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REVIEW ARTICLE – GASTROINTESTINAL ONCOLOGY

Consensus Guidelines from The American Society of Peritoneal Surface Malignancies on Standardizing the Delivery of Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in Colorectal Cancer Patients in the United States

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ABSTRACT

Background. The American Society of Peritoneal Surface Malignancies (ASPSM) is a consortium of cancer centers performing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC). This is a position paper from the ASPSM on the standardization of the delivery of HIPEC.

Methods. A survey was conducted of all cancer centers performing HIPEC in the United States. We attempted to obtain consensus by the modified method of Delphi on seven key HIPEC parameters: (1) method, (2) inflow temperature, (3) perfusate volume, (4) drug, (5) dosage, (6) timing of drug delivery, and (7) total perfusion time. Statistical analysis was performed using nonparametric tests.

Results. Response rates for ASPSM members ($n = 45$) and non-ASPSM members ($n = 24$) were 89 and 33 %, respectively. Of the responders from ASPSM members, 95 % agreed with implementing the proposal. Majority of the surgical oncologists favored the closed method of delivery with a standardized dual dose of mitomycin for a 90-min chemoperfusion for patients undergoing cytoreductive surgery for peritoneal carcinomatosis of colorectal origin.

Conclusions. This recommendation on a standardized delivery of HIPEC in patients with colorectal cancer represents an important first step in enhancing research in this field. Studies directed at maximizing the efficacy of each of the seven key elements will need to follow.

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It has been 30 years since Dr. John Spratt from the University of Louisville reported in *Cancer Research* the first "Clinical delivery system for intraperitoneal hyperthermic chemotherapy."[1] Since then, the treatment of patients with peritoneal surface malignancies has undergone significant transformational changes with meaningful clinical advances. Current multi-modality therapy combines cytoreductive surgery with peritonectomy procedures to remove all visible tumor, coupled with hyperthermic intraperitoneal chemotherapy (HIPEC) to eradicate microscopic residual disease. This comprehensive treatment strategy is playing an ever-increasing role in the management of patients with colorectal cancer with peritoneal dissemination.

Although demonstrating the best survival results for patients with peritoneal carcinomatosis, HIPEC has not been universally embraced by the medical community and many important questions remain to be addressed. A review of the literature shows a wide range of HIPEC delivery, with many methodological variations including the technique, drug selection, and the time of perfusion (Table 1).[2] The American Society of Peritoneal Surface Malignancies (ASPSM) is an organization of health care providers with a particular interest in patients with peritoneal dissemination from gastrointestinal and gynecological malignancies. ASPSM was created to develop guidelines regarding patient selection and standardization of therapies, in order to maximize benefits while minimizing morbidity and overtreatment of this group of patients.[3]

The first official meeting of the society was held in Puerto Rico on February 21, 2010 during the Regional Cancer Therapy meeting organized by Dr. David Bartlett from the University of Pittsburgh Medical Center. During this meeting, society subcommittees were created and goals and objectives for the Society were outlined and discussed.

The first goal established for the society was: "Standardization of HIPEC Delivery in the United States." During the next couple of years, the ASPSM would work on a proposal for standardizing the delivery of HIPEC in various disease processes treated within the United States. These would include: colorectal cancer, ovarian cancer, peritoneal mesothelioma, and low- and high-grade appendiceal cancer. Once this goal was accomplished, the Group would look forward to collaborating with other centers outside of the United States and identify the optimal agreed-upon way to deliver HIPEC. Currently, there are 103 ASPSM members, 52 from the U.S. and 51 from 12

TABLE 1 Comparison of HIPEC technique in patients with colorectal cancer

Institution	Method	Drugs	Dosage	Timing	Outflow temperature	Duration
United States						
Washington Hospital Center	Open	IP MMC	15 mg/m^2	All at time 0	41 °C	90 min
		IP Dox	15 mg/m^2			
		IV 5FU	400 mg/m^2			
		IV Leu	20 mg/m^2			
Wake Forest University	Closed	MMC	40 mg	30 mg at time 0	40 °C	120 min
St Agnes Hospital	Closed	MMC	40 mg	30 mg at time 0	42 °C	90 min
			10 mg at 45 min			
University California San Diego	Closed	MMC	10 mg/L perfusate up to 60 mg	2/3 at time 0	41–42 °C	60 min
				1/3 at 45 minutes		
Germany						
Regensburg University	Closed	MMC	20 mg/m^2	All at time 0	41–42 °C	60 min
		Dox	15 mg/m^2			
		Oxali	300 mg/m^2			
Spain						
MD Anderson España	Open	Oxali	460 mg/m^2	All at time 0	43 °C	30 min
Sweden						
Uppsala University	Open	IP Oxali	460 mg/m^2	All at time 0	41 °C	30 min
		IV 5-FU		1 hour before		
United Kingdom						
Basingstoke	Open	MMC	15 mg/m^2	All at time 0	42 °C	60 min
Switzerland						
Kantonsspital St Gallen	Open	MMC	25 mg/m^2	1/3 every 30 min	42 °C	90 min

