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REVIEW ARTICLE

Management of peritoneal metastases – Basic concepts

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Summary

Despite the fact that cytoreductive surgery (CRS) and hyperthermic perioperative chemotherapy (HIPEC) is conceptually simplistic, optimal implementation of this combined treatment remains complex. Multiple patient-related variables, methodologic variables, and pharmacologic variables need to be considered in devising an optimal treatment strategy. Working through these variables considering the pathophysiology of peritoneal metastases and their possible treatments is more likely to provide guidance in terms of successful management than multiple randomized controlled trials. The principles of management include: 1) A surgical technology involving peritonectomy procedures and visceral resections that will result in a complete cytoreduction. 2) Treatment of patients at a maximal low peritoneal cancer index (PCI) will maximize the benefits especially in those patients who have high grade peritoneal metastases from gastric cancer, colorectal cancer, or ovarian malignancy. 3) Tumor cell entrapment should be avoided by preventing major surgical procedures prior to the definitive treatment with CRS and HIPEC. 4) Mechanical removal of cancer cells and small nodules by mechanical irrigation prior to HIPEC is necessary. 5) A response must be generated using cancer chemotherapy to eradicate small volume residual disease that will remain even after a complete cytoreduction by visual inspection. 6) The benefits of multiple cycles of normothermic intraperitoneal and intravenous chemotherapy (NIPEC) used long-term to help preserve the surgical complete response needs to be integrated into the overall plan of management. Currently, with peritoneal metastases from high grade disease perioperative chemotherapy usually fails to maintain the surgical complete response. Major modifications of the perioperative chemotherapy using HIPEC, early postoperative intraperitoneal chemotherapy (EPIC) and NIPEC long-term will go far towards optimizing the treatment of peritoneal metastases no matter what the primary gastrointestinal or gynecologic malignancy is being treated.

Key words: *Cytoreductive surgery, hyperthermic perioperative chemotherapy (HIPEC), early postoperative intraperitoneal chemotherapy (EPIC), normothermic intraperitoneal chemotherapy (NIPEC), peritonectomy*

Introduction

The management of peritoneal metastases requires a combination of cytoreductive surgery and perioperative chemotherapy. This is theoretically correct, however, optimal implementation of these two principles into an operative event is far from straightforward. As CRS and HIPEC have evolved over the past two decades, multiple variables have been identified as a result of continued research efforts by dedicated investigators. There is a near universal opinion regarding the surgery; most centers agree that the more complete the cytoreduction, the greater benefits that will occur from this combined treatment. In contrast, it is obvious from a survey of the literature concerning peritoneal metastases that no standardized HIPEC treatment currently exists. Table 1 identifies patient-related variables, methodological variables for HIPEC, and pharmacologic variables that are currently available for use either in the operating room as HIPEC, in the early postoperative period as EPIC, or long term as NIPEC. Nearly 30 variables can be identified in the surgical literature as

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Table 1. Possible variables in the application of cytoreductive surgery and hyperthermic perioperative chemotherapy as a treatment for peritoneal metastases

Patient-related variables
4 different diseases (colorectal appendiceal, gastric, ovarian)
20+ unusual indications for CRS and HIPEC
Prevention protocols
Treatment protocols
Extreme treatment protocols
Methodologic variables
HIPEC vs EPIC
No hyperthermia (<41°C) vs moderate hyperthermia (≥41-43°C) vs extreme hyperthermia (>43-45°C)
Carrier solution volume - 3L vs 1.5 L/m^2 vs 6L
Carrier solution type - saline vs 1.5% dextrose PDS vs D5W vs lactated Ringer's solution vs dextran solutions
Intraperitoneal irrigations – saline vs distilled water vs 0.75% peroxide vs Betadine
Volume of intraperitoneal irrigation – Extensive intraperitoneal lavage (10L one liter at a time) vs other
Open vs closed vs Coliseum vs Landager vs closed then open
Timing – 30 min vs 60 min vs 90 min vs 180 min
IP epinephrine vs no epinephrine
Chemotherapy solutions vs aerosols
Pharmacologic variables
Route of administration – IP vs IP and IV
Naked drugs vs nanoparticles
Single vs multiple drugs
Mitomycin C
Oxaliplatin
Cisplatin
Doxorubicin
5-fluorouracil
Melphalan
Gemcitabine
Carboplatin
Docetaxel
Paclitaxel
Pemetrexed
Mitoxantrone

differences in the application of CRS and HIPEC as a treatment for peritoneal metastases.

