



Case series

Case series on high grade appendiceal cancer with peritoneal and liver carcinomatosis undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC)

Susmit Prosun Roy, 1st Author^{a,b}, Nayef Al Zhahrani, Surgeon and Supervisor of the article^{b,c}, Shoma Barat, Data Manager and Statistician^{d,e}, David L. Morris, Surgeon, Supervisor of Unit and Research and Head of Department^{b,e,f,g,h,*}

^a General Surgery, John Hunter Hospital, University of Newcastle, Newcastle, Australia

^b Liver and Peritonectomy Unit, St George Hospital, Kogarah, Australia

^c College of Medicine, Al Imam Mohammad Ibn Saud Islamic University, Riyadh, Saudi Arabia

^d Southeast Sydney Local Health District, Australia

^e University of New South Wales, Australia

^f Liver and Peritonectomy Unit, St George Hospital, Kogarah, Australia

^g UNSW, St George and Sutherland Clinical School, NSW 2052, Australia

^h St George and Sutherland Clinical School, Kogarah, NSW 2217, Australia

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ABSTRACT

Background: Pseudomyxoma Peritonei (PMP) is a mucin producing cancer with appendix as primary site. Cytoreductive Surgery (CRS) combined with hyper-thermic intraperitoneal chemotherapy (HIPEC) is an established form of therapy known to prolong survival in patients with PMP and peritoneal carcinomatosis.

Methods/patients

In our case series, we present five cases of PMP with synchronous liver and peritoneal metastasis treated with CRS and HIPEC.

It is a very rare condition which needs more research to be able to comment on overall survival.

Results: However, in our study, we found lower age, female gender and complete cytoreduction in surgery to be favourable predictors for improved morbidity.

Conclusion: In our experience, CRS/HIPEC seem to be feasible for patients with PMP with synchronous liver and peritoneal metastasis.

1. Introduction

Appendiceal cancers are very rare. In USA, incidence has been reported as approx. ~0.12 per 100,000 people per year [1] without any known risk factors for development. Out of the different classifications of neoplasms of the appendix, mucinous adenocarcinoma is approximately 37% closely followed by colonic type adenocarcinoma (27%) and adenocarcinoid (19%). The lowest incidences are recorded for appendiceal cancers of Signet ring cell (6%) and Malignant carcinoid (11%) types [2].

Pseudomyxoma peritonei (PMP) is a disease most commonly characterised by abundant mucin producing cancer where the primary site is

vermiform appendix [3]. Multiple studies have suggested cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) prolongs survival in patients with appendiceal cancer and peritoneal metastasis [4–8]. Following CRS to remove all visible tumor deposits, HIPEC is aimed to eradicate microscopic tumor deposits as a locoregional treatment. It is achieved by reaching intra-peritoneal concentration of cytotoxic drugs approximately 20 times more than systemic concentrations (intravenous). The most commonly used drugs for HIPEC are Cisplatin, Mitomycin-C (MMC), Oxaliplatin (Oxali), 5-Fluorouracil (5-FU) [9].

To date there are no studies looking at appendiceal cancer with synchronous metastasis to the peritoneum and liver who have undergone CRS and HIPEC.

* Corresponding author at: St George and Sutherland Clinical School, Kogarah, NSW 2217, Australia.

E-mail addresses: susmitprosunroy@gmail.com (S.P. Roy), nayefalhariri@hotmail.com (N. Al Zhahrani), Shoma.Barat@health.nsw.gov.au (S. Barat), david.morris@unsw.edu.au (D.L. Morris).

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Abbreviations

M	Male
F	Female
AA	Appendiceal Adenocarcinoma
CC	Completeness of Cytoreduction
PCI	Peritoneal Cancer Index
LOS	Length of Stay (in days)

We present a case series of five patients who had metastatic appendiceal cancer to the liver and peritoneum who were treated with CRS and HIPEC along with liver resection.

2. Methods

A retrospective analysis was performed on a prospectively maintained database of patients who underwent CRS and HIPEC at St George Hospital between January 1996 and January 2018. Our institution performed 1257 CRS-HIPEC procedures during this period. We identified the review was carried out using patient relevant medical records and operation reports. All the patients were pre-operatively consented to have their information to be used for research purpose (by South Eastern Sydney Local Health District Human Research Ethics Committee).

