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Outcomes of HIPEC and Cytoreductive Surgery Following Radiotherapy and Excision of Rectal Carcinoma

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Abstract

Introduction: Rectal and rectosigmoidal carcinoma is traditionally treated with a combination of surgery and either adjuvant or neoadjuvant radiotherapy. Local peritoneal recurrence may be treated with cytoreductive surgery (CRS) and heated intraperitoneal chemotherapy (HIPEC). Given the toxicity of radiotherapy and HIPEC on the bowel, we aim to determine post-operative outcomes of patients with combined treatment.

Method: Our prospective database from 1996 to 2014 was searched for patients with radiotherapy and primary excision, followed by CRS and HIPEC. 5 patients were identified and analysed for post-operative complication and survival.

Results: Survival post-CRS range from 11 to 45 months with 2 of the 5 patients still living. In the 3 patients that died, 2 had metastatic recurrence while 1 had recurrent post-HIPEC fistulae causing death.

Conclusion: CRS and HIPEC after adjuvant or neoadjuvant radiotherapy for rectal carcinoma are associated with considerable morbidity but can also achieve relatively longer term survival compared to no CRS or HIPEC.

Keywords: HIPEC; Cytoreductive surgery; Radiotherapy; Rectal carcinoma; Outcomes

Introduction

Colorectal carcinoma (CRC) continues to prove a significant burden with both the second highest incidence and mortality rate amongst neoplasms [1]. Localised peritoneal spread, termed peritoneal carcinomatosis (PC) has traditionally had a poor prognosis [2]. Sugarbaker's relatively recent pioneering of cytoreductive surgery (CRS) with perioperative intraperitoneal chemotherapy has increased survival in appropriately selected patients [2-4]. The incidence of PC has been estimated between 4-7% in patients presenting at primary surgery and 4-19% in patients with recurrence [5-6]. However these techniques do come at the risk of significant post-operative complication. Bowel complications including fistulae formation and anastamotic leak are all relatively common and attributed to the combination of cytotoxic effects of heated intraperitoneal chemotherapy (HIPEC) and extensive surgery [7]. Adjuvant or neoadjuvant radiotherapy, used especially in rectal and rectosigmoidal carcinoma, also predispose to significant gastrointestinal complications; the extent of which is proportional to the radiation dose [8]. Poor wound healing and gastrointestinal complaints have been described in rectal cancer irradiation [8-10]. The cumulative toxicity of intraperitoneal chemotherapy and radiotherapy may result in poorer post-operative outcomes, the true extent of which has not been studied. We report a 5 patient series of patients with primary rectal or rectosigmoidal carcinoma who received adjuvant/neo-adjuvant radiotherapy prior to peritoneal recurrence and treatment with CRS and HIPEC.

Materials and Methods

Cytoreductive surgery criteria

Our unit receives a high volume of patients with peritoneal and liver metastatic disease. Our selection criteria for patients with peritoneal carcinomatosis of colorectal origin include an intraoperative peritoneal cancer index (PCI) less than 15, or less than 10 if liver metastases are present. Typically patients of a reasonable performance status undergo thorough radiological workup with computerised tomography (CT) scan of the chest, abdomen and pelvic, PET scan

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Table 1: Patient Details and Primary Disease Characteristics.

Patient	Age at Primary Surgery	Sex	Primary Tumour Location	TNM Staging at presentation	Radiotherapy Treatment	Time between radiotherapy and CRS (months)
1	63	M	Rectum	T3N1M0	Neoadjuvant: 50.4Gy 28 Fractions	35.5
2	46	M	Rectum	T3N1M0	Neoadjuvant: 50.4Gy 28 Fractions	41.1
3	54	F	Rectum	T4bN0M0	Adjuvant: 50.4Gy 28 Fractions	50.4
4	57	F	Rectosigmoid	T4aN2M0	Adjuvant: 50.4Gy 28 Fractions	28.6
5	62	M	Rectosigmoid	T4bN0M0	Adjuvant:50.4Gy 28 Fractions	6

Table 2: Patient Cytoreduction and HIPEC Details.

Patient	Operation Time (hours)	PC I	Cytoreduction Status	HIPEC Chemotherapeutic Agent (duration)	EPIC (duration)	LOS (days)	Morbidity Grade	Time post-CRS: status
1	7	3	Complete	Mitomycin C (90 min)	No	6	0	35 months: Alive, lung recurrence
2	10	5	Complete	Oxaliplatin (30 min)	No	23	2	31 months: Alive, recurrence free
3	8	6	Complete	Mitomycin C (90 min)	Yes, 5-FU (5 days)	21	3	45 months: Deceased, bladder recurrence
4	5.5	4	Complete	Mitomycin C (90 min)	Yes, 5-FU (5 days)	24	2	12 months: Deceased, liver recurrence
5	9.5	2	Complete	Mitomycin C (120 min)	Yes, 5-FU (5 days)	206	4	17 months: Deceased, recurrent fistula post-surgery

and hepatic arteriography and portography. Scans are reviewed in a multidisciplinary meeting attended by radiologists, surgeons and oncologists to determine if the patient is suitable for intervention with CRS and HIPEC.