Randomized trials adequately powered to answer important questions concerning these variables are not likely to be completed in a timely manner. Although there may be some important trials that would select the most important differences in treatment, no comprehensive answers will soon be available. For this reason, this review seeks to establish the principles of management for an optimal CRS and HIPEC. The goals of this manuscript are to establish the requirements for patient management for surgery, and for perioperative drug delivery. These are optimal strategies that need to be universally incorporated into treatment plans at all peritoneal surface oncology treatment centers.

Principles of management

For this manuscript there are six principles of management to be applied in CRS and HIPEC treatments for peritoneal metastases. First, the surgical technology to achieve a complete cytoreduction needs to be incorporated into practice. Secondly, patients need to be treated at a maximal low PCI. Third, tumor cell entrapment, as a part of the natural history of surgically treated gastrointestinal malignancy, must be prevented. Fourth, mechanical removal of cancer cells and small nodules by irrigation is mandatory. Fifth, the small volume residual disease that remains after even the most complete cytoreductive surgery must be combined with a maximal tolerable cancer chemotherapy response. And sixth, the benefits of NIPEC used long term to preserve the surgical complete response must be considered (Table 2).

A reasonable assumption to pursue is that the cytoreductive surgery is the more powerful treatment that needs to be initiated prior to the less robust treatment, which is the chemotherapy (HIPEC, EPIC, and NIPEC). The cytoreductive surgery is a combination of peritonectomy procedures and visceral resections with a goal of no visible disease at the completion of the surgical event. Table 3 presents the six most important parietal peritonectomy procedures and itemizes

Table 2. Principles of management of peritoneal metastases

1.	The surgical technology to achieve a complete cytoreduction needs to be incorporated into practice.
2.	Patients must be treated at a maximal low peritoneal cancer index (PCI).
3.	Patients must be managed to maximally avoid tumor cell entrapment.
4.	Mechanical removal of cancer cells and small nodules by irrigation is mandatory
5.	Small volume residual disease requires treatment that will result in a maximal cancer chemotherapy response.
6.	The benefits of normothermic intraperitoneal chemotherapy (NIPEC) used long term must be considered.

Table 3. Surgical technology to achieve a complete response

Peritonectomy procedures	*Visceral resection*
Anterior parietal	Greater omentum
Right subphrenic	Spleen
Left subphrenic	Uterus and ovaries
Pelvic	Rectosigmoid colon
Omental bursa	Right colon
Mesenteric	Lesser omentum
	Stomach

the visceral resections that are most commonly required for complete cytoreduction.

The chemotherapy strategies are, at this point in time, limited to HIPEC, EPIC, and NIPEC. The perioperative chemotherapy complements the surgery by the eradication of minimal residual disease on the surfaces of the abdomen and pelvis. Perioperative chemotherapy is an attempt to preserve the surgical complete or near complete response that was achieved with the peritonectomy and visceral resections.

Strategies to initiate treatments with the lowest possible peritoneal cancer index

In every peritoneal surface malignancy studied to date, the lower the PCI, the more likely a patient is to benefit from CRS and HIPEC. Patients with a large extent of disease (high PCI), as seen with pseudomyxoma peritonei, may realize great benefit. However, even with this minimally aggressive malignancy, a low PCI is associated with an improved prognosis [1]. Patients with high-grade peritoneal metastases from gastric cancer must have a low PCI (<10) to expect long-term benefit [2]. To treat all patients with a maximal low PCI must be the goal of all peritoneal metastases management.

Proactive treatment of the primary cancer

Perhaps the most meaningful efforts to utilize low PCI come through proactive treatments initiated early in the natural history of gastrointestinal cancer [3-5]. Prophylactic HIPEC used in selected patients at the time of primary cancer resection should theoretically result in the lowest PCI possible in the natural history of the patient's disease. Table 4 lists the clinical and intraoperative histopathologic variables that identify patients for prophylactic (adjuvant) HIPEC or HIPEC plus EPIC. It also provides the expected incidence of local recurrence and/or peritoneal metastases expected in the absence of prophylactic perioperative chemotherapy [6]. Prevention of local recurrence and peritoneal metastases has been reported as a successful strategy for appendiceal, colorectal, gastric, and pancreas cancer.

