

ORIGINAL ARTICLE

Outcomes of cytoreductive surgery and HIPEC for pseudomyxoma peritonei of appendiceal origin from two Indian centers: A preliminary five-year experience

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Summary

Purpose: To evaluate the short-term outcomes of patients of pseudomyxoma peritonei (PMP) of appendiceal origin treated with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) at two tertiary Indian centers.

Methods: Data was prospectively collected from January 2011 to January 2016. Palliative procedures were excluded. HIPEC was performed by the coliseum technique using either a mitomycin or oxaliplatin-based regimen.

Results: 77 procedures were performed on 71 patients. The average time interval between diagnosis and CRS was 15.3 months. Of the tumors, 22.1% were high grade, 77.9% low grade and 24.6% intermediate grade. The median peritoneal carcinomatosis index (PCI) was 26 (>25 in 70.1% and >30 in 38.9%). Completeness of cytoreduction score (CCS)-1 was achieved in 75.3% (CC-0 in 42.9%). The mean number of bowel anastomoses was 1.1 and the mean number of or-

gans resected per patient was 3.3. Of the 77 patients, 71% had resection of 3 or more organs and 50.6% had resection of 4 or more organs. Grade 3-4 complications occurred in 42.9% of the patients and the perioperative mortality was 5.2%. The projected 5-year overall survival (OS) was 62.3% and the 3-year disease-free survival (DFS) was 71% at a median follow up of 13 months.

Conclusion: CRS and HIPEC can be used to treat PMP with an acceptable morbidity and mortality in Indian patients. Lack of early referrals leads to a large portion of patients presenting with extensive disease and an inferior survival which should improve with increasing awareness about the procedure and its results.

Key words: appendiceal tumor, cytoreductive surgery, HIPEC, Indian experience, pseudomyxoma peritonei

Introduction

With the implementation of CRS and HIPEC for treating PMP of appendiceal origin, experienced centers have reported a median survival of 196 months (16.3 years) and a median progression-free survival (PFS) rate of 98 months (8.2 years) [1-3]. However, conferring such treatment has been associated with a learning curve for the surgeon as well as the institute that is known to peak at around 130 cases [4,5]. Appropriate pa-

tient selection is as important as acquiring the technical skills required to perform the procedure and has significantly contributed to the improvement in results both in terms of morbidity and mortality as well as survival over the years [5,6]. In India, CRS and HIPEC have been used only for the last 5 years [7].

This manuscript presents a prospective study of the short term outcomes of patients of PMP of

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appendiceal origin treated with CRS and HIPEC at two tertiary Indian centers in the first 5 years of their experience.

Methods

Data was prospectively collected from January 2011 to January 2016 by the two surgeons performing the procedure which was also the beginning of our experience with CRS and HIPEC. Patients with PMP of appendiceal origin were included. Patients in whom a palliative procedure was planned (N=12) or were lost to follow up (N=2) were excluded. Tumors were classified according to the WHO classification into low grade PMP and high grade PMP (including patients with any percentage of signet ring cells) [8]. We defined a subgroup of patients with extensive disease presenting with 'obstructive symptoms' i.e. those who had a reduced intake with or without radiological features of subacute or acute intestinal obstruction, some having an ECOG performance status (PS) of 2-3. The preoperative work up included a CT scan, a review of the biopsy and tumor markers CEA and CA 19-9 apart from other routine investigations. Peritonectomy procedures and visceral resections were performed as per the principles and techniques described elsewhere [9,10]. HIPEC was performed by the coliseum technique maintaining an intra-abdominal temperature of 42-43 °C using either the oxaliplatin-based regimen (oxaliplatin 460mg/m²) described by Elias et al. or the mitomycin and adriamycin (15mg/m² each) combination regimen from the Washington Cancer Center [11,12]. Bidirectional chemotherapy was given with both regimens comprising of intravenous 5-fluorouracil 400mg/m² and leucovorin 25mg/m². Complications were graded according to the CTCAE version 4 [13]. Patients were followed up till death from any cause. Time to recurrence was calculated from the date of surgery. The prior surgical score (PSS), PCI, tumor grade and CCR were recorded [14].

Statistics

The data was analyzed using SPSS version 20.0 and p<0.05 was considered significant. Kaplan-Meier survival curves, Cox proportional hazards regression models, Pearson chi square test, Fischer exact test and Student's t-test were used for calculating the survival data and for the univariate and multivariate analysis of various prognostic variables impacting survival and grade 3-4 complications.

