Clinical Outcomes of Patients with Extensive Peritoneal Carcinomatosis Following Cytoreductive Surgery and Perioperative Intraperitoneal Chemotherapy

YEQIAN HUANG[1], NAYEF A. ALZAHRANI[1,2], TERENCE C. CHUA[3], YA RUTH HUO[1] and DAVID L. MORRIS[1]

[1]*Department of Surgery, University of New South Wales, St George Hospital, Sydney, NSW, Australia;*
[2]*College of Medicine, Imam Muhammad ibn Saud Islamic University, Riyadh, Kingdom of Saudi Arabia;*
[3]*Department of Gastrointestinal Surgery, Royal North Shore Hospital, St Leonards, NSW, Australia*

Abstract. *Aim: The aims of this study were to explore clinical outcomes and assess the learning curve for cytoreductive surgery and perioperative intraperitoneal chemotherapy (PIC) for patients with a high peritoneal cancer index (PCI). Patients and Methods: This was a retrospective study of patients with a PCI of 20 or more following CRS and PIC. Outcomes in five successive groups based on the operation date were analyzed. Results: Three hundred and five patients were included in the study. The median overall survival (OS) was 89.3 months (95% confidence interval=58.9-107.6 months). OS at 1, 3 and 5 years of our study cohort was 89.4%, 70.4% and 57.5%, respectively. In terms of the learning curve, the mean duration of operation and hospital mortality decreased (p<0.001 and p=0.006 respectively). A trend for decreasing intensive care unit stay (p=0.497), high dependency unit stay (p=0.042) and total hospital stay (p=0.202) were also recorded. Conclusion: A high PCI alone should not be a contraindication for cytoreductive surgery and PIC in specialized centres.*

Peritoneal carcinomatosis occurs in 10% to 30% of patients with gastrointestinal cancer at the time of their initial surgery or at a site of disease recurrence (1). In the past, peritoneal carcinomatosis was considered to be a terminal condition, associated with a median survival of about 6 months (2). In the 1990s, Sugarbaker introduced an innovative technique combining cytoreductive surgery (CRS) and perioperative intraperitoneal chemotherapy (PIC) (3). Following a long period of follow-up and acquisition of clinical data of treated patients, this combined approach is considered as a standard for selected patients with peritoneal carcinomatosis from colorectal carcinoma (CRC), low-grade appendiceal pseudomyxoma peritonei (PMP), diffuse malignant peritoneal mesothelioma (DMPM) and appendiceal carcinoma (4).

The peritoneal cancer index (PCI) grades the extent of peritoneal deposits within the abdominal cavity and comprises an aggregate score incorporating the distribution of the tumour deposits and size of the lesions. PCI is recognised to be an important prognostic factor in appendiceal cancer, CRC and DMPM (5-7). The leading surgeons from high-volume centres have worked towards to establishing criteria for CRS through a consensus statement published through the American Society of Peritoneal Surface Malignancies (8). The consensus statement recommended that patients should undergo a thorough diagnostic workup and the PCI be used as a scoring system to guide their further management. Patients without distant disease should be offered further assessment for completeness of cytoreduction. However, those with distant dissemination should be only offered systemic therapy (8). High-volume peritoneal disease does entail more major surgery, which is associated with greater morbidity, and some have considered this a relative contraindication (4).

With almost 20 years of experience in CRS, we have acquired a small sub-group of patients treated off protocol under the auspices of a multidisciplinary team consensus who have had extensive peritoneal carcinomatosis. The primary aim of this study was to explore the clinical outcomes of patients with peritoneal carcinomatosis and a high PCI (PCI ≥20). The secondary aim was to assess the learning curve for CRS and PIC for those patients.

Correspondence to: Dr. Nayef A. Alzahrani, Hepatobiliary and Surgical Oncology Unit, Department of Surgery, St George Hospital, University of New South Wales, Level 3 Pitney Building, Gray Street, Kogarah, Sydney, NSW 2217, Australia. Tel: +61 291132590, Fax: +61 291133997, e-mail: nayefalhariri@hotmail.com

Key Words: Peritoneal cancer index, cytoreductive surgery, perioperative intraperitoneal chemotherapy.

Patients and Methods

Setting. This was a retrospective study of prospectively collected data of patients with peritoneal carcinomatosis who underwent CRS and PIC by one surgical team at the St George Hospital in Sydney, Australia between Jan 1996 and Sep 2015.

Patients. Inclusion criteria included patients who had a good performance status (World Health Organisation Performance Status ≤2), and a histological diagnosis of peritoneal carcinomatosis from CRC, PMP, DMPM and appendiceal carcinoma. Patients with a PCI≥20 were included in this study. Exclusion criteria included histological diagnoses of peritoneal carcinomatosis from other primary types of cancer and debulking surgery. PCI was further divided into three groups for comparison (group A: 20-24; group B: 25-29; group C: ≥30).