All patients were evaluated for suitability to undergo CRS and abdominal HIPEC during weekly multidisciplinary team meetings comprising of surgical oncologists, medical oncologists, radiologists, intensive care specialists, anesthetists, cancer care nurses, research staff, ethicists and other allied health staff. Pre-operatively, all patients underwent physical examinations, pathological examinations (blood), imaging tests. To investigate the cause for their symptoms, all the patients underwent CT scan of Abdomen and Pelvis. This was followed by CT scan of the chest as part of staging process and to help in planning for the procedure. The blood tests included measuring their level of tumor markers namely Carcinoembryogenic Antigen (CEA) levels amongst others.

All the patients were operated by a highly experienced and same surgical team. St George Hospital is the leading center for peritonectomy surgery in Australia performing the highest number of CRS and HIPEC in the country.

Follow up was organized every 3 months with CT chest, abdomen and pelvis alongside tumor markers (CEA) for the first year. Then the follow up comprised every 6 months for next year and then yearly. All the radiologic findings were discussed at the Multi-disciplinary Team (MDT) meetings.

We present a case series of five patients who had metastatic appendiceal cancer to the liver and peritoneum who were treated with CRS and HIPEC along with liver resection. This case series has been reported in line with the PROCESS Guidelines 2020 [10]. This has been registered with research registry with unique identification number (researchregistry7762) [11].

3. Case presentations**3.1. Case - 1**

A 74-year-old lady presented to our Emergency with gradually worsening generalized abdominal pain with distension and vomiting for almost a week. As part of investigations to diagnose the cause of her presentation, she underwent CT-scan of her abdomen and pelvis. The imaging suggested extensive metastatic disease in the liver, spleen, right adrenal and peritoneal metastatic deposits.

This patient was pleasantly confused and lived in her own house supported by her husband, son, and daughter in law.

She had history of Alzheimer's dementia, Cerebrovascular accident, Type 2 Diabetes, Dyslipidemia, Osteoporosis and Chronic Kidney Disease.

Ten years prior to her final presentation, she was operated for an appendiceal mass while presenting as acute appendicitis. In that presentation, she had undergone laparotomy with Right hemicolectomy, Omentectomy, Bilateral Salpingo-oophorectomy, partial cystectomy.

On her final presentation, as part of CRS, the patient underwent peritonectomy, liver resection, splenectomy, right adrenalectomy and extensive adhesiolysis. Intra-operatively, there was an iatrogenic injury to Inferior Vena cava (IVC) and diaphragm.

Histology suggested metastatic mucinous adenocarcinoma (high grade) within liver and peritoneal deposits of low-grade mucinous tumor.

Post-operative period was complicated by a non-ST elevation myocardial infarction (NSTEMI) and sepsis.

She continued to deteriorate despite high level of support and monitoring.

Respecting the family's wishes, the cardio-respiratory supports were eventually withdrawn, and comfort measures were instituted. She survived a total of 10 days post-operatively.

3.2. Case - 2

A 70 year old gentleman, presented to the Emergency Department of our hospital with ongoing abdominal pain and worsening nausea.

Living with his supportive son, the patient had limited mobility around the house and block where he lived using 4-wheel walker. His past medical history was significant for Type 2 Diabetes, Hypertension, Dyslipidemia, Previous Myocardial Infarction and Gout. His past surgical history only included bilateral knee replacements for Osteo-arthritis without any prior abdominal operation.

CT scan suggested near obstructing right colonic mass most likely arising from the appendix with extensive ascites and presence of extensive intra-peritoneal metastasis. He underwent peritonectomy and HIPEC for high grade appendiceal carcinoma. Operation wise, he underwent right hemicolectomy, omentectomy, cholecystectomy, tumor resection off the bladder and simultaneous resection of Liver (Segment 3).

Histology suggested invasive, high grade, non-mucinous adenocarcinoma present deep to distal of ileocaecal valve involving all the layers of bowel wall. It was positive for lymphovascular invasion, lymph node metastasis, peritoneal, omental and urinary bladder wall metastasis.

It was hard to differentiate between caecal and appendiceal cancer. The tumor marker CA 19.9 was elevated while CEA levels were normal suggesting the diagnosis to be more consistent with appendiceal tumor.

