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Review Article

Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in the Management of Peritoneal Surface Malignancies of Colonic Origin

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Introduction

Treatment options for patients with unresectable metastatic disease have improved significantly in the past few years. A review of the published data in the treatment of patients with Stage IV colorectal cancer, outlining the surgical and medical therapeutic options demonstrates that medical management, with combinations of cytotoxic chemotherapy, and/or biological agents, has resulted in an unprecedented median survival > 20 months.[1]

Peritoneal involvement in colorectal cancer occurs in approximately 30% of patients. In 8% of these patients peritoneal dissemination is diagnosed at the time of primary colorectal surgery and 25% present with recurrent disease confined to the peritoneal cavity.[2] The management of disease limited to the peritoneal cavity has been controversial. However, at the present time, there is no published data that outlines the impact of these new systemic therapy regimens when given to patients with colorectal cancer with metastatic disease confined to the peritoneum. Therefore, systemic treatment alone is an unproven therapeutic strategy for this particular group of Stage IV patients with limited peritoneal dissemination from a primary or recurrent colon cancer.

Surgical therapy for stage IV colorectal cancer has evolved from the treatment of locally recurrent primary tumors to the routine resection of hepatic metastases, accounting for five year-survival and cure seen in selected patients. Today, surgical therapy for metastatic colorectal cancer and other solid cancer metastases has evolved even further to embrace the concept of complete macroscopic surgical eradication and/or cytoreduction of metastatic disease. Our understanding of the biological and clinical behavior of peritoneal surface malignancies has helped to advance this therapeutic concept beyond clinical research into a viable treatment option with potential for broad application. The present paper will focus on the available scientific evidence of the role of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) in the management of peritoneal surface malignancies of colorectal origin.

Pathophysiology of Peritoneal Carcinomatosis

Peritoneal surface malignancies represent a spectrum of diseases characterized by the rupture of the primary tumor with a predictable pattern of dissemination throughout the abdominal and pelvic regions.[3] However, the significance of free intraperitoneal cells is unknown since after seeding the peritoneal cavity, these cells must complete a series of steps to acquire the potential

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to form tumor deposits. First they need to survive in the peritoneal cavity by evading the immune system. In addition, they need to attach to secondary sites and develop a blood supply for their metabolic needs. Due to the complexity of this process, most tumor cells will fail to develop into a metastatic deposit.

The dissemination of tumor cells in the peritoneal cavity is governed by several factors. The physiologic flow of peritoneal fluid within the abdomen occurs in a clockwise fashion. This explains the predominance of tumor cell implants on the undersurface of the right hemi-diaphragm as they are pulled into this region with every respiratory cycle. A second mechanism of dissemination is due to the phagocytic activity of both the greater and lesser omentum and the appendices epiploicae of the sigmoid colon. Infiltration of the greater omentum by tumor gives rise to the well known "omental cake", a frequent hallmark of peritoneal malignancies. A third driving force of dissemination simply is gravity, resulting in tumor deposits in the pelvis causing pelvic outlet obstruction. In women tumor cells will often attach to the ovaries, usually at the site of a ruptured follicle. Progressive invasion of the ovary leads to the clinical presentation of an ovarian mass. Once peritoneal tumor dissemination and growth has occurred, it will sustain itself through constant re-implantation. With sufficient accumulation of tumor cells in the greater omentum and the lymphatic lacunae of both diaphragms, physiologic flow and absorption of peritoneal fluid will cease and lead to malignant ascites. The protein rich ascites further promotes cancer growth.

