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Biphasic learning curve of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: technical competence and refinement of patient selection

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Abstract

Background: Cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) is routinely used for selected patients with peritoneal metastasis, but can be associated with high complication rates, prolonged hospital stay, and mortality. Our objective was to determine the learning curve of CRS/HIPEC in our institution, representing the largest Asian cohort to date.

Methods: A total of 200 consecutive patients with peritoneal metastasis treated with CRS/HIPEC between 2001 and 2016 were grouped into four cohorts of 50 patients and studied. Primary outcomes were severe morbidity (Clavien-Dindo III-V), procedure-related mortality, and duration of ICU and hospital stays. Secondary outcome was duration of surgery.

Results: Median age was 53 years (10–75). There was no significant age, sex, or histology difference across cohorts. Rates of severe morbidity (23%), and 60 day inpatient mortality (0.5%) were comparable to previously reported data. Decreases in rates of serious morbidity, (34%, 30%, 12%, 14%, $p < 0.01$) and duration of total hospital stay (14, 16, 13, 12 days, $p = 0.041$) were seen across consecutive cohorts. Operation time decreased significantly after the first cohort (10, 7.8, 7.8, 7.2 h, $p < 0.01$), despite increase in average PCI score after the first cohort (8, 14, 12, 13, $p = 0.063$).

Conclusions: Whilst 50 cases were adequate for procedural familiarity and decreased average operation time, significant improvement in rate of serious morbidity was observed after 100 operations. We demonstrate a novel biphasic nature to the learning curve, reflecting initial training in which technical competence is achieved, followed by a subsequent period characterized by increasingly complex cases (higher PCI score) and finally refinement of patient selection.

Keywords: cytoreduction surgical procedures, learning curve, patient selection, peritoneal neoplasms, regional perfusion cancer chemotherapy

Introduction

Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) have achieved good long-term results in treating peritoneal metastasis from colorectal [1], ovarian [2], appendiceal [3], mesothelioma [4] and primary peritoneal neoplasms. An increase in survival durations has been reported at the expense of considerable perioperative morbidity and mortality although patients are able to return to baseline or improved quality of life by 6–12 months [5]. This high complication rate has been attributed to the steep learning curve associated with the procedure, although even in several high volume centers, the complication rate remains high and overall is comparable to major gastrointestinal surgery [6].

Major morbidity in CRS/HIPEC varies widely 12 [7]–67.6% [8], with a median of 31% reported from an analysis of several studies in the literature [9]. Rates of perioperative mortality vary from 0% [10] to 9% [11], with a median of 4% [9].

Traditionally the two key parts of the learning curve assessed are an increase in rates of complete cytoreduction and decreases in procedure-related serious complications or mortality. Estimates from previous studies put the number of cases required to reach surgical proficiency at 130–140 [12–14]. Kusamura et al. reported in 2012 that 140 cases are necessary to ensure surgical proficiency in CRS/HIPEC on the basis of completeness of cytoreduction and serious morbidity [13], and in 2013

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reported a similar number required in a second center [12]. Similarly, Smeenk et al. reported a peak in the learning curve after around 130 procedures had been performed out of a total cohort of 323 on the basis of completeness of cytoreduction [14].

The demonstration from initial studies that the maximal benefit of CRS/HIPEC can only be achieved with complete resection (completeness of cytoreduction score 0 or 1, representing no nodules > 0.5 cm remaining) [15, 16] has established this as an important factor in patient selection, placing the emphasis of learning curve on procedure-related serious complications or mortality.

Materials and methods

Patients

A prospectively maintained, Institutional Review Board approved database of all patients who underwent CRS/HIPEC for peritoneal-based malignancies at the National Cancer Centre Singapore under one of two surgeons from April 2001 through to January 2016, was retrospectively reviewed. Demographics including age, gender, race, and tumor type were included in the database and are reported.

Patients considered for CRS/HIPEC had to be of Eastern Cooperative Group (ECOG) performance status 0 or 1, with no distant metastases. All patients were recommended for CRS/HIPEC after evaluation in a multidisciplinary tumor board. The absence of extra-abdominal disease either via thorax computed tomography (CT) or positron emission tomography (PET)-CT scan and the extent of intra-abdominal disease and its amenability to complete CRS were determined. Extent of intra-abdominal disease assessed intraoperatively was reported according to peritoneal carcinomatosis index (PCI). All patients had complete cytoreduction (completeness of cytoreduction score 0 or 1, representing no nodules > 0.5 cm remaining).

CRS/HIPEC proceeded according to previously published techniques. Chemotherapy was infused via a hyperthermia pump (Belmont) into a closed abdomen at a target temperature of 41–42°C for 60 min. No changes to HIPEC technique were made over the course of the study. The chemotherapeutic agent used was determined by the primary surgeon and medical oncologist on the basis of primary malignancy and routine agents did not change over the course of the study. Prior to November 2012, all patients were planned for early postoperative intra-peritoneal chemotherapy (EPIC) with five-FU or paclitaxel. Whether or not patients received EPIC and the duration of EPIC (0–5 days) depended on the presence of surgical complications, and hematological and biochemical derangements. However, EPIC was discontinued from November 2012 onwards as there was insufficient evidence to support the efficacy of EPIC, and some of our patients suffered resultant morbidity from persistent intra-abdominal collections. The remaining 93 patients in this cohort only received HIPEC.

Primary outcomes were severe morbidity (Clavien-Dindo grade III-V), procedure-related mortality (60 day inpatient mortality) and durations of intensive care unit (ICU) and hospital stay. Secondary outcome was duration of CRS/HIPEC.

As complications were primarily postoperative they were categorized according to the Clavien-Dindo postoperative complication classification, with major complications defined as Clavien III and IV rather than NCI-CTCAE classification which is more widely used to evaluate the toxicity of chemotherapy and radiotherapy.

For purposes of comparison, 200 consecutive operations from the cohort were grouped into four cohorts of 50 operations and studied.

Twelve patients underwent a second CRS/HIPEC procedure, and an additional patient underwent a second and third CRS/HIPEC procedure during the study period. Data were analyzed at the procedural level in order to increase the generalizability of results to include patients who undergo multiple procedures. In these instances, listed patient characteristics are representative of the patient's state at the time of each included operation.

Statistics

Continuous variables were expressed as mean ± 1 standard deviation (normally distributed data) or medians with interquartile ranges (nonparametric data) and categorical data as proportions throughout the article.

Clinical variables or surgical outcomes and grouping status were compared using chi-square, Fisher's exact, or analysis of variance (ANOVA) with Tukey post-hoc testing, as appropriate for individual group comparisons. $p < 0.05$ Was considered statistically significant. All statistical analyses were performed using R 3.2.3 [17].

Results

Baseline characteristics of study population

From January 2001 through to December 2015, a total of 200 CRS/HIPEC were performed on 188 patients (Table 1). Time taken to recruit each cohort was 110, 28, 16, and 21 months respectively. Twelve patients underwent CRS/HIPEC twice, and an additional patient underwent CRS/HIPEC three times. All CRS procedures included HIPEC. 104 (52%) of the HIPEC used Mitomycin C, 89 (45%) used cisplatin, 7 (3.5%) used oxaliplatin. Primary histologies were ovarian (32%), colorectal (30%), or appendiceal (21%) neoplasms, primary peritoneal (8%), mesothelioma (5%) and others (6%). The selection of HIPEC regimen was based on primary histology and did not change during the study.

Overall rates of severe morbidity (23%), and 60 day mortality (0.5%) were comparable to previously reported data [18]. After cessation of EPIC, there was a decrease in rate of severe morbidity (34% vs. 14%, $p < 0.01$).

Operations were grouped into four consecutive cohorts of 50 procedures and compared. Groups are

Table 1: Patient demographics.

Category	Parameter	Mean ± SD	Range	Median
Patient characteristics	Age (years)	51.2 ± 11.7	10–75	53
	Gender	49 Male (25 %)		151 Female (76 %)
Intraoperative parameters	Duration (hours)	8.2 ± 2.7	3–16	8
	PCI score	12.4 ± 8.8	0–39	11
Surgical procedures	121 Subdiaphragmatic stripping (61 %), 105 Colectomy (53 %), 54 Small bowel resection (27 %), 50 Cholecystectomy (25 %), 48 Splenectomy (24 %), 36 THBSO (18 %), 18 Gastrectomy (9 %), 7 Bladder resection (4 %), 98 Others (49 %)			
Histology	63 Ovarian (32 %), 59 Colorectal (30 %), 42 Appendix (21 %), 15 Primary Peritoneal (8 %), 9 Mesothelioma (5 %), 12 Others (6 %)			
Primary	61 Adenocarcinoma (31 %), 65 Mucinous (33 %), 21 Serous (11 %), 53 Other (27 %)			
Short-term postoperative outcomes	Severe morbidity	45 (23 %)		
	60 day inpatient mortality	1 (0.5 %)		
	ICU stay (days)	2.2 ± 6.6	0–76	1
	Total hospital stay (days)	19.0 ± 18.1	6–188	14

PCI, peritoneal carcinomatosis index; THBSO, total hysterectomy bilateral salpingo-oophrectomy; ICU, intensive care unit. If not otherwise indicated, values are given as number and (percentage).

named as c1 (first cohort, procedures 1–50), c2 (second cohort, procedures 51–100), c3 (third cohort, procedures 101–150), or c4 (fourth cohort, procedures 151–200). Baseline clinical features are summarized in Table 2 and aside from an increase in proportion of other races undergoing CRS/HIPEC in the third cohort (12, 2, 26, 18 %), did not differ between the groups.

Characteristics of the primary tumors treated with initial resection prior to CRS/HIPEC are summarized in Table 3. Distribution of the locations of the primary tumor or histology did not differ between the groups in the first three cohorts, but an increasing number of other primary types (including gastric, n = 3 and small bowel n = 3) were operated on in the fourth cohort ($p < 0.01$). There was an increase in patients presenting with a history of node positive primary tumors in the initial three cohorts but the percentage decreased in the last cohort (20 %, 24 %, 48 %, 18 %, $p < 0.01$), although the proportion of patients

Table 2: Demographics of consecutive patient cohorts.

	c1 (1–50)	c2 (51–100)	c3 (101–150)	c4 (151–200)	p-Value
Age (years)	50 ± 13	50 ± 12	54 ± 10	52 ± 11	0.32
Female:male	43:7	39:11	33:17	36:14	0.12
Race					0.067
Chinese	42 (84 %)	42 (84 %)	33 (66 %)	37 (74 %)	–
Indian	2 (4 %)	4 (8 %)	2 (4 %)	2 (4 %)	–
Malay	0 (0 %)	3 (6 %)	2 (4 %)	2 (4 %)	–
Others	6 (12 %)	1 (2 %)	13 (26 %)	9 (18 %)	–
Comorbidities					
Hypertension	8 (16 %)	12 (24 %)	13 (26 %)	12 (24 %)	0.64
Diabetes	4 (8 %)	7 (14 %)	2 (4 %)	3 (6 %)	0.28
Ischemic heart disease	0 (0 %)	0 (0 %)	0 (0 %)	1 (2 %)	0.39
COPD	0 (0 %)	0 (0 %)	1 (2 %)	0 (0 %)	0.39
Asthma	1 (2 %)	1 (2 %)	1 (2 %)	2 (4 %)	0.89
Other malignancy	5 (10 %)	6 (12 %)	1 (2 %)	5 (10 %)	0.28
ECOG					0.59
0	45 (94 %)	45 (90 %)	44 (90 %)	48 (96 %)	–
1	3 (6.2 %)	5 (10 %)	5 (10 %)	2 (4 %)	–

COPD, chronic obstructive pulmonary disease; ECOG, Eastern Cooperative group. If not otherwise indicated, values are given as number and (percentage).

Table 3: Primary tumor characteristics of consecutive patient cohorts.

	c1 (1–50)	c2 (51–100)	c3 (101–150)	c4 (151–200)	p-Value
Location					< 0.01
Appendix	9 (18 %)	9 (18 %)	10 (20 %)	14 (28 %)	–
Colorectal	18 (36 %)	13 (26 %)	22 (44 %)	6 (12 %)	–
Ovarian	16 (32 %)	22 (44 %)	15 (30 %)	10 (20 %)	–
Primary Peritoneal	3 (6 %)	1 (2 %)	2 (4 %)	9 (18 %)	–
Mesothelioma	3 (6 %)	4 (8 %)	1 (2 %)	1 (2 %)	–
Others	1 (2 %)	1 (2 %)	0 (0 %)	10 (20 %)	–
Histology					0.42
Adenocarcinoma	17 (0.34 %)	10 (0.2 %)	20 (0.4 %)	14 (0.28 %)	
Mucinous	15 (0.3 %)	16 (0.32 %)	16 (0.32 %)	18 (0.36 %)	
Serous	7 (0.14 %)	6 (0.12 %)	5 (0.1 %)	3 (0.06 %)	
Other	11 (0.22 %)	18 (0.36 %)	9 (0.18 %)	15 (0.3 %)	
Adjuvant chemotherapy prior to CRS/HIPEC	32 (64 %)	42 (84 %)	37 (74 %)	35 (70 %)	0.15
T-stage					0.47
1	1 (2.6 %)	4 (8.7 %)	1 (2.2 %)	1 (2.8 %)	–
2	1 (2.6 %)	2 (4.3 %)	3 (6.7 %)	1 (2.8 %)	–
3	15 (39 %)	24 (52 %)	16 (36 %)	11 (31 %)	–
4	16 (42 %)	11 (24 %)	19 (42 %)	15 (42 %)	–
N-stage					< 0.01
0	20 (53 %)	17 (40 %)	11 (25 %)	19 (58 %)	–
1	4 (11 %)	9 (21 %)	15 (34 %)	5 (15 %)	–
2	6 (16 %)	3 (7.1 %)	9 (20 %)	2 (6.1 %)	–
3	0 (0 %)	0 (0 %)	0 (0 %)	2 (6.1 %)	
M-stage					0.012
0	28 (68 %)	25 (53 %)	29 (63 %)	15 (38 %)	–
1	12 (29 %)	16 (34 %)	16 (35 %)	23 (59 %)	–

CRS, cytoreductive surgery; HIPEC, hyperthermic intra-peritoneal chemotherapy. If not otherwise indicated, values are given as number and (percentage).

with metastatic disease at time of initial presentation (synchronous metastatic disease) rather than at recurrence increased in the final cohort (29, 34, 35, 59 %, $p < 0.012$) across the cohorts. There was no significant difference in T-stage across the cohorts ($p = 0.47$).

Perioperative outcomes are summarized in Table 4. A decrease in rate of serious morbidity was observed (34 %, 30 %, 12 %, 14 %), most noticeably in the third cohort ($p < 0.01$). There was no decrease in length of ICU stay (median 1, 1, 1, 0 days, $p = 0.39$), however total hospital stay decreased (median 14, 16, 13, 12 days, $p = 0.041$).

A significant decrease in the duration of CRS/HIPEC (10, 7.8, 7.8, 7.2 h) was observed after just the first cohort ($p < 0.01$), despite a nonsignificant increase in PCI score seen in subsequent cohorts (8, 14, 12, 13, $p = 0.063$). The only operative procedure that change in frequency across the cohorts was a decrease in the proportion of patients undergoing subdiaphragmatic stripping (86 %, 72 %, 38 %, 46 %, $p < 0.01$).

The complications observed in the cohorts are summarized in Table 5. There was a significant decrease in the rate of respiratory complications across the cohorts (30 %, 14 %, 6 %, 20 % $p = 0.014$) as well as a decreased frequency of intra-abdominal collections (10 %, 22 %, 2 %, 2 %, $p < 0.01$) and bleeding (8 %, 0 %, 0 %, 0 %, $p = 0.019$) after the second cohort.

Discussion

CRS/HIPEC is a relatively recent development in the treatment of peritoneal metastasis, and has demonstrated an increase in survival times at the expense of considerable perioperative morbidity and mortality. Developments in this technique have largely focused on the selection criteria utilized for patients. The demonstration of initial studies that the maximal benefit of CRS/HIPEC can only be achieved with complete resection [15, 16], has been an important factor driving evolution of selection criteria. Improvements have also been made in the perioperative management of patients suggesting that it is not just the

Table 4: Comparison of outcomes across consecutive patient cohorts.

	c1 (1–50)	c2 (51–100)	c3 (101–150)	c4 (151–200)	p-Value
Serious complications	17 (34 %)	15 (30 %)	6 (12 %)	7 (14 %)	< 0.01
60-day inpatient mortality	1 (2.4 %)	0 (0 %)	0 (0 %)	0 (0 %)	0.31
ICU stay (days)	1 [1–2]	1 [1–2]	1 [0–2]	0 [0–1]	0.39
Total hospital stay (days)	14 [12–19]	16 [12–26]	13 [10–18]	12 [9–14]	0.041
Duration of CRS/HIPEC (min)	600 ± 160	470 ± 140	470 ± 160	430 ± 150	< 0.01
PCI score	7.6 ± 4.9	14 ± 8.4	12 ± 10	13 ± 8.4	0.063
Estimated blood loss (mL)	1000 [750–2000]	1000 [500–1500]	1000 [550–2500]	1000 [600–2000]	0.2
Subdiaphragmatic stripping	43 (86 %)	36 (72 %)	19 (38 %)	23 (46 %)	< 0.01
Gastrectomy	4 (8 %)	5 (10 %)	6 (12 %)	3 (6 %)	0.75
Colectomy	24 (48 %)	27 (54 %)	29 (58 %)	25 (50 %)	0.76
Small bowel resection	12 (24 %)	18 (36 %)	15 (30 %)	9 (18 %)	0.21
Splenectomy	13 (26 %)	16 (32 %)	11 (22 %)	8 (16 %)	0.29
THBSO	14 (28 %)	5 (10 %)	6 (12 %)	11 (22 %)	0.062
Cholecystectomy	15 (30 %)	13 (26 %)	12 (24 %)	10 (20 %)	0.71
Bladder resection	2 (4 %)	1 (2 %)	4 (8 %)	0 (0 %)	0.16

ICU, intensive care unit; CRS, cytoreductive surgery; HIPEC, hyperthermic intra-peritoneal chemotherapy; PCI, peritoneal carcinomatosis index; THBSO, total hysterectomy bilateral salpingo-oophorectomy. If not otherwise indicated, values are given as number and (percentage).

Table 5: Oost-operative complications of consecutive patient cohorts.

	c1 (1–50)	c2 (51–100)	c3 (101–150)	c4 (151–200)	p-Value
Acute renal impairment	14 (29 %)	15 (31 %)	8 (16 %)	6 (13 %)	0.098
Respiratory	15 (30 %)	7 (14 %)	3 (6 %)	10 (20 %)	0.014
Pneumonia	5 (10 %)	2 (4 %)	1 (2 %)	1 (2 %)	0.17
Intra-abdominal collection	5 (10 %)	11 (22 %)	1 (2 %)	1 (2 %)	< 0.01
Wound infection	4 (8 %)	1 (2 %)	4 (8 %)	4 (8 %)	0.53
Ileus	0 (0 %)	1 (2 %)	3 (6 %)	3 (6 %)	0.26
Anastomotic leak	2 (4 %)	3 (6 %)	0 (0 %)	1 (2 %)	0.33
Enterocutaneous fistula	3 (6 %)	1 (2 %)	0 (0 %)	0 (0 %)	0.11
Bleeding	4 (8 %)	0 (0 %)	0 (0 %)	0 (0 %)	0.019

Values are given as numbers and (percentage).

learning curve of surgical technique which is important in reducing the high morbidity associated with CRS/HIPEC. In contrast to previous studies which have focused solely on rates of incomplete cytoreduction, mortality and serious morbidity to assess learning curve, we have identified a secondary component in the learning curve related to trends of patient selection and perioperative management.

In our institution, the extent of intra-abdominal disease and its amenability to complete CRS is determined at a multidisciplinary tumor board and with expert radiologists present. Only patients who have absence of extra-abdominal metastases and a high likelihood of complete CRS are subjected to the procedure, and in line with the literature, our practice is not to administer HIPEC if optimal CRS cannot be performed.

In order to assess the learning curve of CRS/HIPEC, we have examined trends in patient selection, technical competence and perioperative management in our institution, representing the largest Asian cohort to date.

Trends in primary tumor selection included an increase, followed by subsequent decrease in the last cohort in tumors presenting with positive nodal status (20 %, 24 %, 48 %, 18 %, $p < 0.01$), whilst there was an increase in the final cohort of patients found to have metastatic disease at initial presentation (i.e. patients presenting for CRS and HIPEC with synchronous peritoneal metastasis) (29, 34, 35, 59 %, $p = 0.012$). There was no significant difference in T-stage across the cohorts ($p = 0.47$). These trends reflect development of a hesitancy about aggressive locoregional surgical treatment in those with node positive tumors, as such tumors carry

a generally higher risk of failure at distant sites. However, there is a recognition of the role of CRS and HIPEC in patients who present with limited synchronous peritoneal metastasis at the time of their diagnosis, although it has traditionally been thought that patients with synchronous metastases tended to have poorer tumor biology compared to those who developed their metastases in a metachronous fashion. We are increasingly seeing referrals for such patients resulting in the increased proportion of patients presenting with synchronous metastases across the cohorts.

As peritoneal disease often responds poorly to systemic chemotherapy, there is a risk that staged resection, with CRS and HIPEC planned for after pseudo-neoadjuvant chemotherapy after resection of the primary tumor, may result in the loss of the window of opportunity for patients who present with synchronous peritoneal metastasis. We have adopted the strategy to administer a short course of pseudo-neoadjuvant chemotherapy, to assess for favorable tumor biology (response or stable disease) and absence of new abdominal or distant metastases prior to CRS/HIPEC, particularly in patients presenting with synchronous metastases.