Unfortunately, at this point in time, not all institutions that are performing primary resections of gastrointestinal cancer have HIPEC and/or EPIC readily available for prophylactic treatments. In this situation, the proactive second-look surgery with HIPEC is indicated [7,8]. This treatment has not been clinically evaluated for gastric or pancreatic malignancy but is a prominent strategy for comprehensive management of appendiceal or colorectal malignancy. Table 5 lists the clinical and histopathologic features that would indicate the need for a second-look surgery with HIPEC. Also shown in this Table is the high predicted incidence of local recurrence and/or peritoneal metastases in this group of patients if they do not receive the proactive second-look HIPEC [5].

A new application of CT to detect T3 and/or T4 colon cancer has been recently reported [9-11]. Using specialized CT technology, the depth of cancer invasion into the bowel wall can be determined with an accuracy of 67% for T-staging [10]. An irregular and bowl-shaped aspect of the external edges of tumor provided excellent sensitivity for T3/T4 inclusion (specificity = 97.7%).

Table 4. Clinical and intraoperative histopathologic features of the primary cancer as an estimate of the incidence of subsequent local recurrence and/or peritoneal metastases to guide proactive treatment with perioperative chemotherapy at the time of primary colorectal resection

Clinical features	*Estimated incidence of peritoneal metastases observed in follow-up (%)*
	Colorectal cancer
1. Peritoneal nodules detected with primary cancer resection	70
2. Ovarian metastases	60
3. Perforation through the primary cancer (free or localized)	50
4. Adjacent organ or structure invasion	20
5. Signet ring histology by endoscopic biopsy	20
6. Fistula formation	20
7. Obstruction of primary cancer	20
Histopathologic features[o]	
8. Positive margin of resection	80
9. Positive peritoneal cytology before or after resection	40
10. Positive imprint cytology	40
11. Lymph nodes positive at or near the margin of resection	20
12. T3/T4 mucinous cancer	40

[o]Requires intraoperative histopathologic assessment by the pathologist who is a member of the multidisciplinary team

Table 5. Clinical and intraoperative histopathologic features of the primary cancer as an estimate of the incidence of subsequent local recurrence and/or peritoneal metastases to guide proactive treatment with perioperative chemotherapy

Clinical features	*Estimated incidence of peritoneal metastases observed in follow-up (%)*
	Colorectal cancer
1. Peritoneal nodules detected with primary cancer resection	70
2. Ovarian metastases	60
3. Perforation through the primary cancer (free or localized)	50
4. Positive margin of resection	80

Thickening of a fascia or the abdominal wall provided good specificity for T4 stage (specificity = 88.1%). Enhancement over 100 HU of at least one peritumoral lymph node was the best criterion of N+ staging (specificity = 67.7%). This new CT technology can be used to identify patients at high risk for local recurrence and peritoneal metastases and initiate HIPEC or EPIC with primary cancer resection.

Neoadjuvant chemotherapy used to induce a low peritoneal cancer index

From a theoretical perspective, it has been suggested that a robust response (complete or near complete disease eradication) by neoadjuvant chemotherapy can better prepare a patient for CRS and HIPEC. The studies of Bijelic et al. in high-grade mucinous appendiceal neoplasms and Passot et al. in patients with colorectal cancer suggest that a response to neoadjuvant chemotherapy is a predictor of profound benefit when CRS and HIPEC were preceded by an effective neoadjuvant chemotherapy [12,13].

Neoadjuvant treatment for gastric cancer with peritoneal metastases

Recent reports suggest that prolonged treatment with combined systemic and intraperitoneal

chemotherapy when monitored by serial laparoscopy can help select primary gastric cancer patients for potentially curative gastrectomy with cytoreductive surgery. Canbay et al. showed that approximately 30% of patients have the disease eradicated from peritoneal surfaces by the bidirectional (combined intravenous and intraperitoneal chemotherapy administration) treatments. They also reported that approximately 30% of those patients who are selected for combined gastrectomy with peritonectomy could achieve a long-term survival with this otherwise devastating clinical situation [14]. Yamaguchi et al. have recently initiated and reported on treatments with intravenous and intraperitoneal paclitaxel [15]. By laparoscopic monitoring, 71% of patients had the disease visibly eradicated from their peritoneal surfaces. Although Yamaguchi et al. did not use HIPEC when resecting residual disease on these patients, they did report approximately 30% long-term benefit.