Liver segment 3, Lymph nodes (anterior and lateral to superior mesenteric artery), and previous wound site all showed positive for metastatic adenocarcinoma.

The patient was closely followed up in our outpatient clinic and he passed away approximately after 19 months from date of his operation.

3.3. Case - 3

A 47-year lady presented to our hospital with worsening generalized abdominal pain and vomiting for last few weeks without any previous significant history.

CT scan suggested small bowel obstruction in presence of ascites and nodules suspicious for metastasis to surrounding intra-abdominal organs.

She was quite fit and active lady prior to her development of above symptoms. She used to live independently with her family of origin living nearby in the same suburb. Prior to the sudden development of the above symptoms, she had never needed hospitalization for any ailment except for an open appendicectomy 15 years back.

Depending on her symptoms and imaging, she underwent

laparotomy followed by peritonectomy and HIPEC for high grade appendiceal cancer. Intra-operatively, she underwent cholecystectomy, Liver resection (Segment 5), Splenectomy, Omentectomy, and Right hemicolectomy.

Histology suggested well to moderately differentiated conventional invasive adenocarcinoma and mucinous adenocarcinoma of appendix with serosal involvement. (T4a).

The patient required Redo-peritonectomy 1 year later for recurrence. Part of this redo-CRS, she underwent Laparotomy, adhesiolysis, hilar dissection and resection of liver (Segment 5 and part of 6) with HIPEC.

This time, histology was positive for metastatic adenocarcinoma in portacaval lymph node. All the other specimens tested negative for malignancy.

Post-operatively, she developed Ileus which was managed conservatively. The patient also had developed a post-operative right sided lateral abdominal wall collection which was percutaneously drained.

The patient was discharged from the hospital 16 days post operatively.

The patient is alive and doing well till her last follow up at approximately 42 months since last operation.

3.4. Case - 4

A 69 year old lady, was initially diagnosed with high grade appendiceal cancer with metastasis in ovary, bladder and Right colon on CT-scan when she was referred to our specialist unit from Acute Surgical Unit. She did not have any major symptoms and had undergone the CT-scan as part of diagnostic work up for her abdominal pain.

She had previous medical history comprising of Type 2 Diabetes, Hypertension and Dyslipidemia. She had no previous history of any abdominal surgeries.

The patient underwent Peritonectomy, Right hemicolectomy, Omentectomy, Bilateral Salpingo-Oophorectomy and partial cystectomy.

On follow up, the patient had recurrences including metastasis in the liver. She underwent two redo-peritonectomies including liver resection and HIPEC.

Histology confirmed widespread mucinous adenocarcinoma as well as metastasis in resected liver segments.

The patient underwent regular follow ups at the liver and oncology clinics. Morbidity wise, the patient was admitted in the hospital a few times for symptomatic management of pain, fever, Small bowel obstruction etc. In her last admission, she was admitted for hypercalcemic, but her general condition deteriorated, and she passed away 26 months following her last surgery.

3.5. Case - 5

A 48 years old lady presented to the hospital with complains of generalized abdominal pain, worsening nausea and vomiting and gradual overall decline in the last 2–3 months before presentation.

CT-scan suggested dilated bowel loops with suspicion for small bowel obstruction without any definite transition point. However, there was presence of a small cystic lesion consistent with mucinous tumor involving the stump of the previous appendicectomy site. There was moderate amount of ascites, presence of copious small intra-peritoneal nodules or masses that were suspicious for high grade appendiceal cancer with extensive metastatic disease.

She hailed from a very supportive family comprising of a stable partner and two kids. She did not have any significant past medical history. She had an emergency appendicectomy 5 years prior but no other bowel surgeries.

Subsequently decision was made for her to have CRS with or without HIPEC. The patient underwent peritonectomy, right hemicolectomy, resection, major liver resection, omentectomy, bilateral ureteric dissection, cholecystectomy, para-aortic lymph node dissection,

diaphragm resection with repair, femoral lymph node dissection and ileostomy.

Histopathology suggested adenocarcinoma of appendix (Grade 2) with presence of metastatic disease in local lymph nodes, ovaries and peritoneum with direct infiltration into adjacent caecum. Cancer was confirmed in liver segments (1, 3, 7 and 8), left femoral lymph nodes.