In order to assess the learning curve, a total of 937 patients who underwent CRS and PIC at our Centre during the study period were divided into five groups according to the date of their operation: Group I: Jan 1996-Aug 2006; group II: Feb 2007-Feb 2010; group III: Feb 2010-Mar 2012; group IV: Nov 2012-Jun 2014; group V: Jul 2014-Sep 2015. The first four groups included 200 patients each; the fifth group include 137 patients. Patients with a PCI ≥20 were selected from each group for comparison in order to assess learning curves for CRS and PIC for patients with extensive peritoneal carcinomatosis. The learning curve assessment method was based on the learning curve at our Centre, which showed clinical outcomes improved after the first 200 cases (9).

Preoperative management. All patients underwent standard preoperative investigations which included physical examination; double contrast-enhanced computed tomography (CT) scans of the chest, abdomen and pelvis; and CT pontography of the liver or primovist (a hepatospecific paramagnetic gadolinium-based contrast agent) magnetic resonance imaging for PMP and CRC and appendiceal carcinoma. Positron-emission tomography was routinely performed in patients with CRC, appendiceal carcinoma and DMPM. Staging laparoscopy was considered in some patients with borderline PCI.

CRS. An initial assessment of the volume and extent of disease was recorded using PCI, as described by Jacquet and Sugarbaker (10). CRS was performed using Sugarbaker's technique (3). All sites and volumes of residual disease following CRS were recorded prospectively using completeness of cytoreductive (CC) score: CC0: no macroscopic residual cancer remaining; CC1: no nodule >2.5 mm in diameter remaining; CC2: nodules between 2.5 mm and 2.5 cm in diameter remaining; CC3: nodules >2.5 cm in diameter remaining (10). CC0 or CC1 was considered as complete cytoreduction, whereas CC2 and CC3 were considered as incomplete cytoreduction. In the early part of our series, PCI was limited to 20 in patients with CRC; this was lowered to 15 in 2012.

Hyperthermic intraperitoneal chemotherapy (HIPEC). After CRS, HIPEC was performed by installation of a heated chemoperfusate into the abdomen using the coliseum technique at approximately 42°C for 30 or 90 min during CRS, depending on tumour type. For PMP, mitomycin C (12.5 mg/m^2) was used for 90 min. For DMPM, cisplatin (100 mg/m^2) and mitomycin C (12.5 mg/m^2) in 1,000 ml normal saline were given over 90 min. For CRC and appendiceal carcinoma, 350 mg/m^2 oxaliplatin in 500 ml of 5% dextrose was given over 30 min.

Table I. *Background characteristics and perioperative outcomes of the whole study cohort*.

Total n=305 patients	
Gender, n (%)	
Male	152 (49.8)
Female	153 (50.2)
Mean age (SD), years	53.6 (13.1)
Mean PCI (SD)	30.1 (6.4)
HIPEC, n (%)	
Yes	302 (99.0)
No	3 (1.0)
EPIC, n (%)	
Yes	150 (49.2)
No	152 (49.8)
Unknown	3 (1.0)
Pathology, n (%)	
CRC	17 (5.6)
PMP	130(42.6)
DMPM	36 (11.8)
Appendiceal carcinoma	122 (40.0)
CC, n (%)	
0/1	294 (96.4)
2/3	10 (3.3)
Unknown	1 (0.3)
Transfusion units, mean (SD), n	8.7 (6.4)
Duration of surgery, mean (SD), hours	11.1 (2.9)
Hospital mortality, n (%)	7 (2.3)
Morbidity grade, n (%)	
0/1/2	128 (42.0)
3/4	174 (57.0)
Unknown	3 (1.0)
ICU stay, mean (SD), days	6.3 (11.9)
HDU stay, mean (SD), days	5.1 (4.9)
Total hospital stay, mean (SD), days	37.0 (30.3)

SD: Standard deviation; PCI: peritoneal cancer index; HIPEC: hyperthermic intraperitoneal chemotherapy; EPIC: early postoperative intraperitoneal chemotherapy; CRC: colorectal cancer; PMP: pseudomyxoma peritonei; DMPM: diffuse malignancy peritoneal mesothelioma; CC: completeness of cytoreduction score; ICU: intensive care unit; HDU: high dependency unit.

Early postoperative intraperitoneal chemotherapy (EPIC). EPIC was only offered to patients with PMP or lack of availability of HIPEC in emergency surgeries. The criteria for EPIC include absence of leakage of the intraperitoneal chemotherapy system, absence of major organ failure, and the ability of the patient to tolerate increased intra-abdominal fluid volume and intra-abdominal pressure with adequate urine output.

The sump drains were clamped during the EPIC infusion *via* the peritoneal catheter port. For patients with PMP, 650 mg/m^2 5-fluorouracil *i.p.* combined with 50 mEq sodium bicarbonate was administered from day 2 to 6. Normally EPIC was administered either in intensive care unit (ICU) or high dependency unit (HDU).