Initiate CRS and HIPEC at first diagnosis of peritoneal metastases in patients undergoing follow-up of their primary disease

All too often, when peritoneal metastases are diagnosed in patients with colorectal cancer as a site of surgical treatment failure, systemic chemotherapy is initiated and then continued for an extended time period. Treatment with systemic chemotherapy is continued until toxicity indicates that no further chemotherapy is possible. Although a brief treatment with systemic chemotherapy may be a judicious management plan at the first diagnosis of peritoneal metastases, the use of multiple cancer chemotherapy agents over a long time period is to be avoided. Patients with peritoneal metastases as patients with liver metastases need to be brought immediately to the attention of the multidisciplinary team. Those who are potential candidates for CRS and HIPEC should move rapidly to this treatment rather than being subjected to extended treatments of multiple cancer chemotherapy agents. The lack of sensitive radiologic tests by which to diagnose small volumes of peritoneal metastases makes the "watch-and-wait policy" an unsuccessful plan in patients who are candidates for an additional surgical intervention.

This failure of radiology of the abdomen and pelvis to adequately monitor small volume disease has been repeatedly demonstrated [16]. It has been suggested by Low and Barone that small volume disease is more adequately diagnosed with the MRI [17]. Tentes and colleagues suggest that there are more efficient radiologic tests [18]. Recent studies with PET-CT suggest that it may diagnose recurrent intestinal-type appendiceal malignancy (non-mucinous peritoneal metastases) and other high-grade gastrointestinal malignancies more accurately and with greater sensitivity than the routine CT scan [19].

Role of laparoscopy in patient selection for a low peritoneal cancer index

Accepting the fact stated above that radiologic tests are inadequate to diagnose a small extent of disease in patients with peritoneal metastases, laparoscopy has been suggested to better select patients for treatment. Valle et al. have presented data suggesting that 14% of patients undergoing a laparoscopy prior to cytoreductive surgery can be shown to have an extent of disease incompatible with complete cytoreduction [20]. In selected patients laparoscopy may be the only diagnostic tool capable of making a diagnosis of progressive low volume peritoneal metastases [21].

Normograms used to select patients with the lowest peritoneal cancer index

A formula for selection of colorectal cancer patients with peritoneal metastases for treatment was proposed by Verwaal and colleagues [22]. Also, the group from Uppsala, Sweden, generated a normogram, which they report minimizes the likelihood of an open and close procedure [23]. Pelz [24] and Esquivel and colleagues [25] have devised the Peritoneal Surface Disease Severity Score (PSDSS). They suggest that a normogram based on patient's symptoms, the CT-PCI, and the histologic assessment of the colorectal malignancy can place patients into four prognostic groups predicting the benefit expected from the CRS and HIPEC.

Jacquet and colleagues identified a list of concerning radiologic features for patients with mucinous colorectal and appendiceal adenocarcinoma to be used preoperatively to select patients for complete cytoreduction using the statistical tool of a decision tree analysis [26]. They determined that two radiologic features, bowel obstruction and tumor masses greater than 0.5 cm on the small bowel, could be used to select patients for an optimal cytoreduction and exclude patients from a sub-optimal cytoreduction. Rivard and colleagues listed 7 concerning radiologic fea-

tures [27]. They concluded that any two of these features predicted in a statistically significant manner incomplete cytoreduction whereas a single concerning radiologic feature did not. Table 6 is a list of concerning radiologic features that had been identified in patients with gastrointestinal malignancy to exclude patients from CRS and HIPEC. In the absence of these features, patients should move in the direction of CRS plus HIPEC without delay.

Optimizing CRS and HIPEC by prevention of tumor cell entrapment

The concept of tumor cell entrapment was introduced by Sethna and Sugarbaker as a prominent part of the natural history of surgically treated gastric cancer [28]. The two essential features of the tumor cell entrapment hypothesis are as follows: First, either prior or at the time of cancer resection, cancer cells may be released into the free peritoneal cavity. T3 or T4 tumors combined with surgical trauma may be a prominent cause for free abdominal or pelvic cancer cells. Cancer in lymph nodes or within the transected lymphatics may result in leakage of malignant cells into the resection site. Likewise, cancer within venous blood that escapes from the cancer specimen may carry with it cancer cells. These free cancer cells will then implant and grow at high volume in and around the resection site but also at lower volume on distant peritoneal surfaces. The second observation contained within the tumor cell entrapment hypothesis is that cancer cells implant, adhere, and then progress more efficiently at a wounded site than on intact peritoneum. This is the phenomenon of metastatic efficiency within a traumatized peritoneal space as compared to the concept of metastatic inefficiency of cancer cells within vascular structures such as the liver. Cancer cells are also stimulated by factors involved in the wound healing process when they are entrapped within a wounded site.

