

CASE STUDY

Cytoreductive Surgery and HIPEC in Elderly Patient with Colorectal Cancer and Peritoneal Metastasis

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ABSTRACT

Background: Colorectal cancer (CRC) patients with peritoneal metastasis have the worst prognosis with a median overall survival of 4.1–8.5 months [1],[2].

Aim: To assess results in the elderly metastatic CRC patient with peritoneal dissemination treated with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) with oxaliplatin.

Case Presented: Patient - 70-year-old female with metastatic CRC and peritoneal carcinomatosis. Prior to surgery, received 12 of chemotherapy FOLFOX + bevacizumab. CRS + HIPEC was performed followed by an uneventful recovery. After surgery, she has received chemotherapy with FOLFIRI. The disease progressed 14 months later. The patient has continued therapy with FOLFIRI, unfortunately, the disease has progressed and oral therapy with ftorafur has commenced. Patients' overall survival so far is 48 months.

Conclusions: Even though we cannot decisively distinguish if results are determined by CRS or additional HIPEC, the presented case shows the importance of a paradigm shift when peritoneal disease in selected patients is viewed as a regional disease rather than diffuse metastatic.

Keywords: Colorectal cancer, Cytoreductive surgery, Hyperthermic intraperitoneal chemotherapy, Peritoneal metastasis.

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1. INTRODUCTION

Colorectal cancer (CRC) is the third most common malignancy and the second leading cause of cancer death globally. There were an estimated number of new cancer cases: 1,148,515 colon and 732,210 rectum and patient deaths: 576,858 colon, and 339,022 rectum cancer worldwide in 2020 [1], [2].

Death from CRC in most cases is the consequence of metastatic spread to distant sites. In general, peritoneal metastases (PM) are under-diagnosed as their detection with routine imaging is difficult, due to their small size and limited contrast resolution in soft tissues. The presence of PM is estimated in 5%–8% synchronous, 4%–19% metachronous, and 40%–80 % in autopsy [3].

Patients with PM have the worst prognosis with median OS 4.1–8.5 months [4], [5]. A paradigm shift occurred when the peritoneal disease was viewed as a regional disease rather than diffuse metastatic disease and the

introduction of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) [6], [7]. This strategy combines surgical removal of all macroscopically visible disease and perfusion of the abdominal cavity with heated chemotherapy to eradicate residual microscopic disease [8].

Weissberger introduced the concept of intraperitoneal chemotherapy in 1955, Dedrick studied the depth of tissue penetration by different drugs and identified that they can penetrate 1–3 mm into tissue. This gave rise to the notion that tumor deposits need to be 2.5 mm or less [9]. Over the years HIPEC has become an effective strategy for the treatment of cancers with PM [10].

There are several clinical assessments at many different institutions in use for the evaluation of PM. Currently; a peritoneal carcinomatosis index (PCI) of greater than 20 is regarded as a relative contraindication to an elective intervention in colon cancer [11]. Case series published a survival rate at 5 years of 50% for PCI < 10, 20% for PCI



TABLE I: RESULTS FROM THREE LARGE MULTICENTER, RANDOMIZED, PHASE III TRIALS

Study	Disease free survival	Overall survival
COLOPEC	In 18 month 69% CRS + HIPEC vs. 69.3% CRS p = 0.99	In 18 month OS 93% CRS + HIPEC vs. 94.1% CRS p = 0.82
PROPHYLOCHIP	3 and 5 year results CRS + HIPEC 44% and 42% vs. CRS 53% and 49% p = 0.82 and p = 0.82	3 and 5 year CRS + HIPEC 79% and 68% vs. CRS 80% and 72% p > 0.5
PRODIGE 7	CRS + HIPEC 13.1 months vs. CRS 11.1 months p = 0.43	CRS + HIPEC 41.7 months vs. 41.2 months CRS, p > 0.5

10–20, and 0% for PCI > 20. Still, there are some groups that use PCI >26 as cut-off [12].

