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Practice patterns, attitudes, and knowledge among physicians regarding cytoreductive surgery and HIPEC for patients with peritoneal metastases

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Abstract

Background: Cytoreductive surgery (CRS) and heated intraperitoneal chemotherapy (HIPEC) is a treatment option for patients with peritoneal metastases shown to provide improved overall survival for appropriately selected patients. However, the availability and utilization of this treatment remains limited. The aim of this survey-based study was to evaluate factors influencing physician treatment choices for peritoneal metastases.

Methods: Surveys were mailed to medical oncologists and surgeons in Virginia, Maryland, and Washington, D.C. Survey questions evaluated access to HIPEC centers, prior experience with referral to HIPEC centers, opinions regarding efficacy, and knowledge regarding outcomes of CRS and HIPEC.

Results: Surveys were mailed to 2279 physicians; 116 eligible surveys were returned. Seventy-five percent of respondents would consider referral to a HIPEC center for appendiceal peritoneal metastasis, while only 50% would consider it for colon cancer and peritoneal mesothelioma. The most common reason for never referring a patient to a HIPEC center was lack of access to a HIPEC specialist (47%) followed by perceived lack of evidence for the treatment modality (31%). Five-year survival after CRS and HIPEC was underestimated while 30-day mortality was overestimated by more than half of respondents.

Conclusions: Referral to HIPEC centers is underutilized among community physicians in practice. Limited access to HIPEC experts is the most common cause for lack of referral, followed by a perception of insufficient evidence for this treatment approach. Lack of familiarity with data regarding outcomes impacts referral patterns and

treatment choices. Possible actions to increase awareness and appropriate utilization of CRS and HIPEC are suggested.

Keywords: cytoreductive surgery, HIPEC, practice patterns, intraperitoneal chemotherapy, survey

Introduction

Peritoneal carcinomatosis has traditionally been approached with therapeutic nihilism and associated with very poor prognosis, with average expected survival of 6–12 months [1,2]. Cytoreductive surgery (CRS) and heated intraperitoneal chemotherapy (HIPEC) has evolved as a treatment option for patients with peritoneal carcinomatosis and has shown significantly improved survival for appropriately selected patients with peritoneal metastases from appendix and colon cancer, peritoneal mesothelioma, ovarian, and other malignancies [3,4]. A recent consensus statement from the 9th International Congress on Peritoneal Surface Malignancies stated that CRS and HIPEC should be considered the treatment of choice for pseudomyxoma peritonei and appendiceal neoplasia with peritoneal carcinomatosis and the standard of care for selected patients with peritoneal mesothelioma and moderate to small volume peritoneal carcinomatosis secondary to colorectal cancer [5]. Multiple recent studies, including a randomized controlled trial, have shown that CRS and HIPEC improve recurrence-free and overall survival in patients with advanced ovarian cancer [6–8]. However, it is estimated that only a small minority of patients who are potential candidates for CRS and HIPEC actually receive it [9]. A recent survey study performed in Canada concluded that physician awareness of CRS and HIPEC as a treatment option for peritoneal carcinomatosis from colorectal cancer is low and could contribute to underutilization of CRS and HIPEC [10]. We performed a formal literature search on the topic and found that there are no published studies investigating physician knowledge of CRS and HIPEC or factors that may influence treatment choices in patients with peritoneal metastases in the United States. As the physician training system as well as the health care system

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overall is significantly different in the United States than in Canada and Europe, we aimed to evaluate patterns of care, including utilization of CRS and HIPEC, among practicing American physicians who see patients with peritoneal metastases and to identify the predominant barriers to patient referral for evaluation at HIPEC centers. We also aimed to assess whether there was a difference between knowledge and treatment choices between general surgeons and medical oncologists.