Surgical intervention is an important contributor to the successful peritoneal implantation and growth of tumor cells. During resection of large primary lesions and in the presence of extensive lymph node involvement large number of tumor cells are released into the peritoneal cavity. The inflammatory response induced by surgical trauma will entrap cancer cells and paradoxically protect them from destruction by the immune system. Trapped tumor cells benefit from the same micromilieu that is produced by the healing process following surgical intervention. Cancer growth is also promoted by fibroblast proliferation and local collagen production.[4]

The Concept of Cytoreductive Surgery and Hyperthermic Intra-Peritoneal Chemotherapy

In the 1990's, Sugarbaker and colleagues proposed cytoreductive surgery and perioperative intraperitoneal chemotherapy as definitive treatment for peritoneal dissemination from appendiceal neoplasms and diffuse malignant peritoneal mesothelioma.[5-7] The successful treatment of peritoneal surface malignancies requires a combined approach that utilizes peritonectomy to remove all visible tumor nodules and intraperitoneal chemotherapy. The addition of perioperative intraperitoneal chemotherapy is thought to prevent the implantation of free intraperitoneal tumor cells and act against microscopic disease left behind after surgical resection of all macroscopic foci. Compared to systemic therapy alone, novel regional intraperitoneal chemotherapy has shown favorable oncologic results and substantially changed the selection, treatment, and prognosis of patients with abdominal and pelvic malignancies such as peritoneal carcinomatosis from appendiceal origin and peritoneal mesothelioma.[8-9] Chemotherapy is given in the immediate perioperative setting and may be continued for the first five postoperative days. The size of the peritoneal implants is of critical importance for the success of this therapy. Only patients with small intraperitoneal tumor nodules that have a limited distribution within the abdomen and pelvis are likely to show prolonged benefit.[10] To properly balance the risks and benefits, judicious patient selection is essential. Both visceral and parietal peritonectomies are necessary for complete cytoreduction, a mandatory component of therapy.[11]

Cytoreductive Surgery

A total of six subsets of peritonectomy procedures have been described. Their utilization depends on the distribution and extent of the disease within the peritoneal space. The following is a brief summary of the six peritonectomy procedures.

1) Parietal peritoneal stripping from the anterior abdominal wall

A single entry into the peritoneal cavity in the upper portion of the incision allows the surgeon to assess the need for a complete parietal peritonectomy. If tumor nodules are palpated on the parietal peritoneum, a complete parietal dissection is necessary. As the dissection proceeds to the peritoneum overlying the paracolic sulcus (line of Toldt) the dissection can proceed rapidly because of the loose connections of the peritoneum to the underlying fatty tissue.

2) Peritoneal stripping of the hemidiaphragms

The peritonectomy of the left and right upper quadrant is begun by progressive stripping of the posterior rectus sheath. Strong traction combined with ball-tip electrosurgical dissection allows separation of peritoneum and tumor deposits from all underlying normal tissue including the diaphragmatic muscle, the adrenal glands, and the superior half of the perirenal fat. The stripping of the diaphragmatic undersurface is continued until the bare area of the liver is encountered. At that point, tumor on the anterior and superior surface of the liver is electroevaporated until completely cleared. With ball-tipped electrosurgical dissection, a thick layer of tumor may be lifted off the dome of the liver by removing Glisson's capsule. The dissection proceeds laterally to the right until the perirenal fat is encountered and cleared. The right adrenal gland is exposed and injury to it carefully avoided as tumor is stripped from the right subhepatic space. Care is taken not to traumatize the vena cava or any of the short hepatic veins emanating from it, particularly those draining the caudate lobe.

3) Greater omentectomy and splenectomy

Greater omentectomy/splenectomy is performed to free the mid-abdomen from large tumor volumes. The greater omentum is elevated and separated from the transverse colon using electrocautery. The peritoneum covering the transverse mesocolon is carefully removed up to the inferior pancreatic edge. The gastroepiploic vessels on the greater curvature of the stomach and the short gastrics are divided. With traction on the spleen, tumor bearing peritoneum anterior to the pancreas is stripped, exposing the splenic artery and vein at the tail of the pancreas. Injury to the main left gastric artery and vein must be avoided to preserve the sole remaining vascular supply to the stomach.