Survival data is inconclusive after CRS + HIPEC. A retrospective systemic review showed a mean OS of 27 months (range 15–63), and a mean 5-year OS of 27% (range 7%–100%) [6], [7]. While three large multicenter trials addressing HIPEC in CRC patients are COLOPEC (Netherlands [13]), PROPHYLOCHIP (France [14]), and PRODIGE7 (France [15]), none of the three trials found the impact of additional HIPEC to CRS regarding patients' disease-free survival or OS. An overview is shown in Table I.

PRODIGE 7 study identified elevated grade 3–5 morbidity in the HIPEC group (p = 0.035). Despite this, post-hoc subgroup analysis showed increased median overall and relapse-free survival benefits in the HIPEC + CRS groups in patients with a PCI score of 11–15 [15], [16].

Some of the negative predictive factors after CRS + HIPEC are the extent of the disease, nodal stage, tumor biology, response systemic therapy, or major complications [7].

CRS + HIPEC reportedly is accompanied by a high treatment-related mortality rate of 0%–8% and a grade 3–4 morbidity rate of 18%–52% in experienced centers. In addition, CRS + HIPEC's negative impact on quality of life (QoL) up to one year after surgery is described [8].

National Comprehensive Cancer Network guideline statement regarding CRS + HIPEC currently is as follows: The panel currently believes that complete CRS and/or HIPEC can be considered in experienced centers for selected patients with limited PM for whom R0 resection can be achieved. However, the significant morbidity and mortality associated with HIPEC, as well as the conflicting data on clinical efficacy, make this approach very controversial [17].

The aim of reporting this case is to assess safety and survival results in the elderly metastatic colorectal cancer patient with PM treated with systemic therapy followed by CRS + HIPEC with oxaliplatin.

2. CASE PRESENTATION

Patient–female, 70 years old presented with pain in the left lower abdomen for several months. In March 2018, she noticed blood in her stool and constipation, which increased in severity and resulted in hospitalization (March 26, 2018). Initial work-up performed in the regional hospital showed: complete blood count (Hgb = 13.7 g/dl), blood biochemistry tests and urinalysis within

the normal range; electrocardiography–sinus bradycardia; normal chest radiography; abdominal ultrasonography–hepatic steatosis; fibro gastroscopy–deformed duodenal bulb, presumably as a result of scarring from previous ulcer and pre pyloric erosive gastritis.

Colonoscopy revealed an obstructing sigmoid *colon mass* 18 cm from the anus; a biopsy was taken from the suspected tumor. CT of the abdomen detected only a pathological mass in the sigmoid region. The patient's past medical history was notable for periodic right goiter joint pain (symptomatic treatment with nonsteroidal anti-inflammatory drugs) and myopia. As examinations showed localized disease of sigmoideum a decision to perform the operation was made.

On April 14 after performing laparotomy peritoneal spread around the sigmoid tumor, pelvic peritoneum, greater omentum, and mesentery of small bowel was discovered. It changed the plan of the operation surgeon and it was taken from the omentum and a colostomy was performed. Pathological examination of the tissues obtained during colonoscopy, revealed grade I adenocarcinoma of the sigmoid colon, and from the surgically resected omental tissues–colorectal type grade II adenocarcinoma.

After the operation patient was sent to the tertiary referral center Riga East University Hospital with the diagnosis of Sigmoid colon cancer cT₄N₃M₁, peritoneal metastasis, stage IV, subacute sigmoid obstruction. The peritoneal Carcinomatosis Index was not mentioned at this stage. Upfront evaluation by a multidisciplinary team suggested systemic treatment. Due to the complaints of pain in the right goiter joint bone scintigraphy was performed, which showed joint deformations but no skeletal metastasis. Tumor molecular diagnostics showed KRAS and NRAS wild-type cancer. The patient's performance status was ECOG 0.

After discