VNIVERSITAT DE VALÈNCIA

Inaugural Speech
Doctor "Honoris Causa" by the Universitat de València

"PERITONEAL METASTASES GASTROINTESTINAL CANCER: A BRIEF HISTORY"

Paul H. Sugarbaker

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INTRODUCTION

Up until the 1980s, carcinomatosis from gastrointestinal malignancy was a lethal condition. The treatments directed at peritoneal dissemination were best supportive care, palliative systemic chemotherapy, and palliative surgery when necessary. None of these treatments were in any way satisfactory. Treatment strategies tha t afforded prolonged survival or a chance for cure did not exist. Over the last three decades progress with two treatment innovations have continued. As a result of cytoreductive surgery (CRS) combined with hyperthermic perioperative chemotherapy (HIPEC), long-term survival has been demonstrated by institutions widely distributed around the globe. The term, "carcinomatosis", has been abandoned because it implies this terminal condition with no substantial benefit from treatments. Rather, this dissemination of cancer into the peritoneal space is now referred to as "peritoneal metastases". This is now a treatable condition in properly selected patients with gastrointestinal cancer and a goal in selected patients is a curative approach. In this manuscript we explore the innovations that have resulted in this profound change in the treatment options of peritoneal metastases from gastrointestinal cancer. Also reported are promising future directions that require immediate exploration in order to continue the optimization of CRS and HIPEC for peritoneal metastases from gastrointestinal cancer.

Cytoreductive surgery and hyperthermic perioperative chemotherapy as a current standard of care

A question of profound importance as the development of treatments for peritoneal metastases has progressed is its current acceptance by the oncologic community as a standard of care. Recent reviews from prominent centers of excellence in oncology would answer this question with a profound yes. Elias and colleagues have advocated that the package combining complete CRS plus HIPEC can be expected to achieve cure in selected patients. They currently use CRS and HIPEC for the treatment of pseudomyxoma peritonei, for peritoneal mesothelioma, and for colorectal peritoneal metastases with limited extent of disease on peritoneal surfaces. Also, in a limited setting this combined treatment is of value for gastric cancer and neuroendocrine cancer to prevent or treat limited disease on peritoneal surfaces. Also, they indicate that certain rare tumors that have a propensity for peritoneal dissemination but a small likelihood of systemic metastases should be considered for CRS and HIPEC. Finally, prophylactic CRS and HIPEC for patients with primary disease and a high risk of peritoneal metastases can be considered of value. Also, results with second-look surgery in selected patients must be considered as an important treatment option. They conclude that complete CRS with HIPEC is an "indispensible tool in the oncologist's armamentarium" (1).

A second prestigious center for cancer treatment has recently described current practice at the Memorial Sloan-Kettering Cancer Center. Kelly and Nash reviewed the literature and summarized the expected results for appendiceal mucinous neoplasms, colorectal cancer, gastric cancer, and diffuse malignant peritoneal mesothelioma. They conclude that long-term survival is

achieved for patients with appendiceal mucinous neoplasms and justifies the perioperative morbidity and possible mortality of this aggressive approach. Cytoreduction with perioperative chemotherapy is "currently the standard of care for this disease". For colorectal cancer, they conclude that colorectal cancer has a likelihood for systemic metastases so that CRS and HIPEC should be routinely combined with systemic chemotherapy. Also, patients with extensive peritoneal disease burden should be treated cautiously. However, CRS and HIPEC can achieve long-term survival with peritoneal metastases from colorectal cancer. For gastric cancer, Kelly and Nash cite the eight randomized trials evaluating CRS and HIPEC or early postoperative intraperitoneal chemotherapy (EPIC) for preventing the progression of peritoneal metastases. Also, promising results in the management of limited peritoneal metastases in patients who can undergo gastrectomy was indicated. Finally, while they could report on no randomized prospective trials of CRS plus HIPEC for malignant peritoneal mesothelioma, observational studies have shown superior median survivals as compared to historical controls with acceptable morbidity and mortality. Currently, an aggressive regional approach to this disease is indicated. Treatment should be limited to patients with epithelioid histology, nuclear grade 1-3, and an absence of gross lymph node metastases (2).

Presently, there are some institutions that do not recognize the great benefits that knowledgeable and skillful application of CRS and HIPEC have for the management of peritoneal metastases. For the most part, these are institutions that do not have experience with these treatment modalities, have not seen the benefits that they can achieve in this otherwise poor prognosis group of patients, and have been unwilling to invest in the requirements necessary to embark on this management strategy. Table 1 lists the national guidelines of

multiple nations around the world that have included CRS and HIPEC as a standard of care for appendiceal mucinous neoplasms with peritoneal dissemination, epithelioid peritoneal mesothelioma, and colorectal cancer with limited peritoneal surface metastases. As shown in Table 1, these national guidelines occurred first in France (3), then in Holland (4), Germany (5), Spain (6), and the United Kingdom (7).

In the United States, the National Comprehensive Cancer Network guidelines have not, as yet, changed to include CRS and HIPEC in these three diseases. However, nearly all insurance companies including Medicare and Medicaid within the United States authorized these treatments as a modality to be used for their insured patients. Clearly, CRS and HIPEC must be considered a treatment option in nations where modern cancer treatments are available.

Conceptual changes that contributed to the progress of cytoreductive surgery and perioperative chemotherapy

Over the last three decades there have been oncologic, physiologic, and pharmacologic advances that have contributed to the progress of the combined treatments of CRS and HIPEC. No doubt, the initial success with the treatment of pseudomyxoma peritonei was a "proof of principle" that the combination of complete cytoreductive surgery along with a perioperative chemotherapy lavage of the peritoneal surfaces could, in a selected group of patients, result in long-term survival and even a cancer cure. Two observations in the appendiceal mucinous neoplasm patients were crucial. First of all, these patients rarely develop metastases to lymph nodes or to the liver (8). Secondly, even

though there was a large volume of mucinous malignancy infiltrating the undersurfaces of the diaphragms, the omentums and the pelvic peritoneum, the small bowel was uninvolved or was uninvolved to the extent that cytoreductive surgery combined with the perioperative chemotherapy lavage could maintain the small bowel in a disease-free state (9).

A second conceptual change in the surgical approach was the development of five different peritonectomy procedures (10). The loose attachment of the parietal peritoneum allowed a complete stripping of the peritoneum from the anterior abdominal wall, the right and left subphrenic spaces, the pelvis, and the omental bursa. Because the visceral peritoneum was more intimately attached to underlying structures such as stomach, small bowel, and large bowel, these peritonectomy procedures were of necessity combined with visceral resections in order to achieve the complete cytoreductive surgery. As time went on refinements of the methodology whereby cancer nodules were removed from the small bowel were published by Bijelic and Sugarbaker (11).

A third conceptual change involves the use of perioperative intraperitoneal chemotherapy. Pharmacologically, a new concept regarding a peritoneal space to plasma barrier was described and provided the rationale for perioperative intraperitoneal chemotherapy administration. The original pharmacologic principles regarding the movement of large molecules placed directly into the peritoneal space in a large volume of physiologic fluid were developed for the most part at the National Institutes of Health, Bethesda, Maryland, USA. The early publications by Flessner, Dedrick, and Schultz in the experimental laboratory and Meyers and Collins and Speyer et al. in the clinic suggested clinical utility of this new route of administration for cancer chemotherapy (12-14).

The importance of drug selection and proper dosimetry of intraperitoneal chemotherapy for vesicant drugs such as doxorubicin and for liver-metabolized drugs such as 5-fluorouracil was described by Sugarbaker et al. (15, 16). The role of molecular size in maintaining this peritoneal space to plasma barrier was clarified early on by Meyers and colleagues (13).

Although little has changed over the course of the last three decades in the pharmacologic principles established by these early investigators, some clarifications of the use of chemotherapy within the peritoneal space have occurred (17). First, it was made clear that the extent of peritonectomy had little to do with the continued presence of the peritoneal space to plasma barrier. Vazquez et al. established that the percentage of the parietal peritoneum removed had little or no impact on the pharmacology of intraperitoneal chemotherapy with 5-fluorouracil (18). Secondly, it was shown that the volume of intraperitoneal fluid used to dilute the chemotherapy solution and thereby fill the peritoneal space had an impact on the pharmacology of intraperitoneal drug instillation. Both Elias and Sideris and Sugarbaker et al. showed that a volume of intraperitoneal fluid had an impact on chemotherapy clearance into the body (19, 20). If both volume and dose of chemotherapy were controlled the systemic exposure could be predicted and the intraperitoneal and systemic effects remained constant from patient to patient.

Perhaps the most clearly demonstrated clinical finding for successful treatment of peritoneal metastases is the absolute requirement for complete visible clearing the peritoneal space of malignant disease in order for intraperitoneal chemotherapy to affect long-term survival (21).

The peritonectomy procedures were described initially by Sugarbaker in 1995 (10). Yonemura and colleagues published similar procedures especially adapted for the management of peritoneal metastases from gastric cancer (22). Extensive visceral resections including total gastrectomy have allowed an extension of the surgical technology and the resulting optimal cytoreduction to a larger number of cancer patients (23).

Surgical technical advances associated with complete cytoreduction with peritonectomy have involved the use of self-retaining retractors and ball-tip high-voltage electrosurgery. A recent advance whose results have not yet been completely realized is the resurfacing of these extensive raw tissue surfaces with anti-sclerotic agents. Also needed is instruction at treatment centers in the advanced surgical technology required for complete cytoreductive surgery.

Early postoperative intraperitoneal chemotherapy (EPIC)

The earliest reports of large numbers of patients with colorectal and appendiceal malignancy showing long-term benefit from cytoreductive surgery combined with perioperative intraperitoneal chemotherapy were for treatment regimens using EPIC (21). The most profound changes in the natural history of a peritoneal surface malignancy as a result of combined treatment seem to be in the minimally aggressive peritoneal surface malignancies such as appendiceal cancer (24). Also, Elias and Pocard showed benefits from CRS with EPIC in colorectal cancer patients (25).

To this day EPIC remains the favored treatment plan for several chemotherapy agents when the intraperitoneal route of administration is favored.

Drugs that have a high rate of hepatic extraction of the chemotherapy agent so that a large proportion of the drug is detoxified with a single pass through the liver are appropriate. These agents include 5-fluorouracil and doxorubicin (15, 26). Also, taxanes, especially paclitaxel, are appropriate for EPIC. This drug is not significantly augmented by heat, works as a cell cycle-specific drug that should be used over the long-term, and is much better tolerated from the perspective of nausea and vomiting post-administration if it is given in divided doses over the first 5 days postoperatively. This drug has an area under the curve ratio of 1000 and prolonged retention within the peritoneal space (27). Recent clinical investigators are testing combinations of HIPEC and EPIC as a perioperative multi-drug treatment plan may determine the optimal combination of these treatment strategies (28).

Heated intraoperative intraperitoneal chemotherapy (HIPEC)

The initial innovative efforts with HIPEC were by the efforts of Spratt et al. in 1980 (29). Shortly thereafter, in 1988, Koja and colleagues in Tottori University, Japan applied the treatments to patients with gastric cancer and peritoneal seeding (30). The reports by Fujimoto from Chiba University, Japan and Yonemura from Kanazawa University, Japan should also be mentioned (31-34). The studies from Japan involved gastric cancer patients with demonstrated peritoneal seeding or gastric cancer with adjuvant intraperitoneal chemotherapy.

Combining cytoreductive surgery with HIPEC was shown in a phase III trial to improve the survival of colon cancer patients with peritoneal seeding (35). Also, a large retrospective multi-institutional study documented that ap-

proximately 25% of colon cancer patients with this combined therapy will be alive and disease-free at 5 years (36). All of the natural history studies suggest that these patients have a median survival limited to 6 months or less (37-39).

An evolution of prognostic indicators useful for patient selection

In the early efforts to manage carcinomatosis, patients were scored as carcinomatosis present versus carcinomatosis absent. In a group of patients with peritoneal seeding, no survival at 3 years was expected in patients with gastrointestinal cancer (37-39). It became apparent that all patients with peritoneal metastases were not the same. Four different scoring systems by which to quantitate peritoneal metastases were described. Perhaps the original one was the "P factor" utilized in the Japanese classification of gastric cancer. P1 (cancer seedlings limited to the stomach itself), P2 (cancer seedlings limited to the space above the transverse colon), and P3 (cancer seedlings located throughout the peritoneal space) has stood the test of time as a useful quantitation of gastric carcinomatosis (40). For more precise quantitation of the distribution and extent of peritoneal metastases the Peritoneal Cancer Index has been utilized. This scoring system combines the distribution of peritoneal metastases and the lesion size of the nodules present throughout the abdomen and especially emphasizes cancerous involvement of the small bowel and its mesentery. The Peritoneal Cancer Index can be scored preoperatively with a CT, at the time of abdominal exploration of the abdomen and pelvis, and after the maximal efforts at cytoreduction have occurred (41). Other methodologies for quantitating peritoneal cancer dissemination are the Gilly Staging System from Lyon, France and the simplified peritoneal cancer index utilized at the Netherlands Cancer Institute (42, 35).