Table II. *Survival outcomes for the whole study cohort.*

Variable	N	Survival data				
		Median overall (95% CI), months	1-Year (%)	3-Year (%)	5-Year (%)	*p*-Value
PCI						0.153
20-24	62	96.0 (40.6-151.4)	93.5	72.5	64.6	
25-29	49	125.5 (61.0-190.1)	87.5	74.7	67.0	
≥30	121	58.5 (43.9073.1)	88.1	67.2	48.6	
CC score						0.849
0/1	228	83.3 (58.0-108.5)	89.3	70.6	57.7	
2/3	3	23.1 (-)	100	50.0	NR	
Morbidity						0.010*
0-2	95	125.5 (-)	93.5	76.4	68.8	
3&4	137	58.5 (47.2-69.8)	86.6	66.2	48.2	

CI: Confidence interval; PCI: peritoneal cancer index; CC: completeness of cytoreduction score.

Postoperative management. Perioperative complications in all patients were graded based on the Clavien-Dindo Classification (CDC) of surgical complications: Grade I: no treatment; grade II: medications only; grade III: surgical, endoscopic or radiological intervention; grade IV: life-threatening complications requiring ICU admission (11). Major morbidity was defined as CDC grade III or IV.

All of patients with aggressive tumour were then followed-up at 3-monthly intervals for the first 12 months and 6-month intervals thereafter until the last time of contact or death. Patients with PMP were seen at 3, 6 and 12 monthly thereafter. The follow-up review included clinical examination, measurement of relevant tumour markers, and assessment of abdominopelvic CT scans.

Statistical analysis. All statistical analyses were performed using SPSS for Windows version 22 (IBM Corporation, New York, NY, USA). Comparison of normally distributed variables was performed using analysis of variance (one way-ANOVA) test. Categorical variables were analysed using the Chi-square test or Fisher's exact test where appropriate. Hospital mortality was defined as any death that occurred during the same hospital admission for CRS. Median overall survival (OS) in months was calculated based on last time of contact or death. Survival analysis was performed using the Kaplan–Meier curves and log-rank test for comparison. Due to lack of survival data for group V at the time of analysis, this group was excluded from the survival analysis. A significant difference was defined as a *p*-value of less than 0.05.

Results

Descriptive characteristics and perioperative outcomes of the whole study cohort. Of a total of 937 patients, 305 patients had a PCI ≥20 and were included in the study. A total of 115 patients with peritoneal carcinomatosis from other primaries were excluded from the study. A total of 32 patients were excluded from the study because they did not receive PIC; another 488 patients with a PCI <20 were also excluded. Table I summarizes the background characteristics and perioperative outcomes of patients with a high PCI.

Survival outcomes. The median OS was 89.3 months [95% confidence interval (CI)=58.9-107.6]. OS at 1, 3 and 5 years of our study cohort was 89.4%, 70.4% and 57.5%, respectively. Table II summarizes survival outcomes of whole study cohort. There was no statistical difference in OS among PCI groups and by CC score (CC0/1 *vs*. CC2/3). However, patients who experienced major perioperative morbidity (*i.e*. CDC grade 3/4) had a significantly lower OS compared to those who did not experience any complication or only experienced non-major complications ($p=0.010$) (Table II).

Table III summarizes the survival outcomes by each histological diagnosis. In the CRC group, patients who experienced a major morbidity perioperatively had a significantly lower OS ($p=0.041$) (Table III and Figure 1). In the PMP group, patients with an extremely high PCI (*i.e*. ≥30) had a significantly lower OS than the other two PCI groups (Table III and Figure 2). There was no statistical difference in OS among PCI groups for patients with CRC, DMPM and appendiceal carcinoma. All patients with CRC, PMP or DMPM underwent complete cytoreduction. The difference in OS between major morbidity grade and non-major morbidity grade did not reach a statistical significance in PMP, DMPM and appendiceal carcinoma groups.

Assessment of learning curve. Table IV compares the background characteristics of patients and clinical outcomes according to the date of surgery. The mean duration of operation decreased significantly with increasing experience ($p<0.001$). There was also a statistical increase in the use of HIPEC, whilst EPIC was used less among the five groups ($p<0.001$ and $p<0.001$ respectively). The difference in the rate of major morbidity among the five groups did not achieve a statistical significance (Table IV). However, hospital mortality was significantly lower (0%) in the most