Patients with operable disease undergo cytoreductive surgery involving anterior parietal peritoneum resection, diaphragm stripping, pelvic stripping, omentectomy, splenectomy, cholecystectomy and abdominal visceral resection if macroscopic disease is visible in these areas. Additionally they receive HIPEC at 41.5 degrees centigrade, with either mitomycin C or oxaliplatin. Post-surgical treatment with Early Post-operative Intraperitoneal Chemotherapy (EPIC) may be delivered via an abdominal port typically with 5-fluorouracil (5-FU).

Patients are given ongoing follow-up with frequent re-imaging and following tumour marker status.

Data collection

Retrospective study of our prospective database searching for patients with primary rectal or rectosigmoidal carcinoma, who received adjuvant or neoadjuvant chemoradiotherapy for their primary tumour. Of the 250 patients with colorectal disease, 43 had rectal/rectosigmoidal primary and only five had received radiotherapy at the time of primary resection. These five patients all suffered recurrence necessitating HIPEC and CRS, and their notes were reviewed. Details of their disease, treatment, post-operative morbidity and long-term follow up were recorded. In all patients complete cytoreduction was possible. The results are included.

Results

Patient 1 presented with stage IIIb rectal adenocarcinoma, treated with neoadjuvant chemoradiation, followed by low anterior resection in 2009. Represented 3 years later with shoulder pain and loose stools and rising tumour markers suggestive of recurrence. Intraoperative examination showed PCI of 3 with no hepatic abnormalities on ultrasound. CRS with cholecystectomy, retroperitoneal lymph node dissection of para-aortic nodes and omentectomy was performed. HIPEC with mitomycin C for 90 minutes. A small bowel oversews and placement of a peritoneal port was performed. His post-operative recovery was relatively rapid at 6 days, without complications. This was followed by 24 weeks of adjuvant chemotherapy with 5-FU and folinic acid (FOL). Unfortunately scans showed multiple lung metastases, 18 months post-surgery. Lesions were not amenable to radiofrequency ablation. The patient was commenced on cetuximab. The lesions are slow growing and the patient is still alive, 36 months after CRS.

Patient 2: presented initially with stage IIc rectal adenocarcinoma treated with neoadjuvant chemoradiation, followed by a low anterior resection in November 2009. Represented 3 years later with a palpable pelvic mass and rising tumour markers suggestive of recurrence. Intraoperative examination showed PCI of 5 with no hepatic abnormalities on ultrasound. CRS with cholecystectomy, appendicectomy, resection of small bowel adherent to the pelvic mass, Hartmann's resection and bilateral ureteric re-implantation. Both small bowel and ureters were adherent to the mass requiring removal and resection. 30 minutes of HIPEC with oxaliplatin. Post-operative stay of 23 days complicated by development of pneumonia with lung atelectasis which was managed with antibiotics. No detected urine or bowel leaks. Adjuvant chemotherapy with FOL, 5-FU, and oxaliplatin. Patient is presently disease free with normal tumour markers and imaging.

Patient 3: presented initially with an 11 cm rectal tumour diagnosed on colonoscopy. Treated with a low anterior resection with mesorectal excision followed by adjuvant chemoradiation in February 2005. On excision there was visible mesorectal tissue involvement and tethering of a loop of ileum to the peritoneal reflection near the tumour. Represented 3 years later with lung lesions and a pelvic wall mass. She had an intraoperative PCI of 6, with no hepatic abnormalities seen on ultrasound. CRS with hysterectomy, Hartmann's procedure, small bowel resection and re-implantation

of the left ureter which was fixed in the pelvic mass. 90 minutes of HIPEC with mitomycin C and insertion of a peritoneal port for 5 days of early postoperative intraperitoneal chemotherapy (EPIC) Post-operative stay of 21 days was complicated by the development of ileus, fevers and urinary tract infection. Readmission 4 days post-discharge for management of a pelvic collection which was drained percutaneously. Adjuvant post-operative FOLFOX-4 regiment with bevacizumab. A right lung lesion was ablated a year after CRS. Unfortunately there was local recurrence on the bladder roof, with rising CEA treated with palliative chemotherapy. She died 45 months post-CRS.