As more publications on peritoneal metastases appeared, an assessment of the completeness of cytoreduction was necessary. It has been suggested that the completeness of cytoreduction score will vary as the invasive character of the malignancy and its response to neoadjuvant chemotherapy vary. A completeness of cytoreduction scoring system has been reported (41).

It is obvious to those working long-term in this field that early interventions in patients who have not had extensive prior surgery provides the best results in terms of survival and the lowest incidence of morbidity and mortality. Some means of assessing the extent of prior surgery was found to be necessary. The prior surgical score was presented by Jacquet and colleagues and shown to have a major impact in determining survival of appendiceal malignancy patients and ovarian cancer patients (24, 41, 43).

An essential adjunct to the assessment of prognosis in these patients is renewed interest in the histomorphology of peritoneal surface malignancy. The work of Ronnett and colleagues clearly shows that the invasive character of a malignant process, as estimated by histology, has a profound effect upon the success of combined treatment (44). Similar emphasis on histomorphology in the outcome of combined treatment in peritoneal mesothelioma patients has been demonstrated by Cerruto et al. and Deraco et al. (45, 46).

Hyperthermia

The perioperative chemotherapy treatments over the last two decades have utilized hyperthermia along with the intraperitoneal chemotherapy with a presumed benefit. The hyperthermia in animal models has been shown to

increase the cytotoxicity of the drugs (47), increase the depth of chemotherapy penetration (48), and perhaps if used long enough and at high enough temperatures, cause apoptosis from the heat itself. A single report by Yonemura and colleagues suggests that intraperitoneal chemotherapy with heat is more effective than the intraperitoneal chemotherapy at body temperature (49). Other studies to confirm the benefits of hyperthermia have not been forthcoming. Also, studies show that EPIC is equivalent to HIPEC in maintaining a surgical complete response and improving long-term survival (50). Certainly, in a patient who has undergone many hours of surgery with the abdomen and pelvis widely exposed often has moderate to profound hypothermia. The 90 minutes of hyperthermic lavage of the peritoneal space returns these patients to an optimal physiologic condition. In this regard, hyperthermia is an essential part of the perioperative cancer treatment.

Peritoneal surface malignancy treatment centers

To the credit of Heald and Moran, the importance of a treatment center in the United Kingdom for pseudomyxoma peritonei patients was made clear. In 1998 this became a reality. Moran and colleagues have added greatly to the quality of care of appendiceal malignancy patients in the UK. In 2002 a second center was established under the direction of Sarah O'Dwyer and colleagues in Manchester, UK. Other designated treatment centers throughout Europe have appeared.

A summary of the evolution of treatments for peritoneal metastases are shown in Table 2. New efforts to further develop and improve the outcome of patients with peritoneal surface malignancy are underway. It has become

clear that the early treatment of minimal residual disease is optimal for these patients. Certainly, a watch and wait policy with referral of symptomatic patients to a peritoneal surface oncology center is no longer acceptable. Second, the perioperative treatments are now many and varied. A bidirectional approach is becoming standard of care. As reviewed by van der Speeten and colleagues, some chemotherapy agents are most appropriate for intravenous use with heat-targeting to the peritoneal cavity (52). Others are more valuable because of their large molecular size and the heat augmentation to be used as part of HIPEC regimen.

Long term intraperitoneal taxanes are now being explored, especially in Japan, for gastric cancer. The high response rate of combined systemic and intravenous chemotherapy reported by Yonemura presents an exciting new direction in which to go with a very poor prognosis group of patients (53). Kitayama also continued the use of adjuvant therapies for patients with peritoneal seeding using a combination of chemotherapy by intraperitoneal port and systemic agents and remains to be fully explored (54).

Finally, to allow treatments to be extended beyond the operating theater a new interest in the use of antisclerosis agents to diminish adhesions postoperatively has occurred. Numerous agents are now available including methylcellulose, polylactide sheets, polyethylene glycol spray, and 5-fluorouracil early postoperative irrigations. Continued studies to maintain the integrity of the peritoneal cavity are needed.