Table III. *Survival outcomes by diagnosis.*

Variable	CRC				PMP				DMPM				Appendiceal Carcinoma			
	N	Median (95% CI), months	5-Year (%)	*p*-Value	N	Median (95% CI), months	5-Year (%)	*p*-Value	N	Median (95% CI), months	5-Year (%)	*p*-Value	N	Median (95% CI), months	5-Year (%)	*p*-Value
Overall	17	18.3 (16.0-20.5)	17.3		105	103.6 (86.0-121.1)	78.4		25	43.2 (22.2-64.2)	43.8		85	58.4 (46.4-70.4)	45.2	
PCI				0.250				0.001				0.702				0.561
20-24	7	19.2 (0-40.1)	NR		29	NR	88.8		8	43.2 (-)	50.0		18	27.6 (0-65.3)	47.7	
25-29	4	3.9 (0-13.4)	25.0		28	125.5 (73.7-177.3)	96.3		3	23.4 (1.2-45.5)	NR		14	58.4 (23.6-93.3)	26.2	
≥30	6	10.9 (0-22.2)	0		48	83.3 (51.9-114.6)	60.0		14	44.3 (12.7-75.9)	41.3		53	58.5 (41.4-75.6)	46.6	
CC score				-				-				-				0.910
0/1	17	18.3 (16.0-20.5)	17.3		104	103.6 (86.0-121.1)	78.4		25	43.2 (22.2-64.2)	43.8		82	58.4 (46.4-70.4)	45.4	
2/3	0	-	-		0	-	-		0	-	-		3	23.1 (-)	NR	
Morbidity				0.041				0.303				0.113				0.235
0-2	8	18.3 (0-44.1)	33.3		47	125.5 (-)	84.4		12	NR	58.9		28	NR	58.9	
3/4	9	10.9 (4.9-17.0)	0		58	103.6 (87.4-119.7)	72.6		13	43.2 (0-64.2)	32.3		57	57.1 (35.8-78.5)	36.3	

CRC: Colorectal cancer; PMP: pseudomyxoma peritonei; DMPM: diffuse malignancy peritoneal mesothelioma; CI: confidence interval; PCI: peritoneal cancer index; CC: completeness of cytoreduction; NR: not reached.

recent two groups (*i.e.* groups IV and V) (p=0.006). The mean HDU stay in group V was almost half of that of group I (3.6 *vs.* 6.9 days). The difference in the mean ICU stay and total hospital stay among the five groups did not reach a statistical difference, however, a trend for decreasing mean ICU and total hospital stay were also observed with the increasing experience (Table IV).

Table V summarises the survival outcomes of the first four groups (*i.e.* groups I to IV). The median OS of group III was not reached yet but it was shown to be greater than 66.2 months. Thus the median OS, and 1-, 3-and 5-year OS in group II and III were much higher than those of group I, although these differences did not achieve statistical significance (p=0.344) (Table V and Figure 3).

Discussion

The combination of CRS and PIC has provided optimal survival outcomes for patients with peritoneal carcinomatosis. CRS and PIC complement each other, whereby CRS aims to remove macroscopic disease and PIC is used to attempt to eradicate any residual microscopic tumour (12). Multiple prognostic factors for peritoneal carcinomatosis have been extensively explored in the past two decades (13-17). One of the important prognostic factors is PCI. It allows the estimation of completeness of cytoreduction and thus survival at the time of surgical exploration of the abdomen and pelvis (13).

The most recent systemic review by Chua *et al.* (2009) assessed morbidity and mortality outcomes of CRS and HIPEC from all tertiary Institutions located in the cities of Amsterdam, Lyon, Milan, Pittsburgh, Shizuoka, Sydney, Uppsala, Washington, Winston-Salem and Villejuif performing this procedure (4). They showed a morbidity rate ranging from 12% to 52% and a mortality rate ranging 0.9% and 5.8% across tertiary institutions (4). The rate of major morbidity in our study cohort was slightly higher than the range given in this review. However, the mortality rate for patients with a high volume of disease was good (2.3%) and consistent with the mortality rate found in the review. The review also showed the mean length of ICU stay ranged from 1 to 5 days (4). Our finding in this study cohort is slightly higher than this range. This could be attributed to the fact that patients in our study cohort had more extensive peritoneal disease, as demonstrated by a high PCI. However, our mean total hospital stay is within the range found reported in this review (7-48 days).

Our survival analyses of the whole study cohort suggest that complications affect negatively survival of patients with CRC. This is consistent with the previous study by Ung *et al.* They analyzed clinical outcomes of 211 patients with peritoneal carcinomatosis from lower gastrointestinal tract origin. They also found major morbidity as a prognostic