Patient 4: presented initially with stage IIIc rectosigmoidal tumour initially treated with anterior resection in January 2004. Lymphatic spread was noted in all 9 of the 9 biopsied nodes. Resection was followed by adjuvant chemoradiation. Represented 2 years later with recurrence of a 6cm segment 4 hepatic recurrence, which was resected, and then 8 months later with pelvic wall recurrence. CRS with small bowel resection and omentectomy was performed followed by 90 minutes of HIPEC with mitomycin C. Post-operative stay of 24 days with 5 days of EPIC was complicated by small bowel obstruction managed conservatively. Recurrence with multiple hepatic metastases occurred 5 months later which was managed with FOLFOX-6 systemic chemotherapy and then treatment with Sirtex sphere implantation but continued to decline and died 12 months post-CRS (Table 1).

Patient 5: presented initially with stage IIc rectosigmoidal tumour in December 2002. Interestingly the mass caused obstruction and perforation producing a retroperitoneal abscess in the psoas muscle. This was treated with a Hartmann's procedure and left hemi-colectomy due to extensive sigmoid involvement. An unfortunate false negative on frozen section biopsy of the abscess meant incomplete resection. Thus, the patient was planned for adjuvant chemotherapy with FOL and 5-FU and radiotherapy.

The patient represented 6 months after for CRS as his tumour was progressing while he was on chemotherapy. Intraoperative examination showed a PCI of 2, and no abnormality on intraoperative liver ultrasound. CRS with small bowel resection, omentectomy and splenectomy was performed with complete excision of the abscess cavity with part of the psoas and iliacus muscles. 2 hours HIPEC with mitomycin C complete and insertion of peritoneal port for 5 days of EPIC Extremely difficult post-operative recovery complicated by pancreatic leak, multiple collections and enteric fistulae and small bowel perforation requiring re-operation. Post-operative stay of 206 days with multiple nosocomial infections during this duration. The patient died 16 months after CRS due to a fistula communicating with a large retroperitoneal sinus. This was complicated by long-term anorexia requiring TPN and respiratory failure from morphine sedation.

As evident from Table 2, post-operative recovery varied from a 6 day LOS with morbidity grade 0 to a 206 day LOS with morbidity grade 4. The survival times post-surgery were 12, 17, 31, 35 and 45 months. 4 of the 5 patients experienced some post-operative complication with a morbidity grade >2. Of these patients 3, 4 and 5, the 3 patients who received EPIC, experienced bowel complications. Patient 3 experienced post-operative ileus, patient 4 experienced small bowel obstructions and patient 5's recovery was complicated by multiple bowel fistulae, pancreatic leaks and perforation.

Discussion

Overall survival outcomes in our 5 patient series are comparable to the overall median survival of 28 months seen in other patients with CRC who underwent CRS and HIPEC at our institution [4]. All 5 patients received complete cytoreduction of their peritoneal recurrence following their CRS. Patients 1-4 have/had been able to enjoy a significant period of remission as a result of their therapy and did not experience any long-term sequelae. From a quality of life perspective, this suggests significant utility in the procedure. Patient 5's presentation with bowel perforation and abscess formation on the psoas muscle was undoubtedly complex. Colorectal cancer leading to perforated bowel is associated with greater risks of recurrence and operative complication [11,12]. However, it should be noted that the patient remained disease-free with negative tumour markers for their life and that death was a result of recurrent fistula, which histopathology showed communicated with the retroperitoneal space. We believe that the man's initial abscess combined with the radiotherapy and HIPEC regime was risk factors for his postoperative fistula. Interestingly the 3 patients who experienced bowel related complications were also the only 3 to have bowel related complications. It has been suggested that combination of EPIC and HIPEC produces a greater rate of complication post-surgery, and the need to avoid combinations when possible. We are unable to find any studies focused on the cumulative effect of preoperative radiotherapy with intraperitoneal chemotherapy and CRS. Klaver et al. [13] demonstrated the efficacy of combined intraoperative radiotherapy with intraperitoneal chemotherapy. In their series of 5 patients with locally advanced rectal carcinoma there were no reports of anastamotic leaks or collections increasing the post-operative stay. The disease free survival of 4 patients at follow-ups of 12, 22, 25, and 34 months suggested an excellent outcome in selected patients [13]. However, their series also showed a patient with recurrent abscess formation following a perforated rectal carcinoma, reinforcing the possibility of HIPEC and radiotherapy to promote complication in some patients.

Comparing HIPEC and CRS with traditional treatments

Peritoneal carcinomatosis of CRC origin treated with systemic chemotherapy alone shows poor tumour response with several studies showing a median survival of approximately 6 months [5,14-16]. Survival may be boosted by additional palliative surgery to 12.6 months [16]. In comparison, a systematic review by Cao et al. [2] demonstrated that combination HIPEC and CRS increases median survival to over 18 months. Results from our institution are encouraging with a median survival of 28 months, with a significant proportion of long-term survivors [4]. This suggests an additional 22 month of life over chemotherapy alone [4]. Despite this, toxicity and complication associated with CRS and HIPEC are both common and severe. Grade III/IV morbidity range from 14-55%, [6,7,17,18] although our institution has shown a steady decline in patients with grade IV morbidity and overall mortality [4]. Peri-pancreatitis (6%), fistula (4.5%), post-operative bleeding (4.5%), haematological toxicity (4.5%) and anastamotic leak (3%) are the most commonly reported complications. A 60 patient series by Jacquet et al. [19] suggested serious complication in 35% of patients most commonly due to bowel-related anastomotic leakage or perforation.

Multiple trials have proven the efficacy of adjuvant and neoadjuvant rectal radiotherapy at reducing local recurrence and death compared to excision alone [20-22]. However, post-operative

complication with radiotherapy and surgery is common, with 48% of patients suffering immediate complications [10] Common complications in these patients, and within the first 6 months of surgery include localised wound infection, abscess, cardiopulmonary complications, bowel obstruction, constipation and non-specific abdominal pains [8,10] This compares with 41% of patients with complications who had surgery alone [10].

Gastrointestinal disorders, including risk of bowel obstruction, abdominal pain, nausea and constipation are the most common long-term adverse effects, 6 months after radiotherapy treatment [22]. Due to these adverse effects, patients who underwent radiotherapy were more likely to express dissatisfaction than those with surgical excision alone [23].

In summary both adjuvant/neoadjuvant radiotherapy and HIPEC with CRS are associated with increased survival at the expense of likely adverse effects. In our patient series, the extent of these adverse outcomes did not deviate from the typical CRS an HIPEC patient. Although patient 5 did experience a difficult recovery, it has been established that a perforated bowel with abscess formation accounts for a higher risk of complication. Thus we believe that previous radiotherapy would benefit from HIPEC and CRS, which is in accordance with our current management practice.

Of course the power of our case series and the conclusions we can draw is restricted by limited patient numbers. Additionally it is gathered from retrospective data which is prone to experimental bias and inability to compare with a standardised control group. However, patients who are diagnosed with rectal/rectosigmoidal carcinoma treated with both radiotherapy and CRS with HIPEC are exceedingly rare and unfeasibly large populations would be required for prospective studies. This necessitates further study to obtain more data in regards to efficacy and complication of CRS and HIPEC following radiotherapy.

Conclusion

Overall complication rates in our series did not extend beyond what is reported in the literature for either radiotherapy or HIPEC alone. Median survival of patients receiving radiotherapy is comparable to those who did not require radiotherapy. There may be an increased risk of complication in radiotherapy and HIPEC in patients with pre-existing abscess, but this should not be an absolute contra-indication to surgery. Further studies to investigate mortality and morbidity in these patients are required.