MMC mitomycin C, *Dox* doxorubicin, *Leu* leucovorin, *Oxali* oxaliplatin

other countries. The purpose of this study is to report the ASPSM recommendation on standardizing the delivery of HIPEC in colorectal cancer patients with peritoneal dissemination in the United States.

METHODS

A questionnaire including seven key HIPEC parameters: (1) open or closed method, (2) inflow temperature, (3) volume of perfusate, (4) drug used, (5) dosage, (6) timing of drug delivery, and (7) total time of perfusion was distributed to all members of the ASPSM and nonmembers on a comprehensive mailing list for all providers interested in peritoneal surface malignancies. The patient population for HIPEC was patients with colorectal cancer with peritoneal dissemination, and the questionnaire was sent to a selected group of cytoreductive surgeons around the United States. Using a modified method of Delphi, to achieve consensus discordant responses were reassessed by the group and expert responses provided as a feedback to the responders. This led to development of consensus. There was no predefined set point for stopping the process, and the ASPSM committee supported the guidelines once there was stability of results. Based on their responses, the ASPSM HIPEC in colorectal cancer committee developed a proposal that included the most common answers to the aforementioned key elements (Table 2). This proposal on how to deliver the HIPEC component in patients with colorectal cancer with peritoneal dissemination undergoing cytoreductive surgery and HIPEC in the United States was sent to two different groups. Group 1 included 45 U.S. ASPSM members. These are surgeons with significant experience and established peritoneal surface malignancy programs at their institutions. Group 2 included 24 non-ASPSM members. Most of the people in this group are also cytoreductive surgeons with well-established programs, but they have not joined the ASPSM.

The expert opinion was circulated among the 69 participants, and they were encouraged to respond to the ideal way of delivery of hyperthermic intraperitoneal chemotherapy. Based on feedback from the responders, the expert consensus was modified and recirculated until stability was seen.

TABLE 2 American Society of Peritoneal Surface Malignancies standardized HIPEC delivery in patients with colorectal cancer with peritoneal dissemination

1	HIPEC method	Closed
2	Drug	Mitomycin C
3	Dosage	40 mg
4	Timing of drug delivery	30 mg at time 0; 10 mg at 60 min
5	Volume of perfusate	3 L
6	Inflow temperature	42 °C
7	Duration of perfusion	90 min

RESULTS

Of the 69 questionnaires, 48 were answered for a 69 % overall response rate from the two groups. The overall responses for groups 1 and 2 were 89 and 33 %, respectively. Of the 40 responses from group 1, ASPSM members, 38 (95 %) agreed with the proposal and were willing to standardize their delivery of HIPEC in patients with colorectal cancer with peritoneal dissemination. Two members (4 %), while they had comments, neither agreed nor disagreed with the proposal. There were only eight responses in group 2, non-ASPSM members. Of these, 5 (62 %) agreed with the proposal and were willing to standardize their delivery of HIPEC and 3 (37 %) did not agree with the proposal (Table 3).

There were a total of five responders between the two groups who did not state that they agreed with the proposal. The most common reason for not agreeing was the drug selection; carboplatin oxaliplatin and bidirectional chemotherapy (IV and IP chemotherapy) were the alternatives proposed.