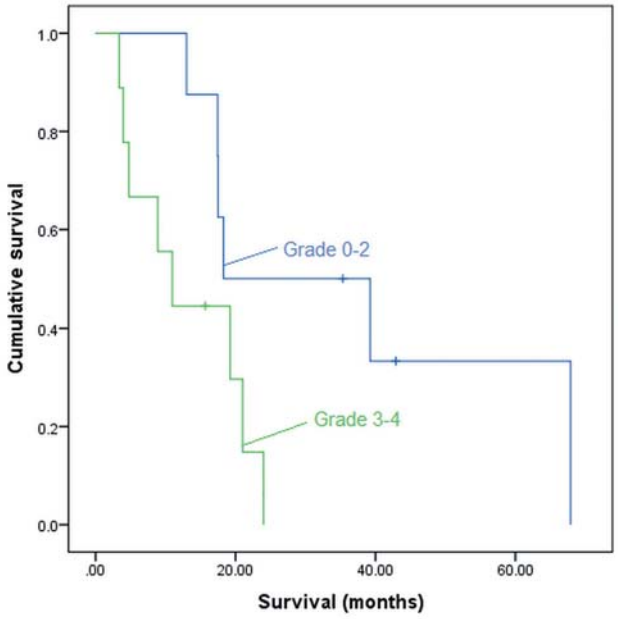

Figure 1. *Kaplan–Meier curve of survival for patients according to morbidity grade (i.e. grade 0/1/2 vs. 3/4) (p=0.041).*

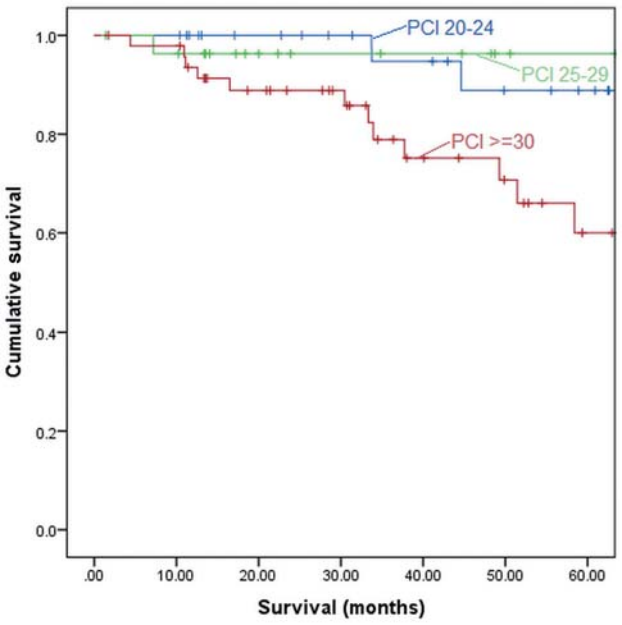

Figure 2. *Kaplan–Meier curve of survival for patients with pseudomyxoma peritonei according to peritoneal cancer index group (p=0.001).*

factor for survival of patients with CRC (18). As did a multicentric study by Chua *et al*. analyzing clinical outcomes of 2,298 patients from 16 specialised centres who underwent CRS and HIPEC for peritoneal carcinomatosis from appendiceal origin (6). They found major postoperative complications to be a negative prognostic factor associated with OS ($p<0.001$).

Importantly, our findings suggest that patients with a high tumor volume for certain diagnoses could still achieve good outcomes. Although a high PCI is associated with poorer survival in patients with PMP, a median survival of 83.3 months, with a 5-year survival of 60% for patients with a PCI≥30 is still encouraging. Similarly, for patients with appendiceal carcinoma, the 5-year survival rate of 46.6% may still be achieved in the context of a high volume of disease. Our results were slightly poorer than the findings in the study by Chua *et al*. (6). They found an encouraging 5-year survival rate of 73% and 56% in their patients with high-volume PMP and appendiceal carcinoma (*i.e*. PCI 31-39), respectively. Such differences in 5-year survival rates between our study and theirs could be due to the learning curves associated with this procedure and variations in protocols in different specialised centres.

A large multi-institutional study by Yan *et al*. analyzed 405 patients with diffuse malignant peritoneal mesothelioma (7). The 5-year OS for our DMPM cohort is slightly lower than the finding in their study cohort (43.2% *vs*. 47%). However, they also included patients with a low PCI (*i.e*. <20) in their

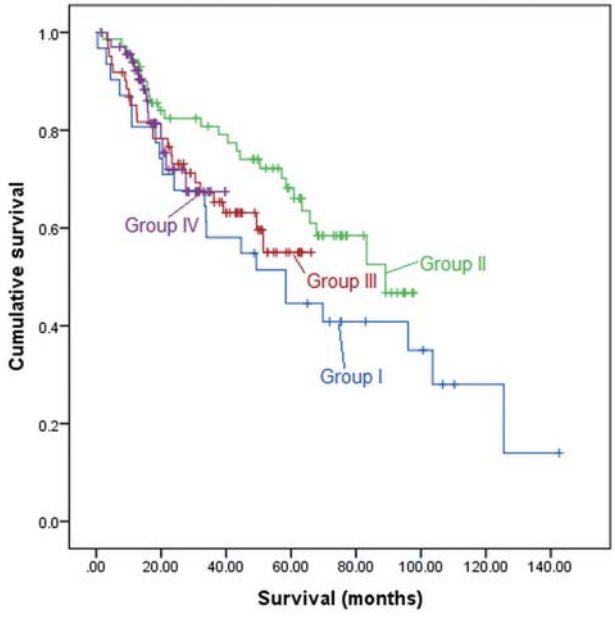

Figure 3. *Kaplan–Meier curves for patients with high peritoneal cancer index according to date of operation (p=0.344) (group I: Jan 1996-Aug 2006; group II: Feb 2007-Feb 2010; group III: Feb 2010-Mar 2012; group IV: Nov 2012-Jun 2014; group V: Jul 2014-Sep 2015).*

study. It is also important to emphasise that we included multicystic mesothelioma in our study because malignant transformation of benign multicystic mesothelioma has been

