genes they identified that were associated with a worse prognosis included the mucin-related genes (mucin 5 and mucin 2) and the trefoil factors genes (1 and 2). Currently, DNA profiling technology, such as next-generation sequencing, is putting genomic profiles of individual patient tumors in the hands of the patients and providers. Hopefully, in addition to increasing our knowledge of tumor genomics and gene expression, this valuable information currently being gathered will also someday be used routinely in direct cancer treatment.

In addition to molecular research, there is a substantial amount of clinical research in peritoneal carcinomatosis currently underway. Numerous clinical trials are examining the role of CRS and HIPEC in the management of peritoneal carcinomatosis from a wide variety of tumors.99 In addition, investigators are also starting to study other aspects of the management of peritoneal carcinomatosis such as the use of near-infrared imaging and indocyanine green to identify peritoneal metastases intraoperatively (ClinicalTrials.gov identifiers NCT02032485 and NCT01982227, respectively). There is also a growing interest in the use of intraperitoneal biologic agents such as catumaxomab (a monoclonal antibody to both the CD3 and epithelial cell adhesion molecules [EpCAM] antigens with efficacy in treating malignant ascites) for the treatment of carcinomatosis from gastric cancer, both in the neoadjuvant setting before CRS and HIPEC as well as in the adjuvant setting after CRS (ClinicalTrials.gov identifiers NCT01504256 and NCT01784900, respectively).100 Another avenue of interest is the prevention of peritoneal carcinomatosis in high-risk patients such as those with T4 colon cancer or gastric cancer with positive peritoneal cytology. Methods proposed to prevent the development of peritoneal carcinomatosis include adjuvant (or prophylactic) HIPEC and extended intraperitoneal lavage (ClinicalTrials.gov identifiers NCT02231086 and NCT01226394, respectively).101 Immunotherapy is also starting to be investigated as a means of treating carcinomatosis. One actively recruiting trial in Germany is examining the safety and efficacy of intraperitoneal attenuated oncolytic vaccinia virus (ClinicalTrials.gov identifier NCT01443260). Another active phase 1/2 immunotherapy trial in Pittsburgh is studying the use of an intranodal and intradermal dendritic cell vaccine with chemokine modulation (ClinicalTrials.gov identifier NCT02151448).

Palliative Care for Peritoneal Carcinomatosis

Despite the progress being made and the active research currently underway in peritoneal carcinomatosis, it remains a highly lethal condition. Even in the face of advanced, incurable disease, it is human nature for patients and their families to hope: either for a cure, more time, or at least a chance to fight. A diagnosis of peritoneal carcinomatosis thrusts patients, families, and providers into a difficult clinical and emotional situation. Current guidelines from the American Society of Clinical Oncology and the National Comprehensive Cancer Network recommend the early initiation of palliative care for patients with advanced, life-threatening cancers.102,103 Recent studies in patients with advanced lung cancer have shown that those who receive an early palliative intervention as part of their treatment actually live longer with a better quality of life despite receiving less cancer-directed therapy.104 It is not unreasonable to expect similar results among patients with other advanced cancers as well.

Although many physicians and patients view a palliative care consult as “giving up,” this could not be further from the truth. Unlike hospice (which is a medical insurance benefit that requires a life expectancy of fewer than 6 months if the life-threatening disease is untreated and the patient forgoes disease-directed treatment), all patients with symptoms from an illness or its treatment are entitled to palliative care. Although most patients’ symptoms can be adequately palliated by their primary physician (either their primary care provider or primary specialist), advanced, life-threatening cancers, such as peritoneal carcinomatosis, can pose additional challenges in terms of physical,
emotional, psychological, spiritual, and social symptomatology. Initiating a palliative care consult before these symptoms become unmanageable will make it seem less like “giving up” when there is an acute need for the expertise of a palliative medicine provider.

One way to overcome the inertia of referring patients to palliative care early is to normalize it. Many institutions have made it part of their cancer center’s protocols to refer all patients with advanced cancer to palliative care from the time of the initial cancer center visit. This allows the palliative care team to tell patients and their families that all patients with advanced cancer are seen by palliative care, and that it is part of the multidisciplinary team effort to care for the patient and family. This also takes the burden off the primary specialist to conduct some of the harder conversations around goals of care and advanced directives and allows he or she to focus on the plan of treatment. Having these difficult conversations early is essential to the comprehensive management of advanced cancers such as peritoneal carcinomatosis and should not be avoided due to provider unease. A palliative care consultant who is an expert in communication can be a huge help with this aspect of the patient’s care.

One of the most dreaded complications of peritoneal carcinomatosis is a bowel obstruction. Bowel obstructions can occur at any point in the gastrointestinal tract from the distal stomach to the rectum. Their management can be complicated and multimodal. The initial management of a patient with a bowel obstruction should include appropriate intravenous fluid resuscitation based on the degree of dehydration, the level of obstruction, and any metabolic abnormalities present. The bowel should be decompressed with a nasogastric tube if the patient is vomiting, and the patient should not be allowed to eat or drink to help decrease gastrointestinal stimulation and secretions. Serial abdominal examinations for signs or symptoms of peritonitis are essential. Imaging studies such as an abdominal series and/or a CT scan of the abdomen and pelvis are helpful to determine the level and nature of the obstruction, the presence of extraluminal air suggesting a perforation, and the presence or absence of ascites.

Patients who are hemodynamically stable, who do not have peritonitis, and who have a normal or only mildly elevated white blood count (especially in the setting of dehydration), can initially be monitored closely (with the measures mentioned above) and given a chance for the obstruction to resolve without an operation. Signs and symptoms of peritonitis or a CT scan suggesting a “closed loop” obstruction (in which a loop of intestine twists around its mesentery) are indications for an urgent surgical intervention. The nature of that intervention is ultimately determined at the time of surgery and may include resecting the section of obstructed intestine if it appears to be an isolated site, performing an intestinal bypass, performing a diverting ostomy (either small or large bowel depending on the location of the obstruction), or placing a decompression gastrostomy tube for venting the stomach if the obstruction cannot otherwise be relieved. These operations tend to be challenging, both technically as well as with regard to decision-making, and they pose a high risk of perioperative morbidity and mortality.105 For these reasons, careful patient selection for a surgical intervention for a malignant bowel obstruction from carcinomatosis is essential. If the obstruction is located in the rectum or rectosigmoid colon or duodenum, it is reasonable to consider an endoscopic stent placement prior to surgery. Although the presence of carcinomatosis has been shown to increase the risk of failure of endoscopic stent placement for colonic obstruction, there is a reported success rate of 77% to 85%.106–109 For patients with a limited prognosis, avoiding an operation that would often involve either an intestinal diversion and ostomy or venting gastrostomy tube becomes an important consideration, and therefore endoscopic colonic stenting offers a significant palliative therapy. For patients for whom it is believed that surgical or endoscopic relief of the bowel obstruction is not feasible, it is reasonable to evaluate them for a percutaneous endoscopic gastrostomy tube placement for gastric drainage.

There are also a number of possible medical interventions for patients with bowel obstructions for whom surgery, other than a venting gastrostomy tube, is not an option. Low-dose dexamethasone can help with bowel wall edema and may help to resolve a partial bowel obstruction as well as treat associated nausea.110,111 Nausea can and should be aggressively treated with combination broad-spectrum antiemetics targeted to the chemoreceptor trigger zone (dopamine receptors), the vomiting center (H1 receptors), and the intestine (cholinergic and 5-HT3 receptors). Octreotide can be used to decrease intestinal secretions and stretching of the bowel wall, which causes visceral pain.112,113 Management of medications can be complicated by not having the entire intestinal tract available for absorption, thereby necessitating the use of other routes of administration (transdermal, transmucosal, subcutaneous, or intramuscular), especially in the outpatient setting.

Another common complication of peritoneal carcinomatosis is ascites. Unfortunately, although the symptom relief from a paracentesis is immediately helpful, it is usually temporary. For patients requiring frequent paracentesis, a tunneled intraperitoneal catheter that can be intermittently connected to a self-contained vacuum drainage system is a good option.105 “These catheters can be placed under local anesthesia either by an interventional radiologist or surgeon. Another option for the treatment of malignant ascites is HIPEC. A number of studies have demonstrated the efficacy of HIPEC in the treatment of patients with malignant ascites.
TABLE 3. Palliative HIPEC for Malignant Ascites

| YEAR | NO. | TUMOR      | AGENT(S)                                    | RESPONSE, % | STUDY      |
|------|-----|------------|---------------------------------------------|-------------|------------|
| 2006 | 14  | Varied     | Cisplatin and doxorubicin or mitomycin      | 100         | Facchiano 2008120 |
| 2007 | 5   | Gastric    | Mitomycin and cisplatin                     | 100         | Facchiano 2012121 |
| 2008 | 1   | Mesothelioma | Cisplatin and doxorubicin                  | 100         | Ong 2012117   |
| 2009 | 52  | Varied     | Cisplatin and doxorubicin or mitomycin      | 98          | Randle 2014116 |
| 2010 | 32  | Ovarian    | Cisplatin and doxorubicin                  | 84          | Antos 2010124 |
| 2012 | 2   | GastricACUP | Mitomycin or cisplatin                     | 100         | Ba 2010123    |
| 2014 | 299 | Varied     | MitomycinCarboplatinOxaliplatinCisplatin   | 93          | Patriti 2008116 |

HIPEC, hyperthermic intraperitoneal chemoperfusion; ACUP, adenocarcinoma of unknown primary.

(Table 3).114–124 Because there is often no CRS involved, this can even be done laparoscopically, which, although less invasive, does still require general anesthesia. For this reason, it makes sense to limit this approach to patients with a longer life expectancy and higher performance status.

Another common complication of peritoneal carcinomatosis is hydronephrosis from ureteral obstruction. Ureteral stent placement is usually reserved until renal function is threatened or the hydronephrosis becomes symptomatic.105 If the ureter cannot be stented, then a nephrostomy tube can be used to drain the obstructed kidney and potentially internalized at a later date.

Tumor cachexia and fatigue are also frequently seen in patients with peritoneal carcinomatosis, and these symptoms are often the most distressing to the patient and family. For patients and families, the obvious explanation for the weight loss and fatigue is poor nutrition. The well-intended natural reaction is to try to aggressively feed the patient despite his or her anorexia, thereby leading to eating-related distress for both the patient and family. Unfortunately, efforts to provide adequate caloric support either parenterally or enteral for a patient with advanced cancer have not been shown to improve lean body weight or fatigue. In fact, the lack of improvement with adequate protein nutrition is part of the definition of cancer cachexia, supporting the notion that this is a systemic process impacting the entire protein-energy balance and metabolism.105 Efforts currently are ongoing to better understand and combat cancer cachexia.

Although fatigue and cachexia often occur together, fatigue is not necessarily due to cachexia and appears to be its own complex, multidimensional symptom. In addition to being related to cancer progression, it may also be due to cancer treatments, comorbid conditions, or deconditioning. There are a number of assessment approaches for fatigue (performance status, functional capacity, fatigue scales), but there is no current gold standard. Interventions for fatigue can be pharmacologic and non-pharmacologic. Nonpharmacologic approaches include education and counseling, assistance with changing schedules that promote less fatigue, and exercise.125 Pharmacologic approaches include interventions similar to those for cancer cachexia, namely corticosteroids, progestins, and psychostimulants. Both cancer cachexia and fatigue are appropriate indications for a palliative care consult.

Earlier palliative care involvement can also help with the transition to hospice when appropriate. Recognition of that time may come first to the oncologist when further cancer-directed treatment is likely to do more harm than good or to the patient and family when they decide that the burden of treatment is not worth the limited potential for more time. Unfortunately, it is rare that both parties arrive at this recognition at the same time. The oncologist may find it easier to continue to treat the patient who insists on continuing to “fight” the cancer even knowing that “fighting” may take time away from the patient. Similarly, the patient may find it easier to keep receiving treatment rather than “disappoint” the oncologist by stopping. With an early palliative care intervention, conversations about hospice as a potential option can be started early, thereby leaving plenty of time to correct any misconceptions. Patients and families can learn that the mission of hospice is neither to prolong life nor hasten death but rather to provide comfort and dignity and optimize the quality of life that is left. It can help to dispel other unfounded concerns such as patients on hospice losing contact with their primary physician, hospice patients being unable to go to the hospital if necessary, patients being unable to come off hospice if a new treatment becomes available, and so on. They will also learn that hospice provides support to both the patient and the family through an interdisciplinary team of providers including physicians, nurses, social workers, chaplains, and volunteers. Hospice also helps families to prepare for their loss and provides bereavement programs after the death.
Conclusions
This is an exciting time to be helping individuals diagnosed with peritoneal carcinomatosis (Table 4). There are now patients for whom aggressive, multimodality treatments can significantly improve survival and even offer the possibility of cure. With the increased efforts in genomic medicine, we are learning more about the mechanism of this disease and hopefully getting closer to finding unique targets for therapy. Through our understanding of the peritoneal-blood barrier, the peritoneal cavity offers an additional route for new, carcinomatosis-specific treatments. A variety of clinical trials now abound for a group of patients who were once “written off.” However, there is still a long way to go. For many patients with peritoneal carcinomatosis, much of the therapy they receive will be palliative in nature. Because of the location and nature of these tumors, the symptoms they create can be complex and challenging to treat. Managing these symptoms well, either by the primary specialist or through the help of a palliative care team, is essential and rewarding. Because of the real threat to the patient’s life posed by the presence of carcinomatosis (or any advanced cancer), it is most important that patients and their families believe that they will not be abandoned as their disease progresses. Open, honest, and compassionate communication is essential to helping both patients and families cope with what is often an impossible situation.

References
1. Chua TC, Moran BJ, Sugarbaker PH, et al. Early- and long-term outcome data of patients with pseudomyxoma peritonei from appendiceal origin treated by a strategy of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. J Clin Oncol. 2012;30:2449-2456.
2. Sadeghi B, Arvieux C, Glehen O, et al. Peritoneal carcinomatosis from non-gynecologic malignancies: results of the EVOCAPE 1 multicentric prospective study. Cancer. 2000;88:358-363.
3. Esquivel J, Lowy AM, Markman M, et al. The American Society of Peritoneal Surface Malignancies (ASPSM) multiinstitutional evaluation of the Peritoneal Surface Disease Severity Score (PSDSS) in 1,013 patients with colorectal cancer with peritoneal carcinomatosis. Ann Surg Oncol. 2014;21:4195-4201.
4. American Cancer Society. Survival rates for ovarian cancer, by stage. cancer.org/cancer/ovariancancer/detailedguide/ovarian-an-cancer-survival-rates. Accessed March 31, 2015.
5. Markman M, Bundy BN, Alberts DS, et al. Phase III trial of standard-dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III ovarian carcinoma: an intergroup study of the Gynecologic Oncology Group, Southwest Oncology Group, and Eastern Cooperative Oncology Group. J Clin Oncol. 2001;19:1001-1007.
6. Alberts DS, Liu PY, Hannigan EV, et al. Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. N Engl J Med. 1996;335:1950-1955.
7. Armstrong DK, Bundy B, Wenzel L, et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. N Engl J Med. 2006;354:34-43.
8. Elit L, Oliver TK, Covens A, et al. Intraperitoneal chemotherapy in the first-line treatment of women with stage III epithelial ovarian cancer: a systematic review with metaanalyses. Cancer. 2007;109:692-702.
9. National Institutes of Health U.S. National Library of Medicine. Clinical advisory: NCI issues clinical announcement for preferred method of treatment for advanced ovarian cancer ctep.cancer.gov/highlights/docs/clin_annce_010506.pdf. Accessed March 31, 2015.
10. Spratt JS, Adcock RA, Muskovin M, Sherrill W, McKeown J. Clinical delivery and chemotherapy. Ann Surg Oncol. 1991;7:499-998.
11. Fujimoto S, Shrestha RD, Kokubun M, et al. Intraperitoneal hyperthermic perfusion combined with surgery effective for gastric cancer patients with peritoneal seeding. Ann Surg. 1988;208:36-41.
12. Fujimoto S, Shrestha RD, Kokubun M, et al. Clinical trial with surgery and intraperitoneal hyperthermic perfusion for peritoneal recurrence of gastrointestinal cancer. Cancer. 1989;64:154-160.
13. Mirnezami AH, Moran BJ, Cecil TD. Sugarbaker procedure for pseudomyxoma peritonei. Tech Coloproctol. 2009;13:373-374.
14. Lo CH, Bohmer RD, Blomfield PI. An evidence-based approach: Sugarbaker protocol and pseudomyxoma peritonei of appendiceal origin. ANZ J Surg. 2008;78:327-328.
15. Bryant J, Clegg AJ, Sidhu MK, Brodin H, Royle P, Davidson P. Systematic review of the Sugarbaker procedure for pseudomyxoma peritonei. Br J Surg. 2005;92:153-158.
16. Jacquet P, Sugarbaker PH. Peritoneal-plasma barrier. Cancer Treat Res. 1996;82:53-63.
17. Dunlop PR, Hand JW, Dickinson RJ, Field SB. An assessment of local hyperthermia in clinical practice. Int J Hyperthermia. 1986;2:39-50.
18. Field SB, Morris CC. The relationship between heating time and temperature: its relevance to clinical hyperthermia. Radiat Oncol. 1983;1:179-186.
19. Leopold KA, Dewhirst M, Samulski T, et al. Relationships among tumor temperature, treatment time, and histopathological outcome using preoperative hyperthermia with radiation in soft tissue sarcomas. Int J Radiat Oncol Biol Phys. 1992;22:989-998.
20. Urano M, Majima H, Miller R, Kahn J. Cytotoxic effect of 1,3 bis (2-chloroethyl)-N-nitrosourea at elevated temperatures: Arhenius plot analysis and tumour response. Int J Hyperthermia. 1991;7:499-510.
21. Dewey WC. Interaction of heat with radiation and chemotherapy. Cancer Res. 1984;44(suppl 10):4714s-4720s.
22. Yan TD, Deraco M, Baratti D, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for malignant peritoneal mesothelioma: multi-institutional experience. J Clin Oncol. 2009;27:6237-6242.
23. Tabrizian P, Shragar B, Jibara G, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis: outcomes from a single tertiary institution. J Gastrointest Surg. 2014;18:1024-1031.
24. Levine EA, Stewart JH 4th, Shen P, Russell GB, Loggie BL, Votanopoulos KL. Intraperitoneal chemotherapy for peritoneal surface malignancy: experience with 1,000 patients. J Am Coll Surg. 2014;218:573-585.

TABLE 4. Key Clinical Points

| 1. Peritoneal carcinomatosis is no longer an absolute death sentence. |
| 2. Modern, multimodality approaches to treatment (including systemic chemotherapy, cytoreductive surgery, and intraperitoneal chemotherapy) have significantly improved outcomes for selected patients with peritoneal carcinomatosis. |
| 3. Outcomes for patients with peritoneal carcinomatosis still depend largely on the origin and histology of the tumor. |
| 4. Novel approaches to treating peritoneal carcinomatosis are the subject of a number of active clinic trials. |
| 5. A multidisciplinary team approach, including early palliative care, is essential to the comprehensive management of peritoneal carcinomatosis. |
Recent Advances in Understanding and Treating Peritoneal Carcinomatosis

25. Gusani NJ, Cho SW, Colovos C, et al. Aggressive surgical management of peritoneal carcinomatosis with low mortality in a high-volume tertiary cancer center. Ann Surg Oncol. 2008;15:754-763.

26. Lerner B. Annals of extreme surgery. New York: Springer; August 11, 2011. nytimes.com/2011/08/30/opinion/the-annals-of-extreme-surgery.html? r=0. Accessed April 1, 2015.

27. Pollock A. Hot chemotherapy bath: patients see hope, critics hold doubts. New York Times. August 11, 2011. nytimes.com/2011/08/12/business/heat-chemo-therapy-bath-may-be-only-hope-for-some-cancer-patients.html. Accessed April 1, 2015.

28. Gonzalez-Moreno S. Peritoneal surface oncology: a progress report. Eur J Surg Oncol. 2006;32:593-596.

29. Esquivel J, Elias D, Baratti D, Kusamura S, Deraco M. Consensus statement on the loco regional treatment of colorectal cancer with peritoneal dissemination. J Surg Oncol. 2008;98:263-267.

30. Helm JH, Mura JT, Glenn JA, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for malignant peritoneal mesothelioma: a systematic review and meta-analysis. Ann Surg Oncol. 2015;22:1686-1693.

31. Minner TJ, Shia J, Jaques DP, Klimstra DS, Brennan MF, Coit DG. Long-term survival following treatment of pseudomyxoma peritonei: an analysis of surgical therapy. Ann Surg. 2005;241:300-308.

32. Vogelzang NJ, Rutherford JJ, Smanowski J, et al. Phase III study of mettxeremix in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol. 2003;21:2636-2644.

33. Feldman AL, Otbuti SK, Pingpank JF, et al. Analysis of factors associated with outcome in patients with malignant peritoneal mesothelioma undergoing surgical debulking and intraperitoneal chemotherapy. J Clin Oncol. 2003;21:4560-4567.

34. Baratti D, Kusamura S, Iusco D, et al. Post-operative complications after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy affect long-term outcome of patients with peritoneal metastases from colorectal cancer: a two-center study of 101 patients. Dis Colon Rectum. 2014;57:858-866.

35. Elias D, Lefevre JH, Chevalier J, et al. Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin. J Clin Oncol. 2009;27:681-685.

36. Esquivel J, Piso P, Verwaal V, et al. American Society of Peritoneal Surface Malignancies opinion statement on defining expectations from cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in patients with colorectal cancer. J Surg Oncol. 2014;110:777-778.

37. Chua TC, Yan TD, Saxena A, Morris DL. Should the treatment of peritoneal carcinomatosis by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy still be regarded as a highly morbid procedure? A systematic review of morbidity and mortality. Ann Surg. 2009;249:900-907.

38. Birkmeyer JD, Siewers AE, Finlayson EV, et al. Hospital volume and surgical mortality in the United States. N Engl J Med. 2002;346:1128-1137.

39. Yan TD, Links M, Fransi S, et al. Learning curve for cytoreductive surgery and perioperative intraperitoneal chemotherapy for peritoneal surface malignancy—a journey to becoming a Nationally Funded Peritoneectomy Center. Ann Surg Oncol. 2007;14:2270-2280.

40. Smeenk RM, Verwaal VJ, Zoetmulder FA. Learning curve of combined modality treatment in peritoneal surface disease. Br J Surg. 2007;94:1408-1414.

41. Moradi BN 3rd, Esquivel J. Learning curve in cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. J Surg Oncol. 2009;100:293-296.

42. Mohamed F, Moran BJ. Morbidity and mortality with cytoreductive surgery and intraperitoneal chemotherapy: the importance of a learning curve. Cancer J. 2009;15:196-199.

43. Kusamura S, Baratti D, Virzi S, et al. Learning curve for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in peritoneal surface malignancies: analysis of two centres. J Surg Oncol. 2013;107:312-319.

44. Kusamura S, Baratti D, Deraco M. Multidimensional analysis of the learning curve for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in peritoneal surface malignancies. Ann Surg. 2012;255:345-356.

45. Yan TD, Black D, Savady R, Sugarbaker PH. Systematic review on the efficacy of cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for peritoneal carcinomatosis from colorectal carcinoma. J Clin Oncol. 2006;24:4011-4019.

46. Chang SJ, Hodeib M, Chang J, Bristow RE. Survival impact of complete cytoreduction to no gross residual disease for advanced-stage ovarian cancer: a meta-analysis. Gynecol Oncol. 2013;130:493-498.

47. Landrum LM, Java J, Mathews CA, et al. Prognostic factors for stage III epithelial ovarian carcinoma treated with intraoperative intraperitoneal chemotherapy: a Gynecologic Oncology Group study. Gynecol Oncol. 2013;130:12-18.

48. Misradaji J. Mucinous epithelial neoplasms of the appendix and pseudomyxoma peritonei. Mod Pathol. 2015;28(suppl 1):S67-S79.

49. Turaga KK, Pappas S, Gamblin TC. Right hemicolecctiony for mucinous adenocarcinoma of the appendix: just right or too much? Ann Surg Oncol. 2013;20:1063-1067.

50. Foster JM, Gupta PK, Carreau JH, et al. Right hemicolecction for primary colorectal cancer: a feasibility pilot. Eur J Surg Oncol. 2020;26:663-668.

51. Goere D, Souadka A, Faron M, et al. Extent of colorectal peritoneal carcinomatosis: attempt to define a threshold above which HIPEC does not offer survival benefit: a comparative study published online ahead of print January 29, 2015. Ann Surg Oncol.

52. Verwaal VJ, van Tinteren H, van Ruth S, Zoetmulder FA, et al. Extensive cytoreductive surgery combined with intraoperative intraperitoneal perfusion with cisplatin under hyperthermic conditions (OXYHEP) in patients with recurrent ovarian cancer: a feasibility pilot. Eur J Surg Oncol. 2000;26:663-668.

53. Carr NJ. Current concepts in pseudomyxoma peritonei. Ann Pathol. 2014;34:9-13.

54. Misradaji J. Appendiceal mucinous neoplasms: controversial issues. Arch Pathol Lab Med. 2010;134:864-870.

55. Wagner PL, Austin F, Maduekwe U, et al. Extensive cytoreductive surgery for appendiceal carcinomatosis: morbidity, mortality, and survival. Ann Surg Oncol. 2013;20:1056-1062.

56. Gockzin G, Schlitt HJ, Piso P. Peritoneal carcinomatosis: patients selection, perioperative complications and quality of life related to cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. World J Surg Oncol. 2009;7:5.

57. Elias D, Blot F, El Omamy A, et al. Cytoreductive surgery with peritoneal carcinomatosis: a high-volume tertiary cancer center. J Surg Oncol. 2008;100:293-296.

58. Fujimoto S, Takahashi M, Mutou T, et al. Improved mortality rate of gastric carcinoma patients with peritoneal carcinomatosis treated with intraoperative hyperthermic chemoperfusion combined with surgery. Cancer. 1997;9:884-891.

59. Gilly FN, Carry PY, Sayag AC, et al. Regional chemotherapy (with mitomycin C) and intra-operative hyperthermia for digestive cancers with peritoneal carcinomatosis. Hepatogastroenterology. 1994;41:124-129.

60. Jacquet P, Sugarbaker PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. In: Sugarbaker PH, ed. Peritoneal Carcinomatosis: Principles of Management. Boston, MA: Kluwer Academic Publishers; 1996:359-374.

61. van der Vange N, van Goethem AR, Zoetmulder FA, et al. Extensive cytoreductive surgery combined with intraoperative intraperitoneal perfusion with cisplatin under hyperthermic conditions (OXYHEP) in patients with recurrent ovarian cancer: a feasibility pilot. Eur J Surg Oncol. 2000;26:663-668.

62. Goere D, Souadka A, Faron M, et al. Extent of colorectal peritoneal carcinomatosis: attempted to define a threshold above which HIPEC does not offer survival benefit [published online ahead of print January 29, 2015]. Ann Surg Oncol.
a peritoneal surface disease severity score in patients with colon cancer with peritoneal carcinomatosis. J Surg Oncol. 2009; 99:9-15.

67. Cashin PH, Graf W, Nygren P, Mahteme H. Patient selection for cytoreductive surgery in colorectal peritoneal carcinomatosis using serum tumor markers: an observational cohort study. Ann Surg. 2012;256:1078-1083.

68. Cersosimo RJ. Management of advanced colorectal cancer, Part I. Am J Health Syst Pharm. 2013;70:395-406.

69. Glimelius B, Cavalli-Bjorkman N. Meta-analysis of preoperative systemic therapy for locoregional control in patients with peritoneal carcinomatosis. Ann Oncol. 2003;14:263-267.

70. Franko J, Shi Q, Goldman CD, et al. Treatment of colorectal peritoneal carcinomatosis with systemic chemotherapy: a pooled analysis of North Central Cancer Treatment Group phase III trials N9741 and N9841. J Clin Oncol. 2012;30:263-267.

71. Elias D, Delperro JR, Sideris L, et al. Treatment of colorectal peritoneal carcinomatosis from colorectal cancer: impact of complete cytoreductive surgery and difficulties in conducting randomized trials. Ann Surg Oncol. 2004;11:518-521.

72. Franko J, Ibrahim Z, Gusani NJ, Holtzman MP, Bartlett DL, Zeh HJ 3rd. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in women with colorectal peritoneal carcinomatosis. Cancer. 2010;116: 3756-3762.

73. Verwaal VJ, van Ruth S, de Bree E, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. J Clin Oncol. 2003;21:3737-3743.

74. Verwaal VJ, Bruin S, Boot H, van Slooten G, van Tinteren H. 8-year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. Ann Surg Oncol. 2008; 15:2426-2432.

75. Elias D, Goere D, Dumont F, et al. Role of hyperthermic intraoperative peritoneal chemotherapy in the management of peritoneal metastases. Eur J Surg. 2014;50: 332-340.

76. Virzi S, Iusco D, Baratti D, et al. Pilot study of adjuvant hyperthermic intraperitoneal chemotherapy in patients with colorectal cancer at high risk for the development of peritoneal metastases. Tumori. 2013;99:589-595.

77. Slooptha DA, Gardenbroek TJ, Crezee J, et al. Feasibility of adjuvant laparoscopic hyperthermic intraperitoneal chemotherapy in a short-term series and patients with colorectal cancer at high risk of peritoneal carcinomatosis. Eur J Surg Oncol. 2014;40: 1453-1458.

78. Sammartino P, Sibio S, Biacchi D, et al. Long-term results after proactive management for loco-regional control in patients with colonic cancer at high risk of peritoneal metastases. Int J Colorectal Dis. 2014; 29:1081-1089.
108. Kim JH, Ku YS, Jeon TJ, et al. The efficacy of self-expanding metal stents for malignant colorectal obstruction by noncolonic malignancy with peritoneal carcinomatosis. *Dis Colon Rectum*. 2013;56:1228-1232.