4) Cholecystectomy with stripping of the hepatoduodenal ligament

If the gallbladder is involved by tumor, a standard cholecystectomy is performed. Blunt dissection of Calot's triangle minimizes injury to the common bile duct and right hepatic artery and allows safe removal of any tumor deposits in this area. The triangular ligament of the left lobe of the liver is then resected, which allows retraction of the left lateral liver segments in order to expose the hepatogastric ligament in its entirety. A circumferential release of this ligament from the fissure between liver segments 1-3 and the lesser curvature of the stomach between right and left gastric arteries is required. After stripping the peritoneum of the lesser curvature, digital dissection with firm pressure from the surgeon's thumb and index finger separates lesser omental fat and tumor from the right and left gastric arteries. As much as possible of the anterior vagus nerve is spared.

5) Stripping the floor of the omental bursa

By anterior and superior retraction of the caudate lobe the entire floor of the omental bursa is exposed. Electroevaporation of tumor from the posterior surface of the left caudate lobe portion may be necessary to achieve this exposure. Ball-tip electrosurgery is used to cautiously divide the peritoneal reflection of the liver onto the left side of the subhepatic vena cava. After the peritoneum is divided Russian forceps assist in bluntly stripping the peritoneum from the superior recess of the omental bursa, the right diaphrgmatic crus, and the portal vein. Electroevaporation of tumor from the liver surface that lies posterior to the hepatoduodenal ligament may be required. Care is taken while stripping the floor of the omental bursa to stay superficial to the right phrenic artery.

6) Resection of rectosigmoid colon, uterus, and cul-de-sac

First the sigmoid colon is divided with a linear stapler just above the superior extend of the carcinomatosis involving the pelvis, usually at the junction of sigmoid and descending colon. The inferior mesenteric artery and vein are divided, thus allowing retraction of the small bowel and the proximal descending colon into the upper abdomen. Ball-tipped electrosurgery is used to circumferentially dissect the peritoneum of the pelvic inlet. Extraperitoneal ligation of the uterine arteries is performed just above the ureter and close to the base of the bladder. In women, the bladder is moved gently off the cervix and the vagina is entered to complete the hysterectomy. Preservation of the lower half of the rectum will allow for a larger stool reservoir and diminish frequent bowel movements.

Criteria for Complete Cytoreduction

By definition complete cytoreduction is equivalent to the eradication of all macroscopic residual tumor deposits greater than 2.5mm. The ability to achieve a complete macroscopic removal of all tumors is assessed

using the following clinical and radiographic criteria:

- ECOG Performance status 2 or less;
- No evidence of extra-abdominal disease;
- No evidence of biliary obstruction;
- No evidence of ureteral obstruction;
- No evidence of intestinal obstruction at more than one site;
- No evidence of gross disease in the small bowel mesentery and absence of several segmental sites of partial obstruction;
- Small volume disease in the gastro-hepatic ligament.

Hyperthermic Intra-Peritoneal Chemotherapy (HIPEC)

To achieve a maximum cytotoxic effect after complete cytoreduction the patient is subjected to HIPEC with Mitomycin C (15 to 35 mg/m^2) at a target intraperitoneal temperature of 39°C to 42°C for 60 to 120 minutes. Although Mitomycin C is the most commonly used drug, other drugs such as Oxaliplatin and combinations of Mitomycin with Cisplatin and Doxorubicin are now being tested with promising early results.[12]

The current technique for HIPEC begins with the preparation of the abdominal cavity for the chemotherapeutic perfusion. Either an open or closed method can be used. Each method has advantages and disadvantages. With the closed method the ability to control spillage of the perfusate and achieve and maintain higher temperatures in a shorter period of time is improved over the open method. With the open method access to the intraabdominal contents is easier, particularly in case of bleeding complications or functional problems with the perfusion catheters. The open approach also improves the ability to assure adequate perfusion of all anatomic sites. With regard to its cytotoxic effect, both techniques are equivalent. With the open method, the patient's skin is lifted to the abdominal retractor creating a "Coliseum" giving the surgeon access to the intra-abdominal contents during perfusion. With the closed technique, a watertight closure of the skin is accomplished before starting the perfusion.

After placing the perfusion catheters inside the abdomen along with two or three temperature probes, the catheters are connected to a roller pump and a heat exchanger and the warm chemotherapy solution (43°C) is perfused for 90 minutes. Creating a hyperthermia environment has several advantages. First, cancer cells are more heat sensitive than normal tissue. Temperatures between 40°C and 44 °C are cytotoxic for cells in a low pO2 and pH environment. This condition is common in tumor tissues due to a hypoxic micromilieu. The preferential cytotoxic effect of hyperthermia on hypoxic tissue is augmented in hypovascular tumor tissue such as that found in peritoneal deposits. Second, hyperthermia increases the tissue penetration of chemotherapy agents. As tissues soften in response to heat, decreased interstitial pressure allows for improved drug penetration. Third and most importantly, heat increases the cytotoxicity of the chemotherapy agents. This synergism occurs only at the interface of the perfusate and the peritoneal/tumor surface.

Following completion of the perfusion the perfusate is removed by suction and reconstructive surgery began. It is emphasized that no intraabdominal sutures are placed until after the chemotherapy perfusion is complete with one exception: closure of the vaginal cuff to prevent leakage of the perfusate.

Under certain circumstances Early Postoperative Intraperitoneal Chemotherapy (EPIC) perfusion with 5-FU can be sustained for five days postoperatively. In patients with symptomatic ascites in whom adequate cytoreduction is impossible, HIPEC can be used for palliation of the intractable ascites.

Standardized surgical techniques as described above, reproducible delivery methods for hyperthermic intra-peritoneal chemotherapy (HIPEC), and observation of patient selection criteria are responsible for the recently published outcomes.[13] These results have spurred the establishment of numerous peritoneal surface malignancy treatment centers in the United States and Europe. Over the last five years, a number of international treatment centers have published their results using cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) for peritoneal carcinomatosis in patients with colorectal cancer. In a randomized controlled trial reported in 2003, superior survival for cytoreductive surgery combined with HIPEC compared to systemic chemotherapy alone was demonstrated.[14] In 2004, a multi-institutional registry study from 28 international treatment centers demonstrated a median survival of 19 months and a 39% three-year survival after cytoreductive surgery and HIPEC in 506 patients with colorectal peritoneal carcinomatosis.[15] In patients with low volume peritoneal carcinomatosis of colonic origin cytoreductive surgery and HIPEC can achieve long-term survival.[15] However, as pointed out by Yan et al in a systematic review of 14 published series, only two were randomized controlled trials with one randomized comparative study.

The remaining 11 reports consisted of observational studies without control groups.[16] Most importantly, the indications, the techniques, and the type of drugs used varied among the reported studies.

The Peritoneal Surface Malignancy Group (PSMG) has attempted to standardize the indications and techniques for the appropriate use of cytoreductive surgery and HIPEC in a recent consensus statement.[17] The statement lists the following principles of standardization with regard to operative technique and patient selection: 1) the goal of peritonectomy is to achieve complete macroscopic cytoreduction, 2) if complete surgical cytoreduction is achieved HIPEC is a mandatory part of the treatment, 3) Mitomycin C remains the drug of choice although recent data indicates the efficacy of intraperitoneal Oxaliplatin combined with systemic biological therapy 4) minor variations in dosage, temperature and delivery method are allowed.

Proper patient selection remains a critically important aspect of the treatment for peritoneal dissemination from colorectal cancer. Long-term survival with cytoreductive surgery and HIPEC can only be achieve with complete cytoreduction. Current evidence clearly indicates that an incomplete cytoreduction of peritoneal disease confers no survival advantage over systemic chemotherapy alone. Therefore patients in which a complete cytoreduction cannot be accomplished do not benefit from this procedure.

Patients found to have peritoneal carcinomatosis and distant metastases should be considered for combinations of cytotoxic chemotherapy and biologic therapy. If they have a good response to systemic therapy and limited liver metatases as the only additional site of disease, cytoreductive surgery and intraperitoneal chemotherapy may be appropriate after a period of observation. There is currently no data indicating whether systemic chemotherapy should be given before or after cytoreductive surgery and HIPEC. However, it is important that patients with limited liver metastases who may be candidates for HIPEC are evaluated by specialized surgical oncologists before initiating systemic therapy alone.

Diagnostic Evaluation

As outlined on the clinical pathway for the management of peritoneal surface malignancies of colonic origin, Figure 1, once a patient is suspected or known to have colorectal cancer with peritoneal involvement, one of the most important steps in the diagnostic work up is the determination if the patient has peritoneal carcinomatosis with or without distant sites of dissemination. To evaluate the extent of peritoneal dissemination and to rule out any hematogenous metastases a complete colonoscopy and a contrast enhanced CT scan of the chest, abdomen and pelvis is performed. A PET scan can be considered if there are any questions about hematogenous metastases or extensive retroperitoneal lymphadenopathy.

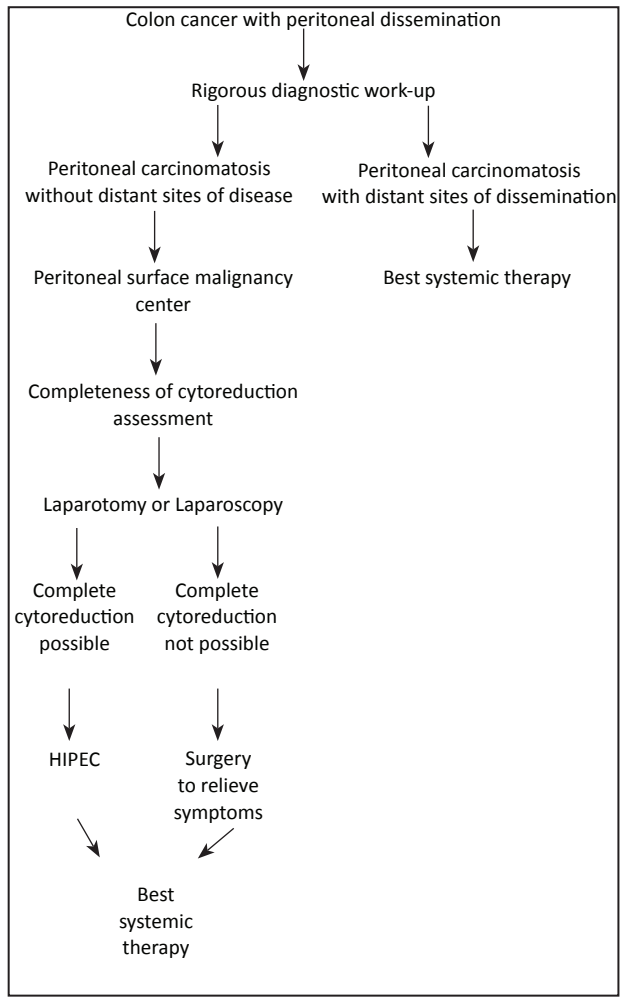

Figure 1 - Clinical pathway for the management of peritoneal surface malignancies of colonic origin

The role of CT scan in the evaluation of peritoneal carcinomatosis has been the subject of two published series.[18-19] The diagnostic accuracy of the CT for peritoneal carcinomatosis is limited, particularly for the detection of small bowel peritoneal implants. Routine CT scans are of limited value in excluding those patients with colorectal cancer peritoneal carcinomatosis that will not benefit from cytoreductive surgery with HIPEC. Therefore, alternative diagnostic methods to correctly stage patients with peritoneal malignancies are needed.

Role of laparoscopy in the evaluation of peritoneal carcinomatosis

Garofalo et al reported on 97 cases of peritoneal carcinomatosis submitted to a staging laparoscopy.[20] In 96 of 97 laparoscopic cases they succesfully assessed the Peritoneal Cancer Index. Only two of 96 cases were understaged. Correlation between laparoscopic and final open assessment of the Peritoneal Cancer Index was good. There was no mortality and no port sites metastases. Patients found to have massive small bowel and mesenteric involvement by staging laparoscopy were excluded from peritonectomy, establishing laparoscopy as a useful staging tool for peritoneal surface malignancies.