Materials and methods

The research has complied with all the relevant regulations and institutional policies, and was conducted in accordance with the tenets of the Helsinki Declaration; the research received approval from the Inova Institutional Review Board (Protocol ID 15–2146) and was granted a waiver of informed consent. This study consisted of a cross-sectional mailed survey of general surgeons and medical oncologists in Maryland, Washington, D.C., and Virginia. Mailing lists of current licensees with a listed specialty of surgery, general surgery, or medical oncology/hematology were obtained from the Virginia and Maryland physician licensing boards and the Washington Physicians Directory. Physicians were eligible to participate if they treated patients with gastrointestinal cancer, determined via an eligibility question at the beginning of the survey. Recipients who did not treat gastrointestinal cancer were asked to return the survey with the remainder of the questions unanswered.

The survey consisted of an independently developed 22-item questionnaire. The questionnaire was pilot-tested among five surgeons and medical oncologists within our institution to assess

readability, comprehension, and completion time. The survey included four items to characterize respondents, nine items to assess practice and referral patterns, four clinical scenarios to assess treatment choices, and five questions to evaluate knowledge of outcomes following CRS and HIPEC.

Survey and cover letters were mailed with prepaid return envelopes. The mailing was repeated twice to nonresponders at 2 and 4 months after the initial mailing. Response rate was calculated using American Association for Public Opinion Research standard definitions and formulas [11]. Chi-square tests and Fisher's exact tests were used to compare categorical responses between general surgeons and medical oncologists. The Wilcoxon–Mann–Whitney test was used to compare years in practice between groups. *P* values were all derived from two-tailed tests and a statistical significance level of $\alpha < 0.05$ was used. Analyses were performed using R 3.2.3 [12].

Results

Of 2279 mailed surveys, 189 were returned undeliverable, 5 were returned blank, and 3 were returned with a refusal to participate. Of the 247 valid surveys that were returned, 131 were from respondents who did not treat patients with gastrointestinal cancer and were excluded. We analyzed the results from 116 eligible surveys.

Respondent characteristics and practice patterns regarding CRS and HIPEC are shown in Table 1. The majority of respondents were general surgeons (79.3%). They most commonly practiced in a community setting (80.9%) and saw fewer than five patients with peritoneal metastases per year (63.8%). With regards to how

Table 1: Survey respondent characteristics and practice patterns.

	Number (%) of respondents, unless otherwise indicated ^a			
	All, <i>n</i> = 116	GS, <i>n</i> = 92	MO, <i>n</i> = 24	<i>p</i> -Value (GS vs. MO)
Please describe the type of hospital where you practice.^b				
Community non-teaching	46 (41.8)	36 (40.9)	10 (45.5)	0.70
Community teaching	43 (39.1)	34 (38.6)	9 (40.9)	0.85
Academic	22 (20.0)	19 (21.6)	3 (13.6)	0.56
Other	5 (4.5)	4 (4.5)	1 (4.5)	> 0.99
How many years have you been in practice? [results given as median (IQR)]				
	20.0 (12.0–30.0)	20.0 (10.0–30.0)	24.5 (18.0–30.0)	0.16
Where did you learn about CRS and HIPEC (primary source)?^b				
Training program (residency or fellowship)	39 (36.4)	34 (39.5)	5 (23.8)	0.18
Peer-reviewed literature and scientific meetings	39 (36.4)	33 (38.4)	6 (28.6)	0.40
From colleagues in my practice or hospital	34 (31.8)	20 (23.3)	14 (66.7)	< 0.001
Other	12 (11.2)	10 (11.6)	2 (9.5)	> 0.99
How many patients with peritoneal metastases from GI cancers do you see on average in a year?				
< 5	74 (63.8)	65 (70.7)	9 (37.5)	0.01
5–15	29 (25.0)	19 (20.7)	10 (41.7)	
> 15	13 (11.2)	8 (8.7)	5 (20.8)	

(continued)

Table 1: (continued)