Results

From January 2011 to January 2016, 77 procedures were performed in 71 patients. The mean time interval between diagnosis and CRS was 15.3 months and >12 months in 32.4% of the patients. The patient characteristics are listed in Ta-

ble 1. Low grade PMP had 77.9% of the patients, 24.6% had intermediate grade, 22.1% had high grade PMP, and 9.1% had signet ring cells. Of the patients, 22.1% had obstructive symptoms and 15.7% had ECOG PS 2-3. Patients with obstructive symptoms were taken up for the combined procedure if they had no more than 2 levels of

Table 1. Patient and therapy characteristics

Characteristics	N (%)
Year of operation	
2011	5 (6.4)
2012	6 (7.7)
2013	11 (14.2)
2014	17 (22.0)
2015	33 (42.8)
2016	5 (6.4)
Time interval between diagnosis and definitive surgery	
<3 months	27 (35.0)
3 months-1 year	25 (32.4)
1-2 years	8 (10.3)
2-5 years	14 (18.0)
>5 years	3 (3.8)
Sex	
Male	32 (41.6)
Female	45 (58.4)
Primary site	
Appendix	77 (100.0)
Ronnet's classification	
DPAM	41 (53.2)
IG	19 (24.6)
PMCA	17 (22.1)
Grade (WHO)	
Low	60 (77.9)
High	17 (22.1)
Signet ring cells	
Absent	70 (90.9)
Present	7 (9.1)
Prior chemotherapy	
Not administered	42 (54.5)
Administered	35 (45.5)
Prior surgery	
Not performed	41 (53.2)
Performed	36 (46.8)
Prior surgical score	
0 (Biopsy alone)	35 (45.4)
1 (Exploration and surgery in 1 region)	10 (12.9)
2 (Exploration and surgery in 2-5 regions)	9 (11.6)
3 (Exploration and surgery in >5 regions)	23 (29.8)
ECOG performance status	
0	24 (31.2)
1	42 (54.5)
2	6 (7.8)
3	5 (6.5)
Obstructive symptoms	
No	60 (77.9)
Yes	17 (22.1)

ECOG: Eastern Cooperative Oncology Group

obstruction, absence of confluent disease on the jejunum and the mesentery, the nutritional status was preserved (albumin >3g/dl) and a CC-0/1 resection was deemed probable by the operating surgeon (Table 1).

Operative findings

The mean PCI was 26 and the median was 28 (range 3-39). Of the patients, 70.12% had a PCI>25 and 38.9% PCI>30. A CC0/1 score was achieved in 75.3% out of which 42.9% had no residual tumor i.e. CC-0. The mean number of bowel anastomoses was 1.1 and the mean number of organs resected per patient was 3.3. Of the patients, 71% had resection of 3 or more organs and 50.6% had resection of 4 or more organs. These findings have been further elaborated in Table 2.

The median intensive care unit (ICU) stay was 6 days (range 1-87) and the median hospital stay was 17 days (range 7-127). Patients with CC-0/1 resections were not offered adjuvant chemotherapy irrespective of the grade, while those with CC-2/3 resections were administered chemotherapy when they became symptomatic.

Grade 3-4 complications

Grade 3-4 complications were observed in 42.9% of the patients and the perioperative mortality was 5.2% (4 patients). The cause of perioperative mortality was bowel perforation leading to sepsis in two patients and neutropenic sepsis associated with leak from bowel anastomosis in the two others. Leak from bowel anastomosis occurred in three patients and an absolute neutrophil count of <1500/mm³ was observed in three patients. The incidence of complications increased with the increase in PCI (p=0.05). The presence of obstructive symptoms, time since diagnosis, prior surgery, prior chemotherapy and the drug regimen used for HIPEC did not have a significant impact on the grade 3-4 complications (Table 2).

Survival

The median follow-up was 13 months (range 3-58) and the mean was 15.4 months. At the last follow up 64.93% were alive and disease-free, 18.1% were alive with disease, 10.3% had died due to disease progression and 6.49% from other causes. The median DFS and OS had not been reached. The mean DFS was 33.29 months (95% CI 27.16-39.42 months, standard error 3.128) and the mean OS was 43.56 months (95% CI 36.64-50.48 months, standard error 3.529). The projected

5-year OS was 62.3%. The cumulative 3-year DFS was 71%.