Table IV. *Comparison of background characteristics and clinical outcomes according to operation date (group I: Jan 1996-Aug 2006; group II: Feb 2007-Feb 2010; group III: Feb 2010-Mar 2012; group IV: Nov 2012-Jun 2014; group V: Jul 2014-Sep 2015).*

	Group I	Group II	Group III	Group IV	Group V	*p*-Value
Total n	38 (12.5)	80 (26.2)	74 (24.3)	72 (23.6)	41 (13.4)	
Age (years)	52.7 (12.5)	51.7 (11.2)	54.7 (12.8)	54.7 (14.4)	54.6 (15.0)	0.534
Diagnosis, n (%)						<0.001
CRC	3 (7.9)	4 (5.0)	7 (9.5)	3 (4.2)	0 (0)	
PMP	27 (71.1)	42 (52.5)	26 (35.1)	27 (37.5)	8 (19.5)	
DMPM	1 (2.6)	12 (15.0)	10 (13.5)	6 (8.3)	7 (17.1)	
Appendiceal carcinoma	7 (18.4)	22 (27.5)	31 (41.9)	36 (50.0)	26 (63.4)	
PCI mean (SD)	27.8 (6.3)	30.2 (6.3)	30.7 (6.6)	30.4 (6.7)	30.6 (6.0)	0.207
CC score						0.613
0/1	36 (94.7)	78 (98.7)	70 (94.6)	70 (97.2)	40 (97.6)	
2/3	2 (5.3)	1 (1.3)	4 (5.4)	2 (2.8)	1 (2.4)	
Duration of surgery, mean (SD), hours	13.5 (4.6)	10.3 (2.3)	11.3 (2.1)	11.0 (2.6)	10.1 (2.0)	<0.001
HIPEC, n (%)	35 (92.1)	80 (100)	74 (100)	72 (100)	41 (100)	<0.001
EPIC, n (%)	24 (63.2)	56 (70.9)	30 (40.5)	30 (41.7)	12 (30.8)	<0.001
Transfusion units mean (SD)	11.3 (9.3)	8.7 (7.4)	9.2 (8.9)	8.0 (9.3)	6.7 (6.1)	0.155
Hospital mortality, n (%)	4 (10.5)	1 (1.3)	2 (2.7)	0 (0)	0 (0)	0.006
Major morbidity, n (%)	24 (63.2)	43 (43.8)	39 (52.7)	46 (63.9)	22 (57.9)	0.581
ICU stay, mean (SD), days	7.7 (13.6)	7.3 (12.5)	4.4 (6.5)	7.0 (16.0)	5.6 (7.7)	0.497
HDU stay, mean (SD), days	6.9 (5.5)	4.8 (4.6)	4.7 (4.6)	5.5 (5.7)	3.6 (3.4)	0.042
Total hospital stay, mean (SD), days	47.6 (44.1)	37.7 (29.5)	34.4 (27.3)	34.5 (25.9)	34.6 (27.2)	0.202

CI: Confidence interval; CRC: colorectal cancer; PMP: pseudomyxoma peritonei; DMPM: diffuse malignancy peritoneal mesothelioma; PCI: peritoneal cancer index; SD: standard deviation; CC: completeness of cytoreduction score; HIPEC: hyperthermic intraperitoneal chemotherapy; EPIC: early postoperative intraperitoneal chemotherapy; ICU: intensive care unit; HDU: high dependency unit.

Table V. *Survival outcomes according to operation date (group I: Jan 1996-Aug 2006; group II: Feb 2007-Feb 2010; group III: Feb 2010-Mar 2012; group IV: Nov 2012-Jun 2014; group V: Jul 2014-Sep 2015).*

	Group I	Group II	Group III	Group IV	*p*-Value
Total=233					
No of patients n (%)	31 (13.3)	72 (30.9)	61 (26.2)	69 (29.6)	
Overall survival					
Median (95% CI), months	58.4 (26.4-90.5)	89.1 (-)	NR	NR	0.344
1-Year, %	80.6	94.4	85.1	92.2	
3-Year, %	58.1	80.8	67.3	67.4	
5-Year, %	44.6	68.2	55.0	NR	

CI: Confidence interval; NR: not reached.

reported (14). One of our patients had malignant transformation from benign cystic mesothelioma to epithelioid and then subsequently to sarcomatoid type. Yan *et al*. did not include multicystic mesothelioma in their study. Although it is difficult to compare our findings of OS of mesothelioma with the literature, a 5-year survival rate of 43.2% with a median OS of 43.2 (95% CI=22.2-64.2) months is still promising.

Our findings of a poor survival outcome for patients with high volume of peritoneal carcinomatosis from colorectal origin are in accordance with the consensus in the literature that a PCI of greater than 20 should be considered as a relative contraindication for surgery (5, 17, 19). A multicentric study by Elias *et al*. reviewed clinical outcomes of 523 patients with peritoneal carcinomatosis from colorectal origin and showed a 5-year survival rate of less than 10% in patients with a PCI >20. Our result is slightly higher, 17.3% 5-year OS is perhaps quite surprising. Whether to offer CRS and PIC to patients with a high-volume of peritoneal carcinomatosis of colorectal origin should be carefully considered.

In the literature, a learning curve associated with CRS and PIC has been well-established (12, 20-22). Our results also

demonstrate a learning curve for this combined procedure for patients with high volume of peritoneal carcinomatosis. A trend for decreasing duration of surgery with increasing experience in CRS for patients with a high volume of disease and an important fall in was shown in our study mortality. The significant differences in the use of HIPEC and EPIC can be explained by the fact that we used EPIC more frequently in the early period due to limited evidence for EPIC use. However, with increasing evidence and our experience, we have improved our protocols over the years.

Most importantly, it was encouraging to observe a reduction in hospital mortality to 0% in our last two study cohorts of 113 patients with PCI ≥20 with more experience in CRS. In addition, there was a trend for a decrease in the mean HDU stay and total hospital stay over the past two decades (from 6.9 to 3.6 days and from 46.6 to 34.6 days, respectively). Although the difference of survival outcomes among the four groups did not reach statistical significance, the 5-year survival rate and median OS were improved in recent groups (group II: 68.2%, 89.1 months; group III: 55.0%, >66.2 months) compared to those who underwent CRS and PIC in the early period (group I: 44.6%, 58.4 months). It is also important to put these outcomes into perspective. It is worth noting that 71.1% of patients in group I were diagnosed with PMP compared to 52.5% in group 2 and 35.1% in group 3. The survival outcomes in group I may have been skewed by the large proportion of patients with PMP. Thus the actual survival differences among groups I, II and III may have been even larger. Similarly, relatively better outcomes for group II compared to group II could be attributed to the different proportions of primary tumor sites. More patients in group III had appendiceal carcinoma and CRC (41.9% *vs*. 27.5% and 9.5% *vs*. 5.0%, respectively).

There exist several limitations in this study that need to be considered when interpreting our results. Firstly, the retrospective nature of this study undoubtedly led to selection bias. Our study is also limited by the small sample size of the DMPM group. Another limitation is that there was still an uncertainty regarding the exact reasons for improved outcomes for patients with extensive peritoneal carcinomatosis. Furthermore, suitability of patients for CRS and PIC are strictly assessed during our weekly multidisciplinary team meeting. This combined approach requires a high level of training and expertise. Centralization of experience in anaesthetic care, medical oncology and nursing in order to provide better perioperative care is often necessary (12, 23).

Conclusion

Our study found encouraging survival results for patients with a high PCI, and an optimal perioperative mortality of 0% in recent years at our Centre. Thus patients with extensive peritoneal disease may still achieve a good survival outcome. In addition, our results also demonstrated a learning curve associated with CRS and PIC for extensive peritoneal disease. Therefore, a high PCI alone should not be a contraindication for CRS and PIC at specialised centres. Patients with extensive peritoneal carcinomatosis should be referred to a specialized centre for a thorough assessment to determine their suitability for CRS and PIC.

Acknowledgements

We express our special thanks to Jing Zhao, MD, for maintaining the peritonectomy database

References

1 Harmon RL and Sugarbaker PH: Prognostic indicators in peritoneal carcinomatosis from gastrointestinal cancer. Int Semin Surg Oncol *2*: 3, 2005.

2 Glehen O, Mohamed F and Gilly FN: Peritoneal carcinomatosis from digestive tract cancer: new management by cytoreductive surgery and intraperitoneal chemohyperthermia. Lancet Oncol *5(4)*: 219-228, 2004.

3 Sugarbaker PH: Peritonectomy procedures. Ann Surg *221(1)*: 29-42, 1995.

4 Chua TC, Yan TD, Saxena A and Morris DL: Should the treatment of peritoneal carcinomatosis by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy still be regarded as a highly morbid procedure?: a systematic review of morbidity and mortality. Ann Surg *249(6)*: 900-907, 2009.

5 Elias D, Gilly F, Boutitie F, Quenet F, Bereder J-M, Mansvelt B, Lorimier G, Dubè P and Glehen O: Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: retrospective analysis of 523 patients from a multicentric French study. J Clin Oncol *28(1)*: 63-68, 2010.