The tumor cell entrapment hypothesis demands that there be a respect for the peritoneum as a first line of defense against progression of peritoneal metastases [29]. If patients with gastrointestinal malignancy show peritoneal metastases or at high risk for the development of peritoneal metastases, special treatments should be initiated in the operating room in order to minimize the possibility for tumor cell entrapment. This concept was discussed earlier under the topic of proactive treatments.

Modification of primary gastrointestinal cancer management to avoid tumor cell entrapment

The logical consequences of tumor cell entrapment indicate that patients with appendiceal cancer, colorectal cancer, and gastric cancer who have a high risk for peritoneal contamination by cancer cells should have a minimal surgical procedure in the absence of HIPEC or EPIC to deal effectively with their primary disease. For example, patients with an obstructed left colon cancer are best served by a diverting ostomy. After brief treatment with neoadjuvant cancer chemotherapy the peritonectomy procedures and perioperative chemotherapy should be initiated. Efforts at the time of the first presentation to perform a large resection with anastomosis in the absence of HIPEC or EPIC should be avoided as this will entrap tumor cells within the retroperitoneal space and perhaps within the anastomotic site.

The paper by Braam and colleagues suggest that second-look HIPEC is an inferior treatment to

Table 6. Concerning radiologic features as a prognostic assessment

- Bowel obstruction or partial obstruction at more than one site
- Non-mucinous ascites
- Mesentery drawn together by tumor (clumped)
- Tumor infiltrating leaves of small bowel mesentery
- Mesenteric or para-aortic lymphadenopathy
- Hydroureter
- Psoas muscle invasion
- Gastric outlet obstruction
- Tumor ≥ 5 cm in lesser omentum or subpyloric space
- Tumor ≥ 5 cm in jejunal regions
- CT-PCI > 20 (excluding pseudomyxoma peritonei)

prophylactic HIPEC [30]. The avoidance of tumor cell entrapment should allow for a greater number of potentially curative reoperative procedures with a reduced incidence of morbidity and mortality and a reduced incidence of ileostomy or colostomy. Also, rectal cancer with peritoneal seeding should not be definitively resected until HIPEC is available with the cancer resection [31]. Tumor cell entrapment within the pelvis is difficult and probably impossible to deal with through pelvic peritonectomy procedures. Likewise, patients with gastric cancer and peritoneal seeding who have gastrectomy and then progression of peritoneal metastases cannot be treated for cure after the gastrectomy has opened up a large amount of retroperitoneal spaces for tumor cell entrapment [32].

The tumor cell entrapment hypothesis mandates that the cytoreductive surgery and the perioperative chemotherapy should occur as concomitant rather than sequential treatments. HIPEC should be used in the operating room immediately following the peritonectomies and visceral resections. Also, EPIC must be administered into the peritoneal space in a large volume of fluid before wound healing closes off large portions of the abdominal and pelvic space with adhesions. Intraperitoneal chemotherapy administered weeks or months after the cytoreductive surgery will result in areas of local-regional treatment failure and represents a theoretically sub-optimal approach to the management of local recurrence and peritoneal metastases. Long term combined intravenous and intraperitoneal chemotherapy (NIPEC) can complement perioperative chemotherapy treatments but can never replace them.

Definitely, the primary gastrointestinal surgery for these patients at risk for local-regional progression is the most important surgery. It is my personal opinion that 90% of the serious and life threatening situations that develop with follow-up predictably occur in approximately 10% of the patients. Those patients who are likely to develop local recurrence and peritoneal metastases need to be identified prior to or at the time of the primary gastrointestinal cancer resection. The treatments offered as the first intervention need to be definitive treatments that seek to prevent the progression of local recurrence or peritoneal metastases. As mentioned earlier, the surgery should remove all visible evidence of disease and then the perioperative cancer chemotherapy eradicate the minimal residual disease.

Mechanical removal of cancer cells by irrigation

In performing cytoreductive surgery large numbers of cancer cells will be present within the ascitic fluid, will be disrupted from peritonectomy specimens, or released from resected tumor nodules on the viscera. Frequently, throughout the cytoreductive surgery the dissection site should be irrigated copiously. This frequent irrigation is to remove blood and tissue debris, to clarify the anatomy for safe subsequent dissection, and to cool the tissues if high voltage electrosurgical dissection has been used. Then, at the completion of one of the five parietal peritonectomy procedures, a large volume irrigation of the peritonectomy site should occur (at least 2 liters of warm saline). After complete removal of the irrigation fluid, laparotomy pads or sterile towels should be placed in the peritonectomy site to prevent cancer cells from being iatrogenically implanted within the peritonectomy. Finally, at the completion of the cytoreduction irrigation with a cytotoxic non-chemotherapeutic agent should occur. Peroxide at 0.25% in 3 liters of warm saline is frequently used. Others use 3 liters of distilled water. Still others utilize a dilute betadine solution. Following this caustic irrigation, 6 liters of warm saline should be used to thoroughly wash all of the parietal and visceral peritoneal surfaces to vigorously irrigate away unattached cancer cells.