Factors affecting survival

Factors like age, sex, prior chemotherapy, prior surgery or prior surgical score had no impact on the DFS and OS. Patients with low grade tumors (p≤0.01), a low PCI (p≤0.01), CC-0/1 score (p≤0.01) and those without obstructive symptoms (p≤0.01) experienced a better DFS, but the only independent predictor was the CC score of 0/1 (p=0.03). The absence of grade 3-4 complications (p≤0.01), low PCI (p=0.05) and CC score of 0/1 (p=0.04) were

Table 2. Operative findings, complications and follow up

Findings	N (%)
PCI	
0-10	9 (11.6)
11-20	8 (10.3)
21-30	30 (38.9)
31-39	30 (38.9)
CC score	
CC-0	33 (42.9)
CC-1	25 (32.5)
CC-2	13 (16.9)
CC-3	6 (7.8)
HIPEC	
Performed	62 (80.5)
Not performed	15 (19.5)
Drugs used	
Mitomycin + adriamycin	38 (49.3)
Oxaliplatin	24 (31.1)
None	15 (19.4)
Grade 3-4 complications	
No	44 (57.1)
Yes	33 (42.9)
Grade 3-4 morbidity according to the organ system affected	
GI	8 (10.4)
Pulmonary	5 (6.5)
Hematologic	10 (13.0)
Cardiovascular	5 (6.5)
Others	5 (6.5)
30 day mortality	
No	73 (94.8)
Yes	4 (5.2)
Return to the operating room	
Total	16 (20.7)
Intraabdominal abscess	2 (2.5)
Bowel perforation	3 (3.8)
Wound dehiscence	2 (2.5)
Intraperitoneal haemorrhage	5 (6.4)
Anastamotic leak	3 (3.8)
Bladder perforation	1 (1.2)
Status	
Alive and disease free	50 (64.9)
Alive with disease	14 (18.1)
Dead due to tumor	8 (10.3)
Dead due to other causes	5 (6.4)