References

1. Australian Institute of Health and Welfare. Cancer in Australia: an overview 2014. Cancer series no. 78. Cat. no. CAN 75. Canberra: AIHW.
2. Cao C, Yan TD, Black D, Morris DL. A systematic review and meta-analysis of cytoreductive surgery with perioperative intraperitoneal chemotherapy for peritoneal carcinomatosis of colorectal origin. Ann Surg Oncol. 2009; 16: 2152-2165.
3. Yan TD, Sim J, Morris DL. Selection of patients with colorectal peritoneal carcinomatosis for cytoreductive surgery and perioperative intraperitoneal chemotherapy. Ann Surg Oncol. 2007; 14: 1807-1817.
4. Alzahrani N, Ferguson JS, Valle SJ, Liauw W, Chua T, Morris DL. Cytoreductive surgery and heated intraperitoneal chemotherapy: long-term results at St George Hospital, Australia. ANZ J Surg. 2015.
5. Jayne DG, Fook S, Loi C, Seow-Choen F. Peritoneal carcinomatosis from colorectal cancer. Br J Surg. 2002; 89: 1545-1550.
6. Koppe MJ, Boerman OC, Oyen WJ, Bleichrodt RP. Peritoneal carcinomatosis of colorectal origin: incidence and current treatment strategies. Ann Surg. 2006; 243: 212-222.
7. Stephens AD, Alderman R, Chang D, Edwards GD, Esquivel J, Sebbag G, et al. Morbidity and mortality analysis of 200 treatments with cytoreductive surgery and hyperthermic intraoperative intraperitoneal chemotherapy using the coliseum technique. Ann Surg Oncol. 1999; 6: 790-796.
8. Birgisson H, Påhlman L, Gunnarsson U, Glimelius B, Swedish Rectal Cancer Trial Group. Adverse effects of preoperative radiation therapy for rectal cancer: long-term follow-up of the Swedish Rectal Cancer Trial. J Clin Oncol. 2005; 23: 8697-8705.
9. Frykholm GJ, Isacsson U, Nygård K, Montelius A, Jung B, Påhlman L, et al. Preoperative radiotherapy in rectal carcinoma--aspects of acute adverse effects and radiation technique. Int J Radiat Oncol Biol Phys. 1996; 35: 1039-1048.
10. Marijnen CA, Kapiteijn E, van de Velde CJ, Martijn H, Steup WH, Wiggers T, et al. Acute side effects and complications after short-term preoperative radiotherapy combined with total mesorectal excision in primary rectal cancer: report of a multicenter randomized trial. J Clin Oncol. 2002; 20: 817-825.
11. Belt EJ, Stockmann HB, Abis GS, de Boer JM, de Lange-de Klerk ES, van Egmond M, et al. Peri-operative bowel perforation in early stage colon cancer is associated with an adverse oncological outcome. J Gastrointest Surg. 2012; 16: 2260-2266.
12. Carraro PG, Segala M, Orlotti C, Tiberio G. Outcomes of large bowel perforations in patients with colorectal cancer. Dis Colon Rectum. 1998; 41: 1421-1426.
13. Klaver YL, Lemmens VE, Nienhuijs SW, Nieuwenhuijzen GA, Rutten HJ, de Hingh IH. Intraoperative radiotherapy and cytoreductive surgery with hyperthermic intraperitoneal chemotherapy. Five consecutive case reports of locally advanced rectal cancer with synchronous peritoneal carcinomatosis. Strahlenther Onkol. 2013 189: 256-260.
14. Chu DZ, Lang NP, Thompson C, Osteen PK, Westbrook KC. Peritoneal carcinomatosis in nongynecologic malignancy: a prospective study of prognostic factors. Cancer. 1989; 63: 364 –367.
15. Sadeghi B, Arvieux C, Glehen O, Beaujard AC, Rivoire M, Baulieux J, et al. Peritoneal carcinomatosis from non-gynecologic malignancies: results of the EVOCAPE 1 multicentric prospective study. Cancer. 2000; 88: 358 –363.
16. Verwaal VJ, van Ruth S, de Bree E, van Sloothen GW, van Tinteren H, Boot H, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. J Clin Oncol. 2003; 21: 3737-3743.
17. Glehen O, Cotte E, Schreiber V, Sayag-Beaujard AC, Vignal J, Gilly FN. Intraperitoneal chemohyperthermia and attempted cytoreductive surgery in patients with peritoneal carcinomatosis of colorectal origin. Br J Surg. 2004; 91: 747-754.
18. Verwaal VJ, van Tinteren H, Ruth SV, Zoetmulder FA. Toxicity of cytoreductive surgery and hyperthermic intra-peritoneal chemotherapy. J Surg Oncol. 2004; 85: 61-67.
19. Jacquet P, Stephens AD, Averbach AM, Chang D, Ettinghausen SE, Dalton RR, et al. Analysis of morbidity and mortality in 60 patients with peritoneal carcinomatosis treated by cytoreductive surgery and heated intraoperative intraperitoneal chemotherapy. Cancer. 1996; 77: 2622–2629.
20. Colorectal Cancer Collaborative Group. Adjuvant radiotherapy for rectal cancer: A systematic overview of 8,507 patients from 22 randomised trials. Lancet. 2001; 358: 1291-1304.
21. Medical Research Council Rectal Cancer Working Party. Randomised trial of surgery alone versus surgery followed by radiotherapy for mobile cancer of the rectum. Lancet. 1996; 348: 1610-1614.

22. Swedish Rectal Cancer Trial. Improved survival with preoperative radiotherapy in resectable rectal cancer. N Engl J Med. 1997; 336: 980-987.

23. Peeters KC, van de Velde CJ, Leer JW, Martijn H, Junggeburt JM, Kranenbarg EK, et al. Late side effects of short-course preoperative radiotherapy combined with total mesorectal excision for rectal cancer: increased bowel dysfunction in irradiated patients--a Dutch colorectal cancer group study. J Clin Oncol. 2005; 23: 6199-6206.