Perioperative chemotherapy needs to achieve a maximal chemotherapy response

As listed in Table 1, there are multiple methodologies by which to administer HIPEC and there are multiple drugs that can be chosen for use in the operating room or in the perioperative period [33]. The drugs used in the operating room are acute phase drugs that are augmented by heat and can exert their effect in the absence of cell proliferation. The agents selected for EPIC are not augmented by heat and require cell division for their optimal effects. Such drugs are 5-fluorouracil and paclitaxel.

Currently, a major flaw in the use of HIPEC may be the lack of drug retention at a high area under the curve (AUC) ratio within the peritoneal space. The cancer pharmacology seems to have assumed that a very high dose of chemotherapy delivered to the abdominal and pelvic surfaces over a short time period will achieve the necessary effect. For example, 400 mg/m^2

of oxaliplatin instilled into the peritoneal space has a half-life of approximately 12 min and a low AUC. By the end of 30 min of hyperthermia the drug is gone.

There are currently two drugs available that show prolonged retention within the abdominal and pelvic space and a sustained AUC. One of these is pegylated liposomal doxorubicin, which can be administered for prolonged HIPEC and maintains a high level of drug within the abdominal and pelvic space for the entire treatment [34]. The AUC ratio of pegylated liposomal doxorubicin is approximately 300. Theoretically, the heat should rapidly deploy the doxorubicin that is contained within the nanoparticle. The second drug, which has proven itself to have great value in the management of peritoneal metastases, is intraperitoneal paclitaxel [35]. This drug has an AUC ratio of 1000. Paclitaxel is used postoperatively usually at low dose over 5 days. The drug is retained within the peritoneal space for approximately 23 hrs. Its local-regional effects are greatly magnified over the systemic effects. Combinations of pegylated liposomal doxorubicin as HIPEC and paclitaxel as EPIC are currently being evaluated.

Normothermic intraperitoneal chemotherapy long term to maintain the surgical complete response

A sixth and final principle of management of peritoneal metastases has not been as well established as the first five. However, focusing on NIPEC used long term is potentially of great value. Its major flaw for more comprehensive utilization is the requirement for an intraperitoneal port long term. These intraperitoneal ports are associated with a moderate to high incidence of adverse events especially when employed for the full six months as in prior treatment plans. There is doubt that NIPEC in ovarian cancer has shown itself to be of benefit. In the work by Armstrong et al., the survival of patients with peritoneal metastases from ovarian cancer was increased from 50 months to 66 months (p=0.03) [36]. Data recently released by Sugarbaker and colleagues show that the long-term intraperitoneal chemotherapy significantly increased long-term survival in patients treated for peritoneal mesothelioma.

Conclusions

In summary, six principles for management of peritoneal metastases have been suggested and the rationale for these basic concepts in the management of patients with peritoneal metastases has been presented. Despite the complexity of the patient management using CRS and HIPEC, one should strive to fulfill these six basic principles when the treatment strategies at any institution for peritoneal metastases are implemented. These basic concepts have allowed the success obtained with the use of cytoreductive surgery and perioperative chemotherapy to occur. Their application in the future will help with continued optimization of the peritoneal metastases treatments.

References

1. Sugarbaker PH. Pseudomyxoma peritonei and peritoneal metastases from appendiceal malignancy. In: Sugarbaker PH (Ed). Cytoreductive Surgery & Perioperative Chemotherapy for Peritoneal Surface Malignancy. Textbook and Video Atlas. Cine-Med Publishing: Woodbury, CT, 2012, pp 57-78.
2. Glehen O, Gilly FN, Arvieux C et al. Peritoneal carcinomatosis from gastric cancer: a multi-institutional study of 159 patients treated by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy. Ann Surg Oncol 2010;17:2370-2377.
3. Sugarbaker PH. Early intervention for treatment and prevention of colorectal carcinomatosis: a plan for individualized care. Surg Oncol Clin N Am 2012;21:689-703 [PMID:23021724].
4. Sammartino P, Sibio S, Biacchi D et al. Long-term results after proactive management for locoregional control in patients with colonic cancer at high risk of peritoneal metastases. Int J Colorectal Dis 2014;29:1081-1089. doi: 10.1007/s00384-014-1929-4. Epub 2014 Jul 1.
5. Tentes AA, Spiliotis ID, Korakianitis OS, Vaxevanidou A, Kyziridis D. Adjuvant perioperative intraperitoneal chemotherapy in locally advanced colorectal carcinoma: preliminary results. ISRN Surg 2011;2011:529876. doi: 10.5402/2011/529876. Epub 2011 May 22.
6. Honoré C, Goéré D, Souadka A, Dumont F, Elias D. Definition of patients presenting a high risk of developing peritoneal carcinomatosis after curative surgery for colorectal cancer: a systematic review. Ann Surg Oncol 2013;20:183-192. doi: 10.1245/s10434-012-2473-5. Epub 2012 Oct 23.
7. Sugarbaker PH. Second-look surgery for colorectal cancer: Revised selection factors and new treat-