For abbreviations see text

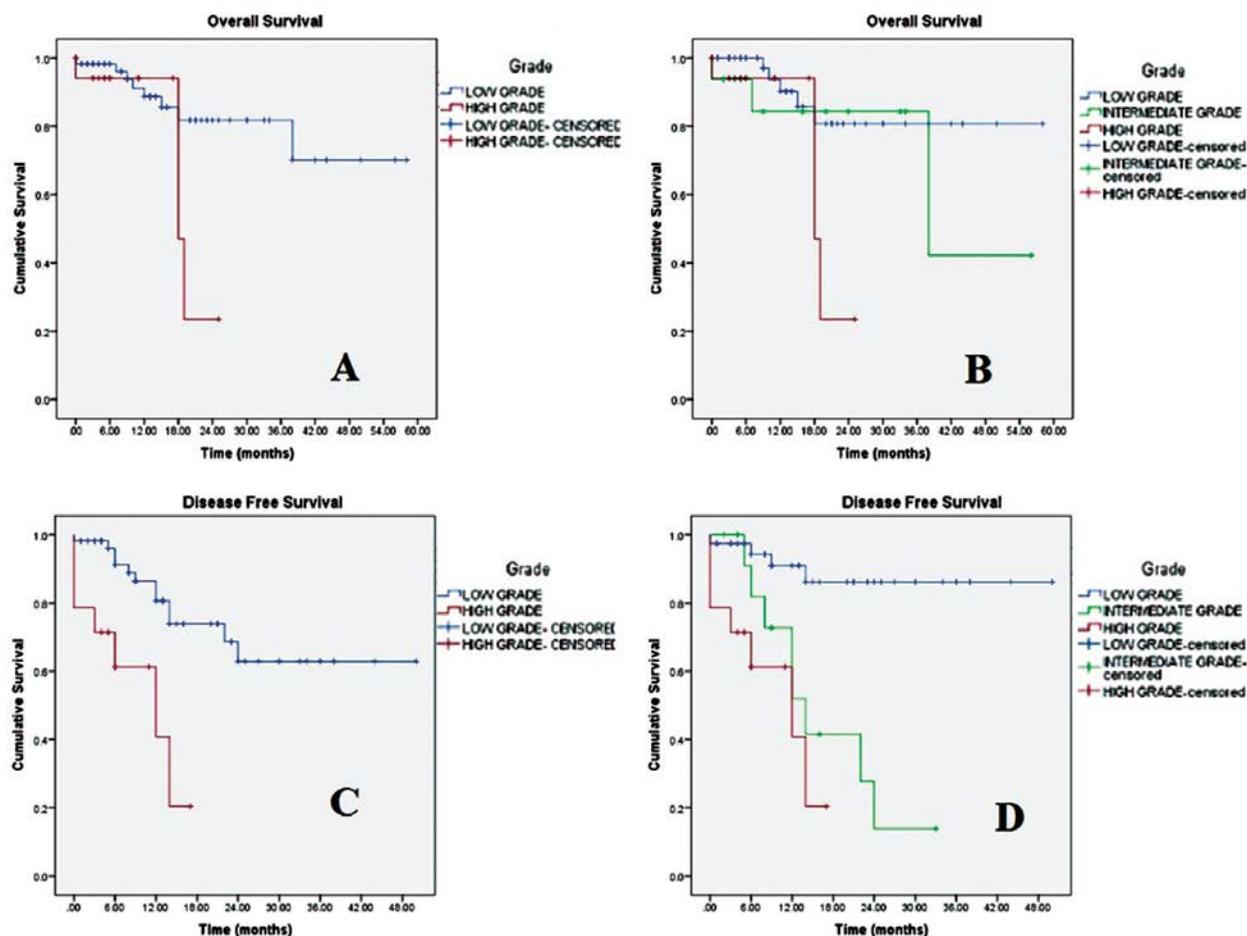


Figure 1. Impact of tumor grade on DFS and OS: **A:** OS in patients with low grade and high grade tumors ($p=0.08$); **B:** OS in low, intermediate and high grade tumors ($p=0.15$); **C:** DFS in patients with low and high grade tumors ($p<0.01$); **D:** DFS in patients with low, intermediate and high grade tumors ($p<0.01$).

the factors favorably affecting OS, the only independent predictor being the absence of grade 3-4 complications ($p\leq 0.01$). When analyzed separately from the low grade tumors, the intermediate grade tumors had a similar DFS as the high grade tumors, but there was no difference in the OS between the 3 groups (Figure 1).

Staged resections

Four patients were planned for a staged second resection due to either CC-2/3 resection or intraoperative hemodynamic instability following a CC-0/1. The second procedure was performed after 6-10 months. All patients, including patients with a previous CC-0/1, had evidence of residual/recurrent disease. A CC-0 resection followed by HIPEC was possible in 3 out of 4 patients. In all the patients the PCI in the second surgery was lower than that during the first procedure (Table 3).

Reiterative CRS and HIPEC

There were three patients who had reiterative

CRS and HIPEC. Two patients were operated by the same surgeon who performed the 1st procedure, one patient had a CRS and HIPEC at a different center and presented with early recurrence. The details of these 3 patients are displayed in Table 3. Incidentally, none of these patients had grade 3-4 complications.

Discussion

This manuscript reports the short-term results of CRS and HIPEC for PMP of appendiceal origin from two tertiary Indian centers in the first 5 years of their experience. In general, there is a lack of awareness about the availability and feasibility of the combined modality treatment, both in terms of tolerance and cost. Patients with PMP are usually treated with systemic chemotherapy or given only supportive treatment including those with limited disease and a pathological diagnosis of adenomucinosis. In this study, the median time lag between diagnosis and CRS was 15.3 months (range 1-107), which is twice as high

Table 3. Staged resections and reiterative procedures

No.	Grade	No. of prior operations	PCI	CC score	HIPEC (drug used)	Time to second operation (months)	PCI	CC score	HIPEC	Current status	DFS (months)
<i>Staged resections</i>											
1	High	0	31	3	-	10	26	3	-	Alive with disease	0
2	Low	8	28	2	-	10	6	0	Oxaliplatin	Alive, disease free	15
3	Low	0	31	1	-	6	12	0	Oxaliplatin	Dead, perioperative mortality	0
4	Intermediate	0	33	2	-	13	8	0	Mitomycin+ adriamycin	Alive, disease free	3
<i>Reiterative CRS and HIPEC</i>											
1	Low	1	35	2	Oxaliplatin	55	18	0	Mitomycin+ adriamycin	Alive, disease free	4
2	Low	3	29	1	Oxaliplatin	24	32	1	Oxaliplatin	Alive, disease free	21
3	Low	3	ND	3	Cisplatin	10	34	1	Mitomycin+ adriamycin	Alive, disease free	3

ND: Not documented. For abbreviations see text

the duration reported in other series [3]. The late presentation led to a significant proportion of the patients presenting with advanced disease (mean PCI 26, PCI>25 in 70.1% and PCI>30 in 38.9%) However, over a period of 5 years, the number of procedures performed for these tumors increase steadily; the first 38 procedures were performed over a period of 34 months and the next 39 over a period of 17 months. A higher incidence of intermediate grade tumors (24.1%) was observed, compared to the incidence of 5-10% reported in other series [3,15,16]. Of the patients, 77.9% of the patients had low grade PMP, including those with intermediate grade and 22.1% had high grade PMP.