A group of French investigators evaluated the role of explorative laparoscopy in 11 patients with peritoneal carcinomatosis.[21] All patients successfully underwent laparoscopic evaluation. The median operating time for the laparoscopic portion of the procedure was 38 min (range 23-75 min). There were no complications. Three patients were judged unresectable by laparoscopy. Seven of the remaining eight patients deemed resectable after laparoscopy were successfully resected. Only one out of 11 patients was understaged by laparoscopy.

These two studies demonstrate that laparoscopy staging is a valuable tool in the difficult selection of patients for complete cytoreduction and HIPEC.

Clinical Results

Recurrence of peritoneal dissemination after cytoreductive surgery and HIPEC is not uncommon. This relapse has been correlated with a number of clinico-pathological parameters, including extent of initial disease, histology, and adequacy of cytoreduction.

World-wide approximately 800 patients have been treated with cytoreductive surgery and HIPEC for colon cancer induced peritoneal carcinomatosis. Current evidence suggests that best results require complete peritoneal cytoreduction and HIPEC. This combined approach is based on the premise that all macroscopic disease is optimally removed and residual microscopic disease adequately addressed by HIPEC. In those patients in which this is achieved two-year survival rates are close to 60% and five-year survival rates approach 40%.[12] However, more so than for apendiceal malignancies, treatment success hinges on complete cytoreduction and those patients that are incompletely cytoreduced can only expect a average survival of 6 months.[12,14]

At the present time, we lack universally accepted and easily reproducible prospective staging and scoring systems that address the quantity and location of the peritoneal dissemination and its impact on the ability to achieve a complete cytoreduction. We also do not have universal agreement on proper patient inclusion and exclusion criteria. Some centers consider patients with few liver metastases proper candidates for this procedure while others see them as an absolute contraindication. In the absence of a large prospective randomized trial that addresses all the above-mentioned issues it is going to be difficult to demonstrate the true impact of cytoreductive surgery and HIPEC on the natural history of colorectal cancer with peritoneal dissemination.

Morbidity, mortality and Quality of Life

The morbidity and mortality of 356 consecutive patients after cytoreductive surgery and HIPEC for peritoneal carcinomatosis has been reported.[22] Eighty-nine percent of the patients had a complete cytoreduction. Seven treatment-related deaths were seen (2%). Line sepsis (17%) and Anemia (14%) were the two most common Grade III morbidities. Eleven percent of all patients required re-operation. The most common reasons for re-explorations were fistula (3.3%), anastomotic leak (2.2%) and bleeding (2%). The overall rate of grade III or IV complications was 40%. The median length of stay was 21 days (11-82 days). The median number of intraoperative blood transfusions was 2 (0-8). Two studies by McQuellon reported the short term and long-term quality of life outcomes in patients with peritoneal carcinomatosis after cytoreductive surgery and HIPEC.[23-24] In the short-term outcome study with 64 patients, the overall quality of life after surgery initially decreased but returned to baseline or better within three to six months after surgery.[23] A follow up study of seventeen three-yr survivors demonstrated that more than 90% of patients had minimal to no limitations on their quality of life with functional assessments that compared favorably to national reference values for their respective age groups.[24]

Future Directions

Modern systemic therapy for patients with Stage IV colorectal cancer generally consists of a combination of cytotoxic chemotherapy and biological agents. Many studies have shown the effectiveness of this approach in

patients with solid organ colorectal metastases. Data on patients with colorectal cancer metastases limited to the peritoneum is scarce.

In the United States approximately 80 to 100 patients with peritoneal carcinomatosis from colorectal cancer are treated annually with cytoreductive surgery and HIPEC. This represents only a small portion of the true denominator, but presumably these patients are being treated with combinations of cytotoxic chemotherapy and biological agents. Clearly, better data is needed in order to determine the most appropriate therapy for these patients.

