The Initial Indian Experience with Cytoreductive Surgery and HIPEC in the Treatment of Peritoneal Metastases

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Received: 26 December 2015 / Accepted: 28 January 2016 / Published online: 2 February 2016
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Abstract Worldwide, cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) has been used for nearly 3 decades to treat peritoneal metastases (PM), improve quality of life, and prolong survival substantially in selected patients. In India, the use of the combined modality of treatment dates back a decade with majority of the efforts taking place within the last 5 years. The first PSOGI workshop (India) held in April 2015, at Bangalore, India offered an opportunity for Indian surgeons performing CRS and HIPEC to share their experience. To study the methodologies of CRS and HIPEC (hospital set up, equipment, training and surgical background) as well as the outcomes in terms of perioperative morbidity and

mortality and short and long term survival of patients treated in India, Indian surgeons who had treated at least 10 patients with this combined modality were invited to present their experience. Data collection was retrospective. Analysis of the pooled data was carried out. Eight surgeons treated 384 patients with CRS and HIPEC over a period of 10 years. The commonest primary sites were ovary (as first line therapy $n = 124$), followed by appendix, including pseudomyxoma peritonei ($n = 99$), colorectum ($n = 77$), recurrent ovary (as second line therapy, $n = 33$), stomach ($n = 15$), primary peritoneal cancer ($n = 10$), peritoneal mesothelioma ($n = 9$) and rare tumors in 17 patients. The weighted mean PCI for all 384 patients was 18.25. 349/384 patients (90.88 %) had a complete cytoreduction (completeness of cytoreduction score of CC-0/1). Grade 3–5 complications developed in 108 patients (27.34 %) and 30 day mortality occurred in 28 (7.29 %) patients. This study showed that CRS and HIPEC can be performed with an acceptable morbidity and mortality in Indian patients. Most of the surgeons are on the learning curve and further improvement in these outcomes is expected over a period of time. Pooling of data related to both common and rare peritoneal cancers would be useful in knowing the disease behavior, response to treatment and outcomes in Indian patients. The 2015 PSOGI meeting provided a unique platform for data presentation with feedback from international experts in the field of peritoneal surface oncology. Future meetings are planned to expand the evaluation of Indian data and progress.

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Keywords HIPEC · Indian Experience · Cytoreductive Surgery · Peritoneal Metastases

Introduction

Over the last 3 decades, the combined modality treatment of cytoreductive surgery (CRS) and hyperthermic intraperitoneal

chemotherapy (HIPEC) had emerged as an effective tool for treating peritoneal metastases (PM) from various malignancies. These patients were previously offered only systemic chemotherapy and /or supportive care and survived for 6–12 months. [1] CRS and HIPEC has the potential to cure peritoneal metastases in appropriately selected patients. [2] It is now widely accepted as the standard of care for PM from pseudomyxoma peritonei, appendiceal tumors and peritoneal mesothelioma. [3, 4] It is effective in prolonging survival in patients with limited peritoneal cancer spread from colorectal cancer. [5, 6] In gastric cancer, in which PM have a much poorer prognosis, CRS and HIPEC is the only modality which has the potential to provide long term survival to selected patients with limited disease spread. [7, 8] CRS and HIPEC is under trial for primary ovarian cancer and has shown to be effective in providing long term survival in patients with recurrent ovarian cancer, even those with platinum resistant disease. [9].

Worldwide, the number of centers offering this therapy has steadily increased. [10] In India, however, this treatment is still offered only at a few centers and most of the experience is limited to the last 5 years. The first workshop on peritoneal surface malignancies in India was organized in April 2015, under the aegis of the Peritoneal Surface Oncology Group International (PSOGI) and offered a platform for Indian surgeons practicing the combined modality treatment to share their experience with their colleagues and international experts. This manuscript is a summary of the experience of Indian surgeons in performing CRS and HIPEC in terms of surgeons background and training, hospital set up where CRS and HIPEC is practiced, equipment used and patient selection. It also presents a pooled analysis of the early outcomes of this therapy in India in terms of perioperative morbidity and mortality, short and long-term survival.