Although frequency of subdiaphragmatic stripping decreased across the study (86 %, 72 %, 38 %, 46 %, $p < 0.01$), there was a nonsignificant increase in overall PCI score (average 8, 14, 12, 13). One explanation is that the distribution of disease may play a role rather than overall extent. The primary tumor type did not change significantly in the first three cohorts, although in the final cohort there was an increased proportion of primary peritoneal (18 %) and other primary tumor types (20 %) ($p < 0.01$). Distribution of disease may reflect the cases that are being referred from gynecology and colorectal surgeons. In the early cohorts, frequent requirement for subdiaphragmatic stripping may reflect a tendency for referrals for disease in the upper abdomen, outside of the normal operative zone of the respective surgeons, whilst they resect pelvic peritoneal lesions themselves. With increasing awareness of the role of CRS/HIPEC, referrals are likely to reflect patients with known peritoneal disease, regardless of the location of the disease.

In this study we observed a decrease in two outcomes over the cohorts. A significant decrease in the primary outcome of serious complications was observed only after 100 consecutive operations (34, 30, 12, 14 % in consecutive cohorts). However, a significant decrease in the secondary outcome of duration of CRS/HIPEC was observed after just the first 50 operations (average of 600, 470, 470, 430 min in consecutive cohorts). Another way of putting this is that there is a decrease in time taken per PCI after the first cohort (1.25, 0.56, 0.65, 0.55 h taken per PCI, or 1.125, 0.49, 0.57, 0.47 h/PCI excluding HIPEC time). This measure remains similar after the first cohort, suggesting that this measure reflects improvement in technical expertise rather than patient selection.

Previous studies have reported that around 130–140 procedures are required to reach competence with CRS/HIPEC [12–14], hence we expected to see an improvement in outcomes by the third cohort of 50 patients. However previous studies have largely focused on rates of incomplete cytoreduction and serious morbidity as surrogates of surgical competency, although these are closely related to patient selection. The practice at our institution to only proceed with CRS/HIPEC if a CC0 or 1 resection is possible limits the comparison to rates of serious complications, with a significant drop most apparent after the first 100 cases (34, 30, 12, 14 %) similar to previously reported learning curves.

A proportion of this decrease is due to changes in management made as a result of increased experience. After the first two cohorts, we ceased early postoperative intraperitoneal chemotherapy (EPIC; 68, 72, 0, 0 %) due to the high rate of intra-abdominal collections and following this, were able to demonstrate a significant decrease in the rate of intra-abdominal collections (10, 22, 2, 2 %). We also began to routinely insert chest tubes intraoperatively for those patients undergoing subdiaphragmatic stripping to avoid the development of postoperative pleural effusion requiring insertion of a chest tube at the bedside, that may explain the decrease in respiratory complications seen after the initial cohort (30, 14, 6, 20 %), which was limited to patients with extensive disease in the last cohort (median PCI 18 vs. 5 in the first cohort). A nonsignificant decrease in rate of acute renal impairment (29, 31, 16, 13 %) was seen after the second cohort and may reflect increased awareness of this complication and optimization of postoperative monitoring and fluid management in response to this.

Finally, a decreased rate of ICU admission (82, 76, 66, 46 %) may reflect increased surgeon experience resulting in decreased operation time and bleeding as well as anesthetist experience with intraoperative fluid resuscitation in this complex combined modality treatment of CRS and HIPEC.

Limitations

The main limitation of the study is that it is a single-institution cohort. The single-institution may limit applicability of the conclusions drawn from our experience to

other centers in which patient demographics or routine perioperative management may differ.

A second major limitation is the difference in accruement time between the two cohorts, particularly between the first and subsequent cohorts such that some of the differences seen may be ascertained to increasing surgeon experience with non-CRS/HIPEC cases, and general changes in perioperative management over the longer time period.

Conclusions

In our experience the learning curve for CRS/HIPEC consisted of two phases; the first 50 cases were adequate to achieve surgical technical familiarity with the procedure as demonstrated by decreased average operation time and a further 50 case for a significant reduction in the rate of serious morbidity. We propose that this represents an initial period of training in which technical competence, reflected by a decreased duration of the procedure is achieved followed by a subsequent period of training resulting in a significant gain in experience, leading to better selection and perioperative management of the patients, and less serious morbidity despite the increasingly complex cases being subjected to CRS/HIPEC.

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