At the present time, a Phase III trial with patients randomized to best systemic therapy versus cytoreductive surgery with HIPEC followed by best systemic therapy is being considered by the Peritoneal Surface Malignancy Group. Figure 2.

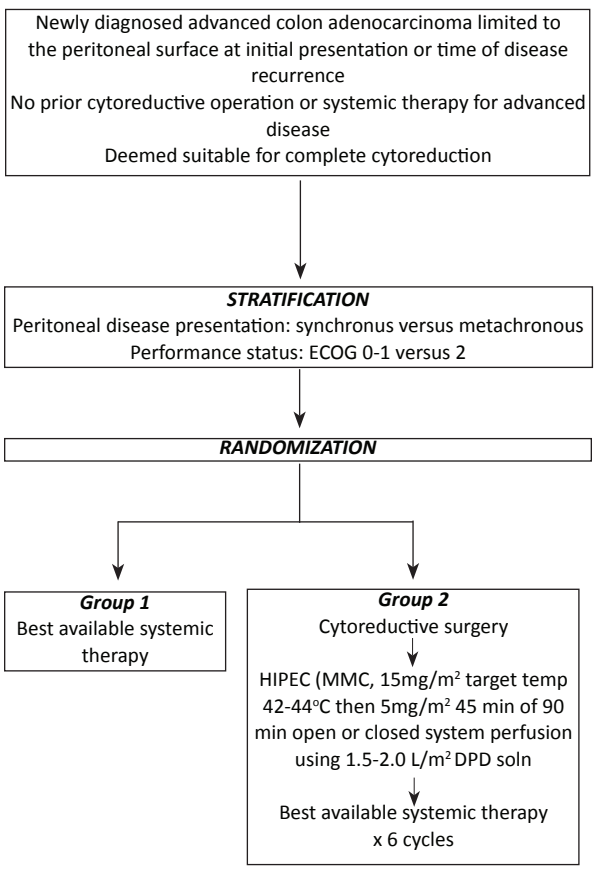

Figure 2 - Study Schema

Summary

Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) continues to play an increasing role in the management of peritoneal surface malignancies of colorectal origin. The prognosis of patients and the responses to cytoreductive surgery and HIPEC depend on the histology, the degree of malignant transformation, the adequacy of the cytoreductive surgery, and the response to systemic therapy. Continuous interaction between medical and surgical oncologists is needed to identify the most appropriate patients for and the most efficient sequence of the available therapeutic modalities.

References

1. Hurwitz HI, Fehrenbacher L, Hainsworth JD, Heim W, Berlin J, Holmgren E, et al. Bevacizumab in combination with fluorouracil and leucovorin: an active regimen for first-line metastatic colorectal cancer. J Clin Oncol 2005; 23:3502-8.
2. Sadeghi B, Arvieux C, Glehen O, Beaujard AC, Rivoire M, Baulieux J, et al. Peritoneal carcinomatosis from non-gynecologic malignancies: results of the EVOCAPE 1 multicentric prospective study. Cancer 2000; 88:58-63.
3. Esquivel J, Sugarbaker PH. Clinical presentation of the Pseudomyxoma peritonei syndrome. BR J Surg 2000; 87:1414-8.
4. Zoetmulder F. Cancer cell seeding during abdominal surgery: experimental studies. In: Sugarbaker PH, editor. Peritoneal carcinomatosis: principles of management. Boston: Kluwer Academic Publishers; 1996. p.155-61.
5. Sugarbaker PH. New standard of care for appendiceal epithelial neoplasms and pseudomyxoma peritonei syndrome. Lancet Oncol 2006; 7:69-76.
6. Sugarbaker PH, Graves T, DeBruijn EA, Cunliffe WJ, Mullins RE, Hull WE, et al. Early postoperative intraperitoneal chemotherapy as an adjuvant therapy to surgery for peritoneal carcinomatosis from gastrointestinal cancer: pharmacological studies. Cancer Res 1990; 50:5790-4.
7. Look M, Chang D, Sugarbaker PH. Long-term results of cytoreductive surgery for advanced and recurrent epithelial ovarian cancers and papillary serous carcinoma of the peritoneum. Int J Gynecol Cancer 2004; 14:35-41.
8. Katz MH, Barone RM. The rationale of perioperative intraperitoneal chemotherapy in the treatment of peritoneal surface malignancies. Surg Oncol Clin N Am 2003; 12:673-88.
9. Sugarbaker PH, Yan TD, Stuart OA, Yoo D: Comprehensive management of diffuse malignant peritoneal mesothelioma. Eur J Surg Oncol 2006; 32:686-91.
10. Verwaal VJ, van Tinteren H, van Ruth S, Zoetmulder FA. Predicting the survival of patients with peritoneal carcinomatosis of colorectal origin treated by aggressive cytoreduction and hyperthermic intraperitoneal chemotherapy. Br J Surg 2004; 91:739-46.
11. Sugarbaker PH. Peritonectomy procedures. Ann Surg 1995; 221:29-42.
12. Elias D, Delperro JR, Sideris L, Benhamou E, Pocard M, Baton O, et al. Treatment of peritoneal carcinomatosis from colorectal cancer: impact of complete cytoreductive surgery and difficulties in con-