Methods

Surgeons practicing CRS and HIPEC for at least one year and having treated a minimum of 10 patients with this combined modality presented their experience. All surgeons followed an outline for data collection and analysis. Data collection was retrospective. Cytoreductive surgery consisted of peritonectomy procedures and visceral resections as described by Sugarbaker. [11] HIPEC was performed by the open or closed technique for duration on 30–90 min depending on the chemotherapy regimen used. The surgeons and institutional background, equipment used, HIPEC methodology, chemotherapy agents and use of EPIC were reported. The results were categorized by the prognostic indicators for peritoneal surface malignancies including peritoneal cancer index (PCI), completeness of cytoreduction score (CCR), and prior surgical score (PSS). Other clinical or treatment variables included the

duration of surgery, blood loss, perioperative morbidity (as per the Dindo-Clavien classification), mortality, follow-up time and disease status. The data was pooled and analyzed.

Results

Training, Experience and Practice Setting

Eight surgeons presented their data and a pooled analysis is reported here. All the data was retrospective. Surgical Oncology is practiced as a broad specialty in India, including most of the regional cancer centers. Most surgeons practicing CRS and HIPEC also treat breast, head and neck and thoracic tumors in addition to the gastrointestinal and gynecological malignancies that can be treated by CRS and HIPEC. Currently, CRS and HIPEC are not taught as part of the surgical oncology training programs in the country and most surgeons pursue training abroad. Table 1 summarizes the training and experience of the individual surgeons and the hospital setting in which CRS and HIPEC was performed.

Table 1 Surgeons' training, experience and practice setting

Training, experience and practice setting.		No. of surgeons
1.	Clinical specialty	
	General surgical oncology	6
	GI oncology	2
2.	Training for CRS and HIPEC	
	None	2
	Workshop	2
	Fellowship with hands on training (assisting surgeries)	4
3.	Years of Experience (in Oncology)	
	5–10	2
	10–15	5
	15–20	1
4.	Type of center	
	Regional cancer center	2
	Government medical college and Hospital	1
	Privately owned cancer center	
	Multispecialty hospital with a cancer cell	5
5.	No of surgeons performing HIPEC	
	2005–2010	2
	2011	4
	2012	6
	2013	7
	2014	8

Patient Characteristics

All eight surgeons agreed on the clinical features appropriate for treatment by CRS and HIPEC. Work up included routine blood investigations, CT/PET scan, diagnostic laparoscopy and biopsy. Patient selection criteria included age < 70 years, no cardiorespiratory or renal failure, ECOG performance status of 0/1, carcinomatosis amenable to effective cytoreductive surgery allowing either a macroscopic complete resection (CC-0), or a small residual tumour volume, with residual cancer nodules <2.5 mm (CC-1). An exception was pseudomyxoma peritonei with extensive disease where a limited debulking was performed. There were no extraperitoneal metastases (excluding patients of colorectal cancer with <3 liver metastases) and no bulky retroperitoneal or upper abdominal lymphadenopathy. Patients with a performance status of 2/3, multilevel small bowel obstruction and biliary

obstruction and in whom complete cytoreduction was not deemed possible were not offered CRS and HIPEC. There were 384 procedures performed from December 2004 – December 2014. The commonest primary site was ovary (as first line therapy $n = 124$), followed by appendix, including pseudomyxoma peritonei ($n = 99$), colorectum ($n = 77$), recurrent ovarian cancer (as second line therapy, $n = 33$), stomach ($n = 15$), primary peritoneal cancer ($n = 10$), peritoneal mesothelioma ($n = 9$) and rare tumors in 17 patients. There were 2 open and close procedures. The patient characteristics are listed in Table 2.