DISCUSSION

Peritoneal dissemination in colorectal cancer patients represents stage IV disease, and therefore it is usually treated with a combination of cytotoxic chemotherapy and biological agents. Currently there is growing evidence to show that just as there is a subset of patients with stage IV disease with liver metastases who have a long-term benefit from the surgical eradication of their metastatic disease, there is a subset of patients with peritoneal dissemination from colon cancer that may benefit from a complete cytoreduction and HIPEC.[4] In addition, the relatively poor response to systemic chemotherapy for peritoneal-based

TABLE 3 Summary of responses from the survey for standardization of recommendations for HIPEC in patients with peritoneal surface malignancies of colorectal origin

Response group characteristics	Agree with standardization	Disagree
ASPSM members ($n = 40$)	95 % ($n = 38$)	5 % ($n = 2$) Preferred carboplatin/oxaliplatin Preferred bidirectional chemotherapy
Non-ASPSM members ($n = 8$)	62 % ($n = 5$)	38 % ($n = 3$)

disease adds credence to the incorporation of peritoneal-based therapies in this disease subtype.

Despite early randomized data suggesting a significant survival benefit with CRS + HIPEC (23 vs. 12 months, Verwaal et al.) and numerous prospective studies validating the same, the lack of standardization of the technique of delivery of HIPEC has led to several criticisms in the scientific and clinical community.[5]

Recent animal-based studies (Klaver et al.[6]) have questioned the role for hyperthermic during the delivery of intraperitoneal chemotherapy. In a model of WAG/Rij rats inoculated with peritoneal carcinomatosis, they found that the rats had an increased median survival with HIPEC versus cytoreduction only (121 vs. 62 days, $p = 0.02$), but hyperthermic perfusion itself had no obvious benefit. Remarkably, normothermic perfusion and hyperthermic perfusion had similar animal outcomes. Yonemura et al.[7] found that there was a survival benefit to hyperthermia in addition to chemoperfusion, but only in the adjuvant setting. The PRODIGE trial comparing cytoreduction to cytoreduction with HIPEC has almost completed accrual, and the preliminary results are awaited.

Nevertheless, the lack of standardization of the technique of delivery of HIPEC has made it difficult to analyze outcomes and pool data from several centers performing this procedure in the country. This has led to barriers with patient care and insurance providers, as well as in the advancement of science. The adoption of a uniform technique in the absence of level I data allows for careful examination of outcomes without potential for significant technical variability.

The American Society of Peritoneal Surface Malignancies was created in an effort to get healthcare providers with a particular interest in the treatment of patients with peritoneal surface malignancies of gastrointestinal and gynecological origin to collaborate on a multidisciplinary approach, to discuss the key issues that are needed in order to advance the science behind the care of this group of patients, and to exchange ideas that could improve their outcome.

An analysis of the present study demonstrates that among the U.S. ASPSM members, there is a high level of interest and willingness on standardizing the delivery of HIPEC in patients with colorectal cancer. It also demonstrates that it is difficult to get healthcare providers to agree or even collaborate on any given project. There are currently approximately 64 hospitals in the United States that have the capabilities of performing cytoreductive surgery and HIPEC. Most of these 64 institutions have only one cytoreductive surgeon, and the vast majority of these centers perform <1 HIPEC per month. So, it is not surprising that there are only 45 members from the United States. On the other hand, it is very encouraging to see that the response rate among them was 89 %. However, it is not surprising that the response rate from the non-ASPSM members was only 33 % even though this group is composed mostly of cytoreductive surgeons.

At this time, much remains to be done to standardize the delivery of HIPEC in the United States and abroad. The organization of the ASPSM represents an important first step. It is hoped that through the efforts of the Society, the collaboration and interaction between medical, surgical and gynecological oncologists will increase and that the recommendation on the standardization of HIPEC delivery in patients with colorectal cancer presented in this manuscript can serve as the first step toward the development of multi-institutional trials directed at individualizing therapies that maximize benefits, while minimizing morbidity and overtreatment of all patients with peritoneal surface malignancy. In addition, standardization will help facilitate better analysis of costs in this changing medical environment. For instance, oxaliplatin, which is commonly used in Europe would cost around 18,000 USD compared with 180 USD for mitomycin. The ability to pool data might also obviate the need for expensive randomized trials, while monitoring outcomes on a real-time basis. However, we realize that standardization is not a substitute for prospective studies to improve the evidence behind the rationale for the specific effects of HIPEC, and we hope that our organization can provide the structure to support such trials in the future.

In conclusion, analysis of these data demonstrates that among U.S. ASPSM members there is a high level of interest and willingness to standardize the delivery of HIPEC in patients with colorectal cancer as outlined. Future studies directed at maximizing the efficacy of each of the seven key elements and the overall role of HIPEC will need to follow.

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