	Number (%) of respondents, unless otherwise indicated ^a			p-Value (GS vs. MO)
	All, n = 116	GS, n = 92	MO, n = 24	
How often do you discuss the management of your patients with peritoneal metastases in a multidisciplinary tumor board meeting before deciding on the treatment recommendation?				0.58
Most of the time (> 80% of cases)	69 (59.5)	55 (59.8)	14 (58.3)	
About half of the time	19 (16.4)	13 (14.1)	6 (25.0)	
Rarely (< 50% of cases)	18 (15.5)	15 (16.3)	3 (12.5)	
Never	10 (8.6)	9 (9.8)	1 (4.2)	
Is there a surgeon with expertise in CRS and HIPEC easily available to your patients?				0.08
Yes	75 (65.8)	56 (61.5)	19 (82.6)	
No	39 (34.2)	35 (38.5)	4 (17.4)	
The HIPEC specialist available to you is:^{b,c}				
In the same hospital where you practice	32 (42.7)	26 (46.4)	6 (31.6)	0.26
< 30 miles away	25 (33.3)	21 (37.5)	4 (21.1)	0.26
> 30 miles away	21 (28.0)	11 (19.6)	10 (52.6)	0.006
For which cancers with peritoneal metastases would you consider CRS and HIPEC as a possible therapeutic option in appropriately selected cases?^b				
Appendiceal cancer	86 (74.8)	65 (71.4)	21 (87.5)	0.12
Colon cancer	57 (49.6)	43 (47.3)	14 (58.3)	0.33
Peritoneal mesothelioma	56 (48.7)	40 (44.0)	16 (66.7)	0.48
Gastric cancer	26 (22.6)	21 (23.1)	5 (20.8)	0.82
Ovarian cancer	59 (51.3)	47 (51.6)	12 (50.0)	0.89
Any cancer with peritoneal metastases	41 (35.7)	37 (40.7)	4 (16.7)	0.03
None	4 (3.5)	3 (3.3)	1 (4.2)	> 0.99

CRS = cytoreductive surgery, GI = gastrointestinal, GS = general surgeons, HIPEC = hyperthermic intraperitoneal chemotherapy, IQR = interquartile range, MO = medical oncologists. ^aPercentages based on non-missing values. ^bRespondents could indicate more than one option. ^cPercentages calculated only from respondents with access to a surgeon with expertise in CRS and HIPEC.

often patients with peritoneal carcinomatosis are discussed by a multidisciplinary tumor board prior to making treatment decisions, 41% of respondents indicated this occurs only half of the time or less often. An expert in CRS and HIPEC was not easily available to approximately one third of respondents. Of those respondents who have a specialist available, 28% indicated that the distance to a HIPEC specialist was greater than 30 miles. Medical oncologists were more likely than general surgeons to report having a HIPEC expert available, although this result was not statistically significant, but were more likely to report that the HIPEC expert was greater than 30 miles away (52.6% vs. 19.6%, $p = 0.006$). Approximately 75% of respondents considered CRS and HIPEC as an appropriate therapeutic option for appendiceal cancer and approximately 50% considered it appropriate for colon cancer, peritoneal mesothelioma, and ovarian cancer. There was no significant difference between medical oncologists and general surgeons regarding these opinions apart from “peritoneal metastases from any cancer”, for which CRS and HIPEC was considered appropriate

by 40.7% of general surgeons compared to only 16.7% of medical oncologists ($p = 0.03$).

Responses to questions regarding referral to a HIPEC center are summarized in Table 2. Many respondents (72.4%) have referred to a HIPEC specialist in the past, with no difference between general surgeons and medical oncologists. The most common reason for never referring a patient to a HIPEC center was lack of access to a HIPEC specialist (46.9%) followed by a perceived lack of evidence for the treatment modality (31.3%). The most common indications that respondents who have referred used for referral were low-grade appendiceal cancer (81.0%) followed by high-grade appendiceal cancer (58.3%), and colon cancer (48.8%). General surgeons were significantly more likely to have referred for low-grade appendiceal cancer than medical oncologists (86.2% vs. 63.2%, $p = 0.02$). More than half (65.4%) of respondents reported that a phase III randomized controlled trial confirming a survival advantage for CRS and HIPEC would influence their decision to refer in the future and 41.3% reported a change in National Comprehensive Cancer Network (NCCN) guidelines would influence their future decisions.

Table 2: Referral patterns of 116 survey respondents regarding cytoreductive surgery and HIPEC.