Operative Findings

As shown in Table 3, the PCI ranged from 3 to 36. The mean PCI ranged from 11 to 24. The weighted mean PCI for all 384 patients was 18.25. HIPEC was performed in patients who

Table 2 Characteristics of patients undergoing CRS and HIPEC

	Characteristic	No. of Patients	Percentage
1.	Primary cancer site	$N = 384$	
	Colorectum	77	20.05
	Ovary (first line therapy)	124	32.29
	Ovary (Second line therapy)	33	8.59
	Stomach	15	3.90
	Appendix (including PMP)	99	25.78
	Primary peritoneal cancer	10	2.60
	Peritoneal mesothelioma	9	2.34
	Rare tumors	17	4.42
	• Sarcomas	5	1.30
	• Gall bladder	1	0.26
	• Recurrent borderline ovarian tumor	1	0.26
	• Fibrolamellar HCC	1	0.26
	• Endometrial carcinoma	2	0.52
	• Granulosa cell tumor	2	0.52
	• SCC cervix	1	0.26
	• Carcinosarcoma of the ovary	1	0.26
	• Desmoplastic small round cell tumor (DSRCT)	1	0.26
	• Small bowel adenocarcinoma	2	0.52
2.	Prior surgery		
	Yes	225	58.59
	No	159	41.41
3.	Prior Chemotherapy		
	Received	250	65.10
	Not Received	134	34.90
	Unknown		
4.	Performance status		
	ECOG 0/1	383	99.73
	ECOG 2	1	0.27
	ECOG 3	0	0.00

Abbreviations: PMP pseudomyxoma peritonei; HCC hepatocellular carcinoma; SCC squamous cell carcinoma

Table 3 Operative findings in 384 patients treated with CRS and HIPEC

	Characteristic	No. of Patients	Percentage
1.	CCR Score		
	CCR-0	333	86.71
	CCR-1	16	4.16
	CCR-2	21	5.46
	CCR-3	14	3.64
2.	Technique of HIPEC		
	Open	338	88.02
	Closed	46	11.97
3.	Drug regimen		
	Oxaliplatin based	70	
	Mitomycin based	102	
	Cisplatin	110	
	Cisplatin + adriamycin	82	
4.	EPIC		
	Performed	114	8.86
	Not performed	270	91.14
5.	Drug used in EPIC	<i>N</i> =114	
	5- FU	33	28.94
	Paclitaxel	81	71.06

achieved complete cytoreduction, defined as a CCR score of CC-0/CC-1. A score of CC-0 was achieved in 333 patients and CC-1 in 16 patients, thus, 349/384 patients (90.88 %) had a complete cytoreduction. Three surgeons performed HIPEC by the closed method while the other 5 performed it using the open method. Five surgeons used custom made machines for delivering HIPEC while 3 others used an indigenous set up comprising of a heart lung machine used in cardiovascular bypass surgery. Two surgeons performed EPIC (Early postoperative chemotherapy). The temperature was maintained at 42–43 degrees intra abdominally during the open method. For the closed method, the inflow temperature was maintained between 42 and 44 degrees Celsius. The duration varied from 30 to 90 min. For CRC, appendiceal tumors and PMP, oxaliplatin or mitomycin based regimens were used. For ovarian cancer, gastric cancer and mesotheliomas, either cisplatin or cisplatin and adriamycin or mitomycin was used. Three surgeons used bidirectional chemotherapy, five did not. The various drug regimens used are listed in Table 3 along with the other operative findings. The average duration of surgery ranged from 90 min to 1140 min (including patients with open and close procedures) and the blood loss ranged from 150 ml to 4500 ml.