Post operatively, she did well and last follow up has been at the Liver clinic 1.7 months from the time of her last operation. [Tables 1 and 2](#) - summarise the findings described above.

4. Results

Five patients who had appendiceal cancer with metastases to liver and peritoneum were identified. The mean age was 61.6 years (SD 11.6 years). The majority of our patients were female (80%). The PCI scores at time of CRS ranged between 4 and 14 with mean PCI score being 7.8 (SD – 3.37). Complete cytoreduction (CC0–1) was achieved in four patients. Only one patient had an incomplete cytoreduction (CC 2).

Mean operating time was 7.9 h (SD - 1). All except one patient underwent blood transfusion. Two patients received two units of pack red blood cells (pRBCs) each while one patient received four units and another received 21 units.

Post operatively, the average length of stay in ICU was 14 days (SD – 15.9, range 1–45). Additionally, the total length of stay in hospital ranged from 10 days to 58 days with a mean of 28.4 days (SD – 17.5).

The histopathology results of all the liver resections showed high grade metastatic adenocarcinoma. No patients had signet ring cells on histopathology. Three out of five patients have died in the time of the study with the lowest survival being only 10 days. The two other patients who died survived for 19.3 months and 26 months respectively from the time of CRS-HIPEC. The remaining alive patients were alive at 41.5 months and 1.7 months respectively.

All patients in our series received hyper-thermic intraperitoneal chemotherapy (HIPEC). Three received oxaliplatin and two received mitomycin C.

In addition to metastasis to the liver, one patient had metastatic recurrence to the adrenal and brain and another to the lung.

5. Discussion

It is rare but appendiceal tumours can present with concurrent peritoneal and liver metastasis. However, in this cases too, curative resection is possible.

There is good volume of literature for patients with colorectal cancer and peritoneal carcinomatosis receiving cytoreductive surgery and HIPEC. Glehen et al. in their retrospective multicentre study of >500 patients suggested clearly that the therapeutic approach combining cytoreductive surgery with peri-operative HIPEC had significantly better long term survival than patients who did not. In their study, they identified complete cytoreductive surgery to be the most important prognostic factor [8].

However, there are no published randomized controlled trials for patients with colorectal cancers associated with liver as peritoneal metastasis treated with cytoreductive surgery and HIPEC. However, in a published systematic review of published literature, it was evident that patients with colorectal cancer with metastasis in the liver as well as in the peritoneum show a trend towards a lower overall survival after curative resection and HIPEC, when compared to patients with isolated peritoneal metastases. The study also suggested patients with metastatic CRC show a tendency towards increased median overall survival after CRS and HIPEC combined with resection of liver metastases when compared to treatment with modern systemic chemotherapy [12].

Nayef et al. in their study of >600 patients with peritoneal carcinomatosis (234 with colorectal primary) who underwent CRS and HIPEC clearly demonstrated overall survival for the patient [13].

To our knowledge, this is the first series reporting the progress and

Table 1

Summarised results - patient characteristics, LOS, nature of resection, histology, outcome.

ID	Age (years)	Gender	Primary	PCI	CC	Op time (Hrs)	Transfusion units	ICU LOS (days)	Total LOS (days)	Type of resection	Histology of liver	Outcome	Length of FU (months)
1	74	F	AA	14	1	8	21	10	10	Right	Metastatic mucinous high grade adenocarcinoma	Died	0.33
2	70	M	AA	6	2	9.5	0	3	20	Seg 3	Metastatic adenocarcinoma	Died	19.3
3	47	F	AA	4	0	6.7	2	11	16	Segment 5	Moderately differentiated adenocarcinoma with areas of necrosis	Alive	41.5
4	69	F	AA	8	1	7	4	45	58	Part seg 1/3	Mucinous adenocarcinoma on surface	Died	26
5	48	F	AA	7	0	8.2	2	1	38	Seg 8, part of 1,3,7	Metastatic adenocarcinoma	Alive	1.7

Table 2

Summary of chemotherapeutic drug used, complications (as per Clavien-Dindo classification), recurrences (if any).