	Number (%) of respondents ^a			
	All, n = 116	GS, n = 92	MO, n = 24	p-Value (GS vs. MO)
Have you ever referred a patient to a HIPEC specialist for potential intervention with CRS and HIPEC?				0.41
Yes	84 (72.4)	65 (70.7)	19 (79.2)	
No	32 (27.6)	27 (29.3)	5 (20.8)	
Select all of the reasons why you have not referred a patient to a HIPEC specialist.^{b,c}				
I don't have access to a HIPEC specialist	15 (46.9)	14 (51.9)	1 (25.0)	0.28
Evidence to support CRS and HIPEC for any indication is insufficient	10 (31.3)	7 (25.9)	3 (75.0)	0.26
The morbidity and mortality of CRS and HIPEC is too high	5 (15.6)	4 (14.8)	1 (25.0)	> 0.99
The NCCN Guidelines do not support use of CRS and HIPEC	1 (3.1)	1 (3.7)	0 (0.0)	> 0.99
What indications have you used to refer patients for CRS and HIPEC?^{b,d}				
Low-grade appendiceal cancer (pseudomyxoma peritonei syndrome)	68 (81.0)	56 (86.2)	12 (63.2)	0.02
High-grade appendiceal cancer	49 (58.3)	38 (58.5)	11 (57.9)	0.96
Colon cancer	41 (48.8)	32 (49.2)	9 (47.4)	0.89
Gastric cancer	14 (16.7)	13 (20.0)	1 (5.3)	0.17
Peritoneal mesothelioma	29 (34.5)	21 (32.3)	8 (42.1)	0.43
Other	6 (7.1)	6 (9.2)	0 (0.0)	0.33
What factors may influence your decision to refer in the future?^b				
A change of the NCCN guidelines	43 (41.3)	35 (42.2)	8 (38.1)	0.73
A phase III RCT confirming a survival advantage for CRS and HIPEC	68 (65.4)	54 (65.1)	14 (66.7)	0.89
Establishing a relationship with a HIPEC center or surgeon	44 (42.3)	34 (41.0)	10 (47.6)	0.58
I would never consider referring a patient	3 (2.9)	2 (2.4)	1 (4.8)	0.50

CRS = cytoreductive surgery, GS = general surgeons, HIPEC = hyperthermic intraperitoneal chemotherapy, MO = medical oncologists, NCCN = National Comprehensive Cancer Network, RCT = randomized controlled trial. ^aPercentages based on non-missing values. ^bRespondents could indicate more than one option. ^cPercentages calculated only from respondents who have not referred patients to a HIPEC specialist. ^dPercentages calculated only from respondents who have referred patients to a HIPEC specialist.

Table 3 summarizes the responses to the knowledge-based questions. Overall survival following CRS and HIPEC reported by specialized centers was underestimated by almost half of respondents for low grade mucinous appendiceal neoplasm with pseudomyxoma peritonei syndrome (47.6%) and more than one third of respondents for colon cancer (38.8%). Two thirds of the respondents (66 of 100) underestimated survival results in peritoneal mesothelioma (Table 3). The majority of respondents overestimated the 30-day mortality of CRS and HIPEC compared to current results published by experienced centers.

Discussion

Our study shows that physicians who treat patients with gastrointestinal cancer, including those with peritoneal metastases, practice predominately in a community setting, see patients with peritoneal malignancy very infrequently, and may not frequently discuss their patients at a multidisciplinary tumor board. This combination of lack

of experience treating patients with peritoneal malignancy and underutilization of a tumor board discussion is likely to significantly influence therapeutic management decisions. Several studies have evaluated the influence of multidisciplinary tumor boards in the management of patients with colorectal cancer, including accuracy of diagnosis and staging, frequency of changes to the individual physician's initial management plan, and adherence to tumor board recommendations [13–15]. A recent systematic review of studies that focused on the role and impact of multidisciplinary tumor boards in a variety of gastrointestinal cancers found that a majority of included studies showed that the treatment plan was altered in 23.0–41.7% of evaluated cases [16]. Some of the included studies also found that the rate of implementation of multidisciplinary tumor board decisions was high at 90–100% of evaluated cases. It is likely that increasing the frequency with which the management of patients with peritoneal carcinomatosis is discussed by a multidisciplinary team prior to treatment decisions, where additional expertise may be available, would increase the frequency of patients being referred to

Table 3: Knowledge of survival and mortality after CRS and HIPEC among 116 survey respondents.

	Number (%) of respondents ^a			p-Value (GS vs. MO)
	All, n = 116	GS, n = 92	MO, n = 24	
Please indicate the 5-year overall survival rate for patients undergoing CRS and HIPEC in an experienced center for the following indications:				
Colon cancer with limited peritoneal spread				
≥ 80%	9 (8.7)	7 (8.6)	2 (9.1)	0.36
30–50%	54 (52.4)	43 (53.1)	11 (50.0)	
≤ 30%	34 (33.0)	28 (34.6)	6 (27.3)	
≤ 5%	6 (5.8)	3 (3.7)	3 (13.6)	
Peritoneal mesothelioma				
≥ 80%	3 (3.0)	3 (3.8)	0 (0.0)	0.13
30–50%	31 (31.0)	20 (25.6)	11 (50.0)	
≤ 30%	44 (44.0)	38 (48.7)	6 (27.3)	
≤ 5%	22 (22.0)	17 (21.8)	5 (22.7)	
Low grade appendiceal neoplasm with pseudomyxoma peritonei				
≥ 80%	54 (52.4)	43 (53.1)	11 (50.0)	0.39
30–50%	33 (32.0)	27 (33.3)	6 (27.3)	
≤ 30%	13 (12.6)	8 (9.9)	5 (22.7)	
≤ 5%	3 (2.9)	3 (3.7)	0 (0.0)	
What is the 30-day mortality after CRS and HIPEC in a specialized center?^b				
20%	2 (2.0)	2 (2.6)	0 (0.0)	0.22
10%	12 (12.2)	8 (10.4)	4 (19.0)	
5%	40 (40.8)	35 (45.5)	5 (23.8)	
≤ 2%	44 (44.9)	32 (41.6)	12 (57.1)	

CRS = cytoreductive surgery, GS = general surgeons, HIPEC = hyperthermic intraperitoneal chemotherapy, MO = medical oncologists. ^aPercentages based on non-missing values. ^bOne patient who selected two answers was excluded.

a HIPEC center. The limited availability of expert HIPEC centers is another possible barrier for this therapeutic option being more widely used. It is important to note that our study was conducted among physicians practicing in Virginia, Maryland and Washington, D.C., where the number of active and high-volume HIPEC centers is significantly higher than in other areas of the US. It is very likely that the issue of availability would be an even more prominent barrier at a national level. This was further confirmed by the fact that lack of access to a HIPEC specialist was the most commonly reported reason for never referring patients for possible treatment with CRS and HIPEC in the past.

Among respondents who have referred patients for evaluation at a HIPEC center, low grade appendiceal neoplasm (pseudomyxoma peritonei) was the most common indication. Despite the rarity of pseudomyxoma peritonei, this result is not surprising, considering that pseudomyxoma peritonei was the disease that formed the basis for development and refinement of CRS and HIPEC and the one with the best survival results following CRS and HIPEC.

Only approximately half of respondents considered CRS and HIPEC as an indication for referral in the past or would consider it in the future for patients with colon cancer. Our results are very similar to those obtained by Spiegle et al. among oncologists and surgeons in Ontario, Canada in 2012, showing that only 46% of respondents were aware of CRS and HIPEC as a therapeutic option in patients with colon cancer peritoneal metastases [10]. Similarly, a Dutch study found limited acceptance of CRS and HIPEC as standard of care for colon cancer (32% of participants did not view CRS and HIPEC as standard despite national guidelines in the Netherlands recommending the use of CRS and HIPEC for appropriately selected patients with colon cancer) [17].

Interestingly, many respondents in our study indicated that a change of NCCN guidelines may influence their future decisions. Therefore, it is possible that awareness and acceptance of CRS and HIPEC for colon cancer could increase following a recent change in the NCCN guidelines which now states that complete CRS and/or intraperitoneal chemotherapy can be considered in experienced centers for select patients with limited

peritoneal metastases for whom R0 resection can be achieved.