Morbidity and Mortality

All patients were initially managed in the intensive care unit and ventilated for a minimum of 12 h. Complications were

reported as per the Clavien-Dindo classification. Grade 3–5 morbidity was seen in 105 patients (27.34 %). The commonest complications were neutropenia seen in 50 patients (13.02 %), anastomotic leak in 30 patients (7.81 %), paralytic ileus in 29 patients (7.55 %), acute lung injury in 18 patients (4.68 %) and sepsis in 17 patients (4.42 %). Some rare complications reported were bladder perforation ($n = 2$), burns needing debridement ($n = 2$), gastric outlet obstruction requiring surgical intervention ($n = 1$), transient ischemic attack ($n = 1$) and empyema requiring decortication ($n = 1$). Thirty eight (9.89 %) patients required a second surgery for the management of complications. Some of the indications for re-exploration were anastomotic leak in 21 patients, bowel perforation in 7 patients, bladder perforation in 2 patients and wound dehiscence in 2 patients. Twenty-eight (7.29 %) patients died within 30 days of surgery, the commonest cause being neutropenic sepsis. There were 2 mortalities within 90 days of surgery. The ICU stay ranged from 2 to 129 days. The average hospital stay was 12 days Table 4 and 5.

Follow-Up and Survival

The median follow-up ranged from 9 months to 18 months. Only 6 surgeons reported the follow-up and current disease status of their patients, i.e. 220/384 patients (57.29 %). Fifty-three percent of the 220 patients were alive without disease and 18 % were alive with disease. Twenty-seven percent of the patients were dead. Due to the lack of complete data survival rates could not be calculated.

Discussion

This manuscript summarizes the efforts of the Indian surgeons in treating peritoneal metastases with CRS and HIPEC. CRS and HIPEC is associated with a well described learning curve which peaks at 130 procedures. [12] Complete cytoreduction

Table 4 Morbidity and Mortality in patients undergoing CRS and HIPEC

	Characteristic	No. of Patients	Percentage
1	Grade 3–5 complications	105	27.34
2	30 day mortality	28	7.29 %
3	Common complications (Grade 1–5)		
	Neutropenia	50	13.02
	Anastomotic leak	30	7.81
	Ileus	29	7.55
	Acute lung injury	18	4.68
	Sepsis	17	4.427
4	Re-exploration	38	9.89 %

Table 5 Follow up of patients treated with CRS and HIPEC

Current status	No. of Patients	Percentage
Dead	60	27.27
Alive and disease-free	121	55.00
Alive with disease	39	17.72
Total	220	

in patients with extensive disease as in some cases of pseudomyxoma peritonei requires major surgery with multivisceral resection and has significant morbidity and mortality. [13] It is not just the technical skill but also decision making that is important. Knowledge of the potential complications, taking measures to minimize them, their early recognition, and definitive management is imperative. Decision making involves case selection, intraoperative strategic plans and alterations required when encountering the unexpected. [13] The learning curve is not just for the surgeon but also for the institution, since this form of treatment cannot be an individual undertaking and requires a team comprising of surgeons, anesthesiologists, intensivists, nurses, medical oncologists, radiologists, pathologists and nutritionists and rehabilitation specialists. [14] The long operative times and ICU care exerts a higher cost over conventional surgery. Though there are no rules governing the use of CRS and HIPEC in India at present, getting institutional support and permission is mandatory. Thus, setting up a HIPEC unit is a challenging task.

CRS and HIPEC has emerged as the standard of care in management of patients with pseudomyxoma peritonei, appendiceal tumors and peritoneal mesothelioma. [15] It can cure certain patient with colorectal PM when the PCI is less than 20 and can significantly prolong survival in gastric cancer patients with a PCI of <12. [7, 16–18] Patient selection is extremely important when undertaking this treatment. One of the reasons for reduction in the morbidity and mortality of the procedure has been an improvement in the patient selection. General criteria like a performance status of 0–1, absence of renal and cardiac dysfunction, normal platelet and white blood cell count are used for all patients. There are disease specific criteria like a PCI of <20 for colorectal cancer and <12 for gastric cancer, absence of bulky retroperitoneal lymphadenopathy, absence of biliary or multilevel small bowel obstruction which are also used in selecting patients. In general, the peritoneal disease should be amenable to complete cytoreduction (CC-0/1) though there is some role of a limited debulking in patients with pseudomyxoma peritonei where complete tumor removal is not possible. A majority of these surgeons treat both gastrointestinal and gynecological malignancies. The common indications in this series were appendiceal tumors and pseudomyxoma peritonei, colorectal PM, gastric PM, advanced and recurrent ovarian cancer, primary peritoneal

tumors like peritoneal mesothelioma and primary peritoneal carcinoma and other rare tumors with PM.