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Table 1. Nations whose treatment guidelines approve cytoreductive surgery and hyperthermic perioperative chemotherapy as a standard of care for selected patients at experienced institutions. The approval is for appendiceal neoplasms, epithelial peritoneal mesothelioma, and colorectal cancer with limited peritoneal metastases.

Nation	Year approved	Reference
France	2003	3
Holland	2003	4
Germany	2010	5
Spain	2012	6
United Kingdom	2013	7

Table 2. Evolution of treatments for peritoneal carcinomatosis from gastrointestinal cancer.

Authors	Year	Event	Reference
Spratt et al.	1980	Suggested a hyperthermic peritoneal perfusion system with the administration of intraperitoneal chemotherapy. University of Louisville, Kentucky.	9
Speyer et al.	1981	Pharmacology of intraperitoneal 5-fluorouracil in humans. National Institutes of Health, Bethesda, Maryland.	14

Koga et al.	1984	Experimental study with prophylactic continuous hyperthermic peritoneal perfusion with mitomycin C. A significant prolongation of survival was obtained when 41.5°C hyperthermia was combined with mitomycin C. Tottori University, Japan.	55
Flessner et al.	1984	Pharmacokinetic studies established the peritoneal plasma barrier. National Institutes of Health, Bethesda, Maryland.	12
Sugarbaker et al.	1985	Randomized controlled study of intravenous versus intraperitoneal 5-fluorouracil documented a diminished incidence of peritoneal carcinomatosis in colon cancer patients. National Institutes of Health, Bethesda, Maryland.	56
Koga et al.	1988	First study of adjuvant intraoperative hyperthermic peritoneal perfusion with mitomycin C in gastric cancer. Tottori University, Japan.	30
Fujimoto et al.	1988	Used intraoperative hyperthermic peritoneal perfusion with mitomycin C combined with extended surgery in patients with gastric cancer and established peritoneal carcinomatosis. After the treatment, 12.8% survived 1 year as compared with 0% after surgery alone. Chiba University, Japan.	31
Sugarbaker	1989	Trial of early postoperative intraperitoneal mitomycin C and 5-fluorouracil in the management of carcinomatosis. Washington Hospital Center, Washington, DC.	21

Sugarbaker	1995	Peritonectomy procedures. Washington Hospital Center, Washington, DC.	10
Yonemura et al.	1996	Suggested peritoneal cavity expander for optimization of intraoperative intraperitoneal hyperthermic chemotherapy delivery in patients with gastric cancer. Kanazawa University, Japan.	57
Sugarbaker and Jacquet	1996	Published methodologies by which to quantitate peritoneal metastases and their management.	41
Yu et al.	1998	Positive results of randomized study on adjuvant early postoperative intraperitoneal chemotherapy for gastric cancer. Kyungpook National University, Taegu, Korea.	58
Moran	1998	Pseudomyxoma peritonei treatment center designated for the United Kingdom. North Hampshire Hospital, Basingstoke, England.	59
Urano et al.	1999	In vivo chemohyperthermia parameters defined. Memorial Sloan- Kettering, New York.	47
Pestieau and Sugarbaker	2000	Benefit of cytoreductive surgery and perioperative chemotherapy in the management of primary colorectal cancer with synchronous peritoneal metastases.	60

Verwaal et al.	2002	Prospective randomized trial showing superiority of comprehensive CRS plus HIPEC for carcinomatosis from colon cancer. Netherlands Cancer Institute, Amsterdam.	35
Glehen et al.	2004	Multi-institutional study from 28 institutions describing benefit of CRS and perioperative chemotherapy utilizing prognostic indicators.	36
Verwaal and Zoetmulder	2004	Dutch guidelines declare CRS and HIPEC standard of care for peritoneal metastases from colorectal cancer.	4
Elias et al.	2008	Systematic second-look for patients at high risk for recurrence.	61
Elias, Gilly and Glehen	2008	Association of French Surgeons Monograph describing results of CRS and perioperative chemotherapy for appendiceal, colorectal, gastric, small bowel and ovarian cancer plus peritoneal mesothelioma.	62
Elias, Gilly and Glehen	2009	French guidelines declare CRS and perioperative chemotherapy standard of care for peritoneal metastases from colorectal cancer.	3
Piso et al.	2013	German guidelines declare CRS and HIPEC standard of care for peritoneal metastases from colorectal cancer.	5
Moran and O'Dwyer	2013	United Kingdom guidelines declare CRS and HIPEC standard of care for peritoneal metastases from colorectal cancer.	7

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