ment options for greater success. Int J Surg Oncol Volume 2011 (2011), Article ID 915078, 8 pages, doi:10.1155/2011/915078.

8. Elias D, Goéré D, Di Pietrantonio D et al. Results of systematic second-look surgery in patients at high risk of developing colorectal peritoneal carcinomatosis. Ann Surg 2008;247:445-450.
9. Dighe S, Blake H, Koh MD et al. Accuracy of multidetector computed tomography in identifying poor prognostic factors in colonic cancer. Br J Surg 2010;97;1407-1415.
10. Leufkens AM, van den Bosch MA, van Leeuwen MS, Siersema PD. Diagnostic accuracy of computed tomography for colon cancer staging: a systematic review. Scand J Gastroenterol 2011;46:887-894.
11. Sibileau E, Ridereau-Zins C, Vanel D et al. Accuracy of water-enema multidetector computed tomography (WE-MDCT) in colon cancer staging: a prospective study. Abdom Imaging 2014;39:941-948.
12. Bijelic L, Kumar AS, Stuart OA, Sugarbaker PH. Systemic chemotherapy prior to cytoreductive surgery and HIPEC for carcinomatosis from appendix cancer: Impact on perioperative outcomes and short-term survival. Gastroenterol Res Pract Volume 2012; 2012: Article ID 163284, 6 pages
13. Passot G, You B, Boschetti G, Fontaine J et al. Pathological response to neoadjuvant chemotherapy: a new prognosis tool for the curative management of peritoneal colorectal carcinomatosis. Ann Surg Oncol 2014;21:2608-2614. doi: 10.1245/s10434-014-3647-0. Epub 2014 Mar 26.
14. Canbay E, Mizumoto A, Ichinose M et al. Outcome data of patients with peritoneal carcinomatosis from gastric origin treated by a strategy of bidirectional chemotherapy prior to cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in a single specialized center in Japan. Ann Surg Oncol 2014;21:1147-1152. doi: 10.1245/s10434-013-3443-2. Epub 2013 Dec 20.
15. Yamaguchi H, Kitayama J, Ishigami H, Emoto S, Yamashita H, Watanabe T. A phase 2 trial of intravenous and intraperitoneal paclitaxel combined with S-1 for treatment of gastric cancer with macroscopic peritoneal metastasis. Cancer 2013;119:3354-3358. doi: 10.1002/cncr.28204. Epub 2013 Jun 24.
16. Vicens RA, Patnana M, Le O et al. Multimodality imaging of common and uncommon peritoneal diseases: a review for radiologists. Abdom Imaging 2014 Aug 20. [Epub ahead of print]
17. Low RN, Barone RM. Combined diffusion-weighted and gadolinium-enhanced MRI can accurately predict the peritoneal cancer index preoperatively in patients being considered for cytoreductive surgical procedures. Ann Surg Oncol 2012;19:1394-1401. doi: 10.1245/s10434-012-2236-3.
18. Courcoutsakis N, Tentes AA, Astrinakis E, Zezos P, Prassopoulos P. CT-Enteroclysis in the preoperative assessment of the small-bowel involvement in patients with peritoneal carcinomatosis, candidates for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Abdom Imaging 2013;38:56-63. doi: 10.1007/s00261-012-9869-3.
19. Pfannenberg C1, Königsrainer I, Aschoff P et al. 18F-FDG-PET/CT to select patients with peritoneal carcinomatosis for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Ann Surg Oncol 2009;16:1295-1303. doi: 10.1245/s10434-009-0387-7. Epub 2009 Feb 28.
20. Valle M, Federici O, Garofalo A. Patient selection for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy, and role of laparoscopy in diagnosis, staging, and treatment. Surg Oncol Clin N Am 2012;21:515-531. doi: 10.1016/j.soc.2012.07.005.
21. Jayakrishnan TT, Zacharias AJ, Sharma A, Pappas SG, Gamblin TC, Turaga KK. Role of laparoscopy in patients with peritoneal metastases considered for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC).World J Surg Oncol 2014;12:270. doi: 10.1186/1477-7819-12-270.
22. 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;91:739-746.
23. Cashin PH, Graf W, Nygren P, Mahteme H. Comparison of prognostic scores for patients with colorectal cancer peritoneal metastases treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Ann Surg Oncol 2013;20:4183-4189. doi: 10.1245/s10434-013-3204-2. Epub 2013 Aug 22.
24. Pelz JO, Stojadinovic A, Nissan A, Hohenberger W, Esquivel J. Evaluation of a peritoneal surface disease severity score in patients with colon cancer with peritoneal carcinomatosis. J Surg Oncol 2009;99:9-15. doi: 10.1002/jso.21169.
25. Esquivel J, Lowy AM, Markman M, Chua T, Pelz J, Baratti D, Baumgartner JM, Berri R, Bretcha-Boix P, Deraco M, Flores-Ayala G, Glehen O, Gomez-Portilla A, González-Moreno S, Goodman M, Halkia E, Kusamura S, Moller M, Passot G, Pocard M, Salti G, Sardi A, Senthil M, Spilioitis J, Torres-Melero J, Turaga K, Trout R. The American Society of Peritoneal Surface Malignancies (ASPSM) Multiinstitution 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. doi: 10.1245/s10434-014-3798-z. Epub 2014 May 23.
26. Jacquet P, Jelinek JS, Steves MA, Sugarbaker PH. Evaluation of computed tomography in patients with peritoneal carcinomatosis. Cancer 1993;72:1631-1636.
27. Rivard JD, Temple WJ, McConnell YJ, Sultan H, Mack LA. Preoperative computed tomography does not predict resectability in peritoneal carcinomatosis. Am J Surg 2014;207:760-764; discussion 764-5. doi: 10.1016/j.amjsurg.2013.12.024. Epub 2014 Mar 12.
28. Sethna KS, Sugarbaker PH. New prospects for the control of peritoneal surface dissemination of gastric cancer using perioperative intraperitoneal chemotherapy. Cancer Therapy 2004;2:79-84.
29. Sugarbaker PH. Peritoneum as the first line of defense in carcinomatosis. J Surg Oncol 2007;95:93-96.
30. Braam HJ, Boerma D, Wiezer MJ, van Ramshorst B.