The main drawback of our study is the short median follow up of 13 months at which the median OS and DFS had not been reached. The projected 5-year OS was 62.3% and the 3-year DFS was 71%. These results are inferior to a 5-year survival of 69-75% reported by established centers [3,17]. Prior chemotherapy, prior surgery and the PSS had no impact on DFS or OS. A low PCI had a favorable influence on both DFS and OS (p<0.01 for DFS and p=0.05 for OS), but was not an independent prognostic factor. A high PCI is known negatively impact both DFS and OS and makes surgery technically difficult, but there is no cut off beyond which a complete CRS cannot be

attempted, and even patients with a PCI of 31-39 can experience a prolonged survival [3]. Elias et al. have defined a huge PMP as a PCI of more than 28 [18]. Of our patients 57.1% had a huge PMP.

We achieved a CC-0/1 in 59% of the patients with a huge PMP compared to 97% in patients with a PCI of <28. Overall, we achieved a complete cytoreduction (CC-0/1) in 75% of the patients which is similar with the reported rates of 66-83% [3,17,19].

Patients with a CC-0/1 experienced a better DFS and OS as compared to those with a CC-2/3 resection (p<0.01 for DFS and p=0.04 for OS). CC-0/1 was an independent predictor for DFS (p=0.03) but not for OS (p=0.06) which could be due to the short median follow up as patients with debulking (CC-2/3 resections) also experienced a prolongation of survival [20]. Considering the extent of CRS as defined by Wagner et al., 71% of our patients had an extensive CRS (defined as > 2 anastomoses or > 3 organ resections) and 19.2 % had an extreme CRS (defined as ≥ 3 anastomoses or ≥ 5 organ resections) [21].

In 4 patients we had to do a staged resection. Though this approach is not widely practised, Esquivel et al. in his review of 98 patients who had undergone a second look surgery concluded that because of the indolent nature of appendiceal tumors, a second look with CRS and HIPEC could be

beneficial provided there was no increase in the PCI from the previous procedure, even in patients who did not have a complete CRS in the first procedure [22]. We have not had to perform any such staged resection in our last 25 cases, perhaps indicating better case selection and improved surgical skill and experience.

For high grade tumors the median DFS and OS were 12 and 18 months respectively which is similar to the median DFS and OS of 14.4 and 18 months reported by Levine et al. in their series of 110 high grade appendiceal tumors [23]. The intermediate grade tumors had a median DFS of 14 months which is similar to that of high grade tumors. Tumors with focal areas showing high grade features on a background of a low grade tumors were classified as hybrid/intermediate grade and since we observed a higher incidence than has been reported, we reviewed these reports for a second time to ensure the correctness of grading. For the low grade tumors the median DFS and OS had not been reached. A low tumor grade was an independent predictor of a longer DFS ($p=0.03$), however it did not affect the OS which again could be attributed to the short median follow up of 13 months.

Early recurrence is known to occur in patients with PMP and is attributed to either tumor biology or technical reasons [24]. Of the patients who had a complete cytoreduction, 14 (18.1%) developed a recurrence within 24 months. Eleven of 14 patients had either intermediate or high grade tumors (7 intermediate grade, 4 high grade).

The grade 3-4 morbidity was 42.9% and the perioperative mortality was 5.2%. These rates are

higher than the reported rates of 22-34% for grade 3-4 morbidity and 2-4% for perioperative mortality [25,26]. This could be attributed partly to our limited experience and in part to the high tumor burden. Both surgeons had spent considerable training time at established centers, and continued mentorship through clinical meetings and personal communications with experts further helped them in dealing with complex situations.

Conclusions

PMP of appendiceal origin can be treated with an acceptable morbidity and mortality in Indian patients with CRS and HIPEC. Lack of early referral leads to a large portion of patients presenting with extensive disease. Half of the patients underwent surgery in the last one year of our experience leading to a short median follow up. One fourth of the patients also had intermediate grade tumors that behaved more like high grade tumors. An increase in awareness about the treatment and timely referrals combined with an increase in our experience could improve these results in the future.

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Conflict of interests

The authors declare no conflict of interests.

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