Awareness of peritoneal mesothelioma as an indication for CRS and HIPEC was also lower than 50%. This result is disappointing considering the excellent overall survival results reported after CRS and HIPEC for peritoneal mesothelioma [18,19].

We hypothesized that lack of familiarity with the results of CRS and HIPEC, both in terms of survival (for various indications) and morbidity and mortality, would be present among physicians. Indeed, we found that 5-year overall survival results were underestimated for all diseases by a significant proportion of respondents. On the other hand, many respondents thought the 30-day mortality after CRS and HIPEC was 5% or more which is significantly higher than what is currently reported by experienced centers in the US [20].

Overall, our study shows gaps in knowledge and lack of awareness of CRS and HIPEC among American physicians are significant and similar to those found in studies performed in Canada and the Netherlands, despite differences in health care systems, physician training, and practice environments.

There are limitations in our study, primarily the low response rate (11%) which is lower than in the previously mentioned Canadian study (44%) and the Dutch study (23%). This lower rate is likely due to the methodology used to distribute the survey (mail only) and the kind of

mailing lists used in our study. We chose to use administrative databases of licensed practitioners within the three states which do not allow selection based on subspecialty status. In this way, we hoped to cast a wider net and increase the absolute number of responses albeit at the expense of a decreased overall response rate. It is reasonable to assume that subspecialty physicians who do not treat cancer patients at all and are not interested in peritoneal surface malignancies (for example, plastic, vascular, and cardiothoracic surgeons, hematologists, etc.) were mostly among the nonrespondents. Therefore, even though the calculated response rate was lower in our study than that of the two studies evaluating this topic in other countries, the differences in the methodology of survey distribution make a direct comparison of response rates difficult.

Regarding implications and potential effects of the results of our study, several possible actions could be proposed based on the results that could increase the number of patients being referred for evaluation to HIPEC centers in the future. These are summarized in Table 4.

In summary, patient referral to HIPEC centers is underutilized among community physicians. The main reasons for lack of referral include limited access to HIPEC experts, insufficient direct experience managing peritoneal metastases, and lack of knowledge regarding indications and outcomes for CRS and HIPEC. Several

Table 4: Possible actions to increase awareness and acceptance of CRS and HIPEC based on possible reasons for underutilization.

Reasons for underutilization of CRS and HIPEC	Possible actions to increase awareness and utilization of CRS and HIPEC
Physicians making treatment decisions have insufficient direct experience with managing peritoneal metastases	<ul style="list-style-type: none"> –Discuss all patients with peritoneal metastases at multidisciplinary tumor board meetings –Harness technology to make HIPEC experts' input available at local hospitals' tumor board meetings
Limited access to HIPEC experts	<ul style="list-style-type: none"> –Increase number of HIPEC treatment centers –Create national registry of HIPEC centers to increase awareness and accessibility –Create regional networks connecting referral base to regional HIPEC centers
Lack of knowledge regarding indications for CRS and HIPEC	<ul style="list-style-type: none"> –Include CRS and HIPEC as treatment option in national guidelines –Increase multidisciplinary interaction of surgeons with expertise in HIPEC with other specialists by participation in local, regional, and national non-surgical meetings –Increase availability of educational content online
Lack of knowledge regarding outcomes of CRS and HIPEC	<ul style="list-style-type: none"> –Create national registry of HIPEC centers with transparent results and established quality benchmarks –Increase multidisciplinary interaction of surgeons with expertise in HIPEC with other specialists by participation in local, regional, and national non-surgical meetings –Increase availability of educational content online

actions might increase community physicians' awareness and appropriate patient referral by addressing these reasons. Such actions might include the establishment of a transparent national HIPEC registry, the inclusion of CRS and HIPEC in therapeutic guidelines, the requirement for systematic presentation of patients with peritoneal metastasis at multidisciplinary tumor board meetings, and the creation of online educational resources for knowledge dissemination.

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