Hyperthermic intraperitoneal chemotherapy during primary tumour resection limits extent of bowel resection compared to two-stage treatment. Eur J Surg Oncol 2013;39:988-993. doi: 10.1016/j.ejso.2013.06.002. Epub 2013 Jun 28.

31. da Silva RG, Sugarbaker PH. Analysis of prognostic factors in seventy patients having a complete cytoreduction plus perioperative intraperitoneal chemotherapy for carcinomatosis from colorectal cancer. J Am Coll Surg 2006;203:878-886 [PMID:17116556 DOI: 10.1016/j.jamcollsurg.2006.08.024]
32. Yang XJ, Huang CQ, Suo T et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy improves survival of patients with peritoneal carcinomatosis from gastric cancer: final results of a phase III randomized clinical trial. Ann Surg Oncol 2011;18:1575-1581. doi: 10.1245/s10434-011-1631-5. Epub 2011 Mar 23.
33. Van der Speeten K, Stuart OA, Sugarbaker PH. Pharmacology of perioperative intraperitoneal and intravenous chemotherapy in patients with peritoneal surface malignancy. Surg Oncol Clin N Am 2012;21:577-597. doi: 10.1016/j.soc.2012.07.013.
34. Jokerst JV, Lobovkina T, Zare RN, Gambhir SS. Nanoparticle PEGylation for imaging and therapy. Nanomedicine (Lond) 2011;6:715-728. doi: 10.2217/nnm.11.19.
35. Mohamed F, Sugarbaker PH. Intraperitoneal taxanes. Surg Oncol Clin N Am 2003;12:825-833.
36. Armstrong DK, Bundy B, Wenzel L, Huang HQ, Baergen R, Lele S, Copeland LJ, Walker JL, Burger RA; Gynecologic Oncology Group. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. N Engl J Med 2006;354:34-43.