Of the 384 patients, a complete cytoreduction was attained in 349 patients (90.88 %). This is at par with the rates reported in current literature. The mean weighted PCI in the series was 18.5. The PCI was higher in patients with patients with pseudomyxoma peritonei, ovarian cancer and peritoneal mesothelioma where there is no cut off for selecting patients.

Grade 3–5 complications developed in 108 patients (27.34 %) and 30 day mortality occurred in 28 (7.29 %) patients. The morbidity observed in this series is similar to that reported in recent publications. The mortality is on the higher side (0–12 % for experienced centers). [19, 20] Only 4/8 surgeons had spent time in training at a center performing CRS and HIPEC. At the time of presentation 7/8 surgeons had not reached the recommended 130 cases and were still on the learning curve. All but 2 had performed under 50 cases. Most surgeons have a substantial experience in performing cytoreductive surgery alone which could be one of the reasons for the acceptable morbidity. This also indicates that the tolerance of Indian patients to this procedure is not different from those of other races around the world. Dose reductions of 25–33 % were used in <10 % of the patients.

Follow-up of 220/380 patients was limited so that it was impossible to calculate the survival data. The median follow up was 14 months. At the time of reporting, 60 (27.27 %) patients were dead, 39 (17.72 %) were alive with disease and 121 (55 %) were alive and disease-free. All the data collection and storage was done by the individual surgeons and many patients were lost to follow-up. This highlights the need for a more schematic data collection and storage. A registry could serve the purpose of data collection and storage and also be helpful in tracking patients. Some less common tumors like appendiceal tumors and pseudomyxoma peritonei ($n = 99$, 26 %), primary peritoneal cancer ($n = 9$, 2.6 %) and peritoneal mesothelioma ($n = 9$, 2.3 %) were treated by this group. A registry for further analysis of the outcomes of these patients could provide valuable information on disease pathology, behavior, treatment patterns and outcomes. The French network for rare diseases (RENAPE) is a network of surgeons, pathologists, health care providers that treat rare peritoneal cancers and organizes the diagnosis, treatment planning, treatment and research related to these rare tumors. There are other registries like the HYPER-O registry for ovarian cancer in the US and the International Mesothelioma Registry in Milan. [21] In other countries there are collaborative groups of surgeons treating peritoneal surface malignancies like the American Society of Peritoneal Surface Malignancies, the French surgical society AFC (Association Française de Chirurgie), FROGHI (FRench Oncologic and Gynecologic HIPEC Group) and the Canadian HIPEC collaborative group. [22, 23] This PSOGI meeting provided a platform for the Indian surgeons performing CRS and HIPEC to present their experience before a panel of

international experts and pioneers in this field, as well as an opportunity to collaborate and pool data in the future.

Conclusions

Peritoneal surface oncology is an emerging specialty in India. CRS and HIPEC can be performed with an acceptable morbidity and mortality in Indian patients. Most of the surgeons are still on the low end of the learning curve and further improvement in these outcomes is expected over a period of time. A longer and detailed follow up of patients is needed to calculate the survival data. Pooling of data related to both common and rare peritoneal cancers would be useful in knowing the disease behavior, treatment patterns and outcomes in Indian patients. The PSOGI meeting provided a unique platform for the same and future meetings will have more elaborate presentations on the Indian data. A registry in India for patients treated with CRS and HIPEC would further help this cause.

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