ducting randomized trials. Ann Surg Oncol 2004; 11:518-21.
13. Elias D, Raynard B, Farkhondeh F, Goéré D, Rouquie D, Ciuchendea R, et al. Peritoneal carcinomatosis of colorectal origin. Gastroenterol Clin Biol 2006; 30:1200-4.
14. Verwaal VJ, van Ruth S, de Bree E, van Sloothen GW, van Tinteren H, Boot H, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal origin. J Clin Oncol 2003; 21:3737-43.
15. Glehen O, Kwiatkowski F, Sugarbaker PH, Elias D, Levine EA, De Simone M, et al. Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer: a multi-institutional study. J Clin Oncol 2004; 22:3284-92.
16. Yan TD, Black D, Savady R, Sugarbaker PH. A systemic review on the efficacy of cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for peritoneal carcinomatosis from colorectal carcinoma, J Clin Oncol 2006; 24:4011-9.
17. Esquivel J, Sticca R, Sugarbaker P, Levine E, Yan TD, Alexander R, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in the management of peritoneal surface malignancies of colonic origin: a consensus statement. Ann Surg Oncol 2007; 14:128-33.
18. de Bree E, Koops W, Kröger R, van Ruth S, Verwaal VJ, Zoetmulder FA. Preoperative computed tomography and selection of patients with colorectal peritoneal carcinomatosis for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Eur J Surg Oncol 2006; 32:65-71.
19. Yan TD, Haveric N, Carmignani CP, Bromley CM, Sugarbaker PH. Computed tomographic characterization of malignant peritoneal mesothelioma. Tumori 2005; 91:394-400.
20. Garofalo A, Valle M. Staging videolaparoscopy of peritoneal carcinomatosis. Tumori. 2003; 89(4 Suppl):70-7.
21. Pomel C, Appleyard TL, Gouy S, Rouzier R, Elias D. The role of laparoscopy to evaluate candidates for complete cytoreduction of peritoneal carcinomatosis and hyperthermic intraperitoneal chemotherapy. Eur J Surg Oncol 2005; 31:540-3.
22. Sugarbaker PH, Alderman R, Edwards G, Marquardt CE, Gushchin V, Esquivel J, et al. Prospective morbidity and mortality assessment of cytoreductive surgery plus perioperative intraperitoneal chemotherapy to treat peritoneal dissemination of appendiceal mucinous malignancy. Ann Surg Oncol 2006; 13:635-44.
23. McQuellon RP, Loggie BW, Fleming RA, Russell GB, Lehman AB, Rambo TD. Quality of life after intraperitoneal hyperthermic chemotherapy (IPHC) for peritoneal carcinomatosis. Eur J Surg Oncol 2001; 27:65-73.
24. McQuellon RP, Loggie BW, Lehman AB, Russell GB, Fleming RA, Shen P, 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.