109. Caceres A, Zhou Q, Iasonos A, Gerdes H, Chi DS, Barakat RR. Colorectal stents for palliation of large-bowel obstructions in recurrent gynecologic cancer: an updated series. *Gynecol Oncol*. 2008;108:482-485.

110. Laval G, Marcelin-Benazech B, Guirimand F, et al; French Society for Palliative Care; French Society for Digestive Surgery; French Association for Supportive Care in Oncology; French Society for Digestive Cancer. Recommendations for bowel obstruction with peritoneal carcinomatosis. *J Pain Symptom Manage*. 2014;48:75-91.

111. Feuer DJ, Broadley KE. Corticosteroids for the resolution of malignant bowel obstruction in advanced gynaecological and gastrointestinal cancer. *Cochrane Database Syst Rev*. 2000;(2):CD001219.

112. Laval G, Rousselot H, Toussaint-Martel S, et al; SALTO Study Group. SALTO: a randomized, multicenter study assessing octreotide LAR in inoperable bowel obstruction. *Bull Cancer*. 2012;99:E1-E9.

113. Mariani P, Blumberg J, Landau A, et al. Symptomatic treatment with lanreotide microparticles in inoperable bowel obstruction resulting from peritoneal carcinomatosis: a randomized, double-blind, placebo-controlled phase III study. *J Clin Oncol*. 2012;30:4337-4343.

114. Valle M, Van der Speeten K, Garofalo A. Laparoscopic hyperthermic intraperitoneal peroperative chemotherapy (HIPEC) in the management of refractory malignant ascites: a multi-institutional retrospective analysis in 52 patients. *J Surg Oncol*. 2009;100:331-334.

115. Randle RW, Swett KR, Swords DS, et al. Efficacy of cytoreductive surgery with hyperthermic intraperitoneal chemotherapy in the management of malignant ascites. *Ann Surg Oncol*. 2014;21:1474-1479.

116. Patriti A, Cavazzoni E, Graziosi L, et al. Successful palliation of malignant ascites from peritoneal mesothelioma by laparoscopic intraperitoneal hyperthermic chemotherapy. *Surg Laparosc Endosc Percutan Tech*. 2008;18:426-428.

117. Ong E, Diven C, Abrams A, Lee E, Mahadevan D. Laparoscopic hyperthermic intraperitoneal chemotherapy (HIPEC) for palliative treatment of malignant ascites from gastrointestinal stromal tumours. *J Palliat Care*. 2012;28:293-296.

118. Graziosi L, Bugiantella W, Cavazzoni E, Donini A. Laparoscopic intraperitoneal hyperthermic perfusion in palliation of malignant ascites. Case report [in Italian]. *G Chir*. 2009;30:237-239.

119. Garofalo A, Valle M, Garcia J, Sugarbaker PH. Laparoscopic intraperitoneal hyperthermic chemotherapy for palliation of debilitating malignant ascites. *Eur J Surg Oncol*. 2006;32:682-685.

120. Facchiano E, Scarinci S, Kianmanesh R, et al. Laparoscopic hyperthermic intraperitoneal chemotherapy (HIPEC) for the treatment of malignant ascites secondary to unresectable peritoneal carcinomatosis from advanced gastric cancer. *Eur J Surg Oncol*. 2008;34:154-158.

121. Facchiano E, Risio D, Kianmanesh R, Msika S. Laparoscopic hyperthermic intraperitoneal chemotherapy: indications, aims, and results: a systematic review of the literature. *Ann Surg Oncol*. 2012;19:2946-2950.

122. de Mestier L, Volet J, Scaglia E, Msika S, Kianmanesh R, Bouché O. Is palliative laparoscopic hyperthermic intraperitoneal chemotherapy effective in patients with malignant hemorrhagic ascites? *Case Rep Gastroenterol*. 2012;6:166-170.

123. Ba MC, Cui SZ, Lin SQ, et al. Chemotherapy with laparoscope-assisted continuous circulatory hyperthermic intraperitoneal perfusion for malignant ascites. *World J Gastroenterol*. 2010;16:1901-1907.

124. Antos F, Dytrych P, Vitek P, Ryska O, Marvan J, Serclová Z. Malignant ascites–optional management using hyperthermic peroperative chemotherapy (HIPEC) [in Czech]. *Rozh Chir*. 2010;89:237-241.

125. Mitchell SA, Beck SL, Hood LE, Moore K, Tanner ER. Putting evidence into practice: evidence-based interventions for fatigue during and following cancer and its treatment. *Clin J Oncol Nurs*. 2007;11:99-113.