The American Society of Peritoneal Surface Malignancies consensus on standardizing the delivery of hyperthermic intraperitoneal chemotherapy (HIPEC) in colorectal cancer patients in the United States

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Background
Many HIPEC delivery methodological variations exist. The American Society of Peritoneal Surface Malignancies (ASPSM) was created to develop guidelines and standardization of therapies.

Methods
The ASPSM developed a proposal with 7 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. Three groups in the United States were asked to comment on the proposal and state if they were willing to deliver HIPEC in the proposed way. Group 1 included 45 ASPSM members; Group 2, 24 non-ASPSM members and Group 3, 5 medical oncologists.

Results
Responses for groups 1, 2 and 3 were 89%, 33% and 60%. Ninety-five percent of the responders from Group 1, ASPSM members, agreed with implementing the proposal. There were 8 responses in Group 2, non-ASPSM members. Five (62%) agreed with the proposal. There were 3 responses from Group 3, medical oncologists. Two (66%) agreed with the proposal and 1 (33%), only had comments.

Conclusion
This consensus on a standardized delivery of HIPEC in patients with colorectal cancer represents an important first step. Studies directed at maximizing the efficacy of each of the 7 key elements will need to follow.
Introduction

It is a little over 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 (2) (Table 1). 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 sub-committees 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 year 2010, 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 (US) and identify the optimal agreed-upon way to deliver HIPEC. Currently, there are 103 ASPSM members, 52 from the US and 51 from 12 other countries. The purpose of this study is to report The American Society of Peritoneal Surface Malignancies consensus on standardizing the delivery of hyperthermic intraperitoneal chemotherapy (HIPEC) in colorectal cancer patients with peritoneal dissemination in the United States.

Methods
A questionnaire included 7 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. 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 US. Based on their responses, the ASPSM HIPEC in colorectal cancer committee developed a proposal that included the most common answers to the above mentioned 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 3 different groups. Group 1 included 45 United States 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. Group 3 included 5 medical oncologists from the US who have a particular interest in advanced colorectal cancer. These 74 people were asked if they agreed with the proposal and were willing to standardize the way they deliver HIPEC in patients with colorectal cancer by following the proposal as a first step towards the role of HIPEC in peritoneal surface malignancies. This was not a consensus establishing HIPEC as a standard of care in patients with colorectal cancer with peritoneal dissemination.

Results

Fifty one of the 74 questionnaires were answered for a 69% overall response rate from the 3 groups. The overall responses for groups 1, 2 and 3 were 89%, 33% and 60% 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 8 responses in Group 2, non-ASPSM members. Of these, 5 (62%) agreed with the proposal and were willing to standardized their delivery of HIPEC and 3 (37%) did not agree with the proposal. Group 3 included the medical oncologists. Of the 3 responses, 2 (66%) agreed with the proposal and 1 (33%), only had comments.

There were a total of 6 responders between the 3 groups that did not state that they agreed with the proposal. Of these 6 responders, only 3 answered with a response that included what they would consider the ideal proposal. All 3 responders were from Group 2 non-ASPSM members. The most common reason for not agreeing was the drug selection. One of them is interested in using carboplatin, the second individual stated that we should use oxaliplatin as it is currently done in most parts of Europe and the third person wanted to use a combination of intraperitoneal and intravenous chemotherapy.

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 that 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).
A paucity of randomized data comparing it to modern systemic therapies; being considered “experimental” by some insurance companies; concerns about the potential morbidity of the procedure and the multiple variations on how HIPEC is delivered, are amongst the most common reasons why this multi-modality approach of cytoreductive surgery and heated intraoperative intraperitoneal chemotherapy has not been universally accepted.

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 in a multidisciplinary approach, discuss the key issues that are needed in order to advance the science behind the care of this group of patients and exchange ideas that could improve their outcome.

An analysis of the present study demonstrates that amongst the United States 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 in 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 will have only one cytoreductive surgeon and the vast majority of these centers will perform less than one 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 amongst 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 U.S. 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 consensus on the standardization of HIPEC delivery in patients with colorectal cancer presented in this manuscript can serve as the first step towards 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.

Conclusion

Analysis of these data demonstrates that amongst United States ASPSM members, there is a high level of interest and willingness on standardizing the delivery of HIPEC in patients with colorectal cancer. Future studies directed at maximizing the efficacy of each of the 7 key elements and the overall role of HIPEC will need to follow.
References


Table 1. Comparison of HIPEC technique in patients with Colorectal Cancer

<table>
<thead>
<tr>
<th>Institution</th>
<th>Method</th>
<th>Drugs</th>
<th>Dosage</th>
<th>Timing</th>
<th>Outflow Temp</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA Washington Hospital Center</td>
<td>Open</td>
<td>IP MMC</td>
<td>15mg/m2</td>
<td>All at time 0</td>
<td>41° C</td>
<td>90 minutes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IP Dox</td>
<td>15 mg/m2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>IV 5FU</td>
<td>400mg/m2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>IV Leu</td>
<td>20mg/m2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wake Forest University St Agnes Hospital</td>
<td>Closed</td>
<td>MMC</td>
<td>40mg</td>
<td>30mg at time 0</td>
<td>40° C</td>
<td>120 minutes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dox</td>
<td>15 mg/m2</td>
<td>30mg at time 0</td>
<td>42° C</td>
<td>90 minutes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5FU</td>
<td>400mg/m2</td>
<td>10 mg at 45’</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Leu</td>
<td>20mg/m2</td>
<td>2/3 at time 0</td>
<td>41-42</td>
<td>60 minutes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1/3 at 45’</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Germany Regensburg University</td>
<td>Closed</td>
<td>MMC</td>
<td>20mg/m2</td>
<td>All at time 0</td>
<td>41-42</td>
<td>60 minutes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dox</td>
<td>15mg/m2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oxali</td>
<td>300mg/m2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spain MD Anderson España</td>
<td>Open</td>
<td>Oxali</td>
<td>460mg/m2</td>
<td>All at time 0</td>
<td>43° C</td>
<td>30 minutes</td>
</tr>
<tr>
<td>Sweden Uppsala University</td>
<td>Open</td>
<td>IP Oxali</td>
<td>460mg/m2</td>
<td>All at time 0</td>
<td>41° C</td>
<td>30 minutes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5-FU</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>UK Basingstoke</td>
<td>Open</td>
<td>MMC</td>
<td>15mg/m2</td>
<td>All at time 0</td>
<td>42° C</td>
<td>60 minutes</td>
</tr>
<tr>
<td>Switzerland Kantonsspital St Gallen</td>
<td>Open</td>
<td>MMC</td>
<td>25mg/m2</td>
<td>1/3 every 30’</td>
<td>42° C</td>
<td>90 minutes</td>
</tr>
</tbody>
</table>

MMC: Mitomycin C, Dox: Doxorubicin, Leu: Leucovorin and Oxali: Oxaliplatin
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 Zero; 10mg at 60 minutes  
5. Volume of perfusate:  Three liters  
6. Inflow temperature:  42 degrees Celsius  
7. Duration of perfusion:  90 minutes