ID	HIPEC	EPIC	Complications	Notes	Other recurrence
1	MMC	Nil	5		-
2	Oxali	Nil	2		Adrenal, brain
3	MMC	Nil	2		Liver, lung
4	Oxali	Nil	4	Liver was resected due to invasive tumor rather than metastasis	-
5	Oxali	Nil	4		-

outcome of patients who had CRS-HIPEC with liver resection for high grade appendiceal cancer with synchronous liver and peritoneal metastases.

The outcome results are similar to Colorectal cancer but not significantly better as might have been expected in appendiceal cancer. However, as appendiceal cancer is spreading to both liver and peritoneum – its aggressive nature of spread can easily be envisaged.

Post-operative chemotherapy has been shown to have improved progression free survival in patients with HGA cancer treated with CRS and HIPEC. At the same time, there is no evidence for using peri-operative systemic chemotherapy in patients with low grade disease [14].

Mostly the HIPEC chemotherapeutic agent is Oxaliplatin in colorectal tumours. However, at our centre, we have used Mitomycin-C when tumor consistency is soft like in appendiceal malignancy. The Oxaliplatin dose used for HIPEC was 350 mg/m² of the body surface for total duration of 30 min in Dianeal PD4 fluid. The Mitomycin-C dose was calculated at 12.5 mg/m² of the body surface area for over 90 min in plasmalyte solution. At all times, the temperature of the HIPEC was maintained at 42 degree Celsius.

In our study, we could see Gender, age and Cytoreduction Score may play a role in the natural history of high grade appendiceal cancer with synchronous liver and peritoneal metastasis. We have 2 survivors in our case series.

It was reported earlier by Ung et al., that the overall 5 year survival rate in females were almost thrice than that of males in patients suffering from metastatic appendiceal carcinoma [15].

The fact that both the survivors had CC – 0 score also suggests complete cytoreduction to be aimed for a higher survival in these patients. This was in line with Sugarbaker et al. findings in patients with appendiceal cancer having only peritoneal metastasis [16]. In their published study, it was seen that patients with CC-0 and CC-1 had significantly better long term survival compared to patients with incomplete cytoreductions (CC-2 and CC-3). However, there were no significant differences in long term survival between patients with CC-2 and CC-3 categories.

The strengths of the study included uniform surgical approach (CRS) and treatment with HIPEC for all the patients from the same surgical team. Thus, variability in surgical techniques was not a factor here. This is a very high-volume centre for peritonectomies. The database has been maintained in a very systematic manner.

Limitations of the study include very small sample size due to rarity of the disease which resulted in very low abilities to detect differences in overall survival in the patients.

Overall, lower age, female sex and complete cytoreduction (CC-0) seem to be better predictors in overall survival in patients with Appendiceal cancers having synchronous metastasis to the liver and peritoneum who have received CRS and HIPEC.

6. Conclusion

Appendiceal cancer can metastasize to liver and its feasible to do CRS and HIPEC for those patients. It is very rare to find liver metastasis from appendiceal tumours. It would need more research and data collation across specialised centres to develop a universal consensus or guideline to assess feasibility of curative intent in these types of patients.

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Ethical approval

All the patients were pre-operatively consented to have their information to be used for research purpose (by South Eastern Sydney Local Health District Human Research Ethics Committee) – See Ethics committee approval report attached.

Consent

All the patients were pre-operatively consented to have their information to be used for research purpose (by South Eastern Sydney Local Health District Human Research Ethics Committee).

Registration of research studies

None.

Guarantor

All the authors are guarantors for the work.

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CRedit authorship contribution statement

Dr. Susmit Prosun Roy. MBBS, DCH, MS: - Writing – Original Draft; Writing – Review and Editing; Visualisation and Conceptualization.

Dr. Nayef Al Zahrani. MBBS, FRACS:- Writing – Review and Editing; Resources; Investigation. Supervision.

Shoma Barat. BSc (Microbiology), G. Cert (Med Technology), G. Dip (Analytical Chemistry), M. HIM (USYD): - Data Curation.

Prof. David L. Morris. MB, ChB, FRCS, FRCSE, MD, PhD, FRACS: - Writing – Review and Editing; Resources; Investigation. Supervision.

Declaration of competing interest

No conflicts of interest to report from any of the authors.

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