6 Chua TC, Moran BJ, Sugarbaker PH, Levine EA, Glehen O, Gilly FN, Baratti D, Deraco M, Elias D and Sardi A: Early-and long-term outcome data of patients with pseudomyxoma peritonei from appendiceal origin treated by a strategy of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. J Clin Oncol *30(20)*: 2449-2456, 2012.

7 Yan TD, Deraco M, Baratti D, Kusamura S, Elias D, Glehen O, Gilly FN, Levine EA, Shen P and Mohamed F: Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for malignant peritoneal mesothelioma: multi-institutional experience. J Clin Oncol *27(36)*: 6237-6242, 2009.

8 Esquivel J, Sticca R, Sugarbaker P, Levine E, Yan T, Alexander R, Baratti D, Bartlett D, Barone R and Barrios P: Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in the management of peritoneal surface malignancies of colonic origin: a consensus statement. Ann Surg Oncol *14(1)*: 128-133, 2007.

9 Huang Y, Alzahrani NA, Liauw W and Morris DL: Learning curve for cytoreductive surgery and perioperative intraperitoneal chemotherapy for peritoneal carcinomatosis. ANZ J Surg 2015.

10 Jacquet P and Sugarbaker PH: Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. Peritoneal carcinomatosis: principles of management; Springer 359-374, 1996.

11 Dindo D, Demartines N and Clavien P-A: Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg *240(2)*: 205, 2004.
12 Moradi BN and Esquivel J: Learning curve in cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. J Surg Oncol *100(4)*: 293-296, 2009.
13 Harmon RL and Sugarbaker PH, editors. Prognostic indicators in peritoneal carcinomatosis from gastrointestinal cancer. Int Semin Surg Onco; BioMed Central Ltd., 2005.
14 Glehen O, Kwiatkowski F, Sugarbaker P, Elias D, Levine E, De Simone M, Barone R, Yonemura Y, Cavaliere F and Quenet F: Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer: a multi-institutional study. J Clin Oncol *22(16)*: 3284-3292, 2004.
15 Sadeghi B, Arvieux C, Glehen O, Beaujard AC, Rivoire M, Baulieux J, Fontaumard E, Brachet A, Caillot JL and Faure JL: Peritoneal carcinomatosis from non-gynecologic malignancies. Cancer *88(2)*: 358-363, 2000.
16 Glehen O, Mithieux F, Osinsky D, Beaujard A, Freyer G, Guertsch P, Francois Y, Peyrat P, Panteix G and Vignal J: Surgery combined with peritonectomy procedures and intraperitoneal chemohyperthermia in abdominal cancers with peritoneal carcinomatosis: a phase II study. J Clin Oncol *21(5)*: 799-806, 2003.
17 Cashin PH, Graf W, Nygren P and Mahteme H: Cytoreductive surgery and intraperitoneal chemotherapy for colorectal peritoneal carcinomatosis: prognosis and treatment of recurrences in a cohort study. Eur J Surg Oncol *38(6)*: 509-515, 2012.
18 Ung L, Chua TC and Morris DL: Peritoneal metastases of lower gastrointestinal tract origin: a comparative study of patient outcomes following cytoreduction and intraperitoneal chemotherapy. J Cancer Res Clin Oncol *139(11)*: 1899-1908, 2013.
19 da Silva RG and Sugarbaker PH: Analysis of prognostic factors in seventy patients having a complete cytoreduction plus perioperative intraperitoneal chemotherapy for carcinomatosis from colorectal cancer. J Am Coll Surg *203(6)*: 878-886, 2006.
20 Smeenk R, Verwaal V and Zoetmulder F: Learning curve of combined modality treatment in peritoneal surface disease. Brit J Surg *94(11)*: 1408-1414, 2007.
21 Elias D, Gilly F, Quenet F, Bereder J, Sidéris L, Mansvelt B, Lorimier G and Glehen O: Pseudomyxoma peritonei: a French multicentric study of 301 patients treated with cytoreductive surgery and intraperitoneal chemotherapy. Eur J Surg Oncol *36(5)*: 456-462, 2010.
22 Kusamura S, Baratti D, Virzì S, Bonomi S, Iusco DR, Grassi A, Hutanu I and Deraco M: Learning curve for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in peritoneal surface malignancies: analysis of two centres. J Surg Oncol *107(4)*: 312-319, 2013.
23 Yan TD, Links M, Fransi S, Jacques T, Black D, Saunders V and Morris DL: Learning curve for cytoreductive surgery and perioperative intraperitoneal chemotherapy for peritoneal surface malignancy – a journey to becoming a Nationally Funded Peritonectomy Center. Ann Surg Oncol *14(8)*: 2270-2280, 2007.

Received December 21, 2015
Revised January 28, 2016
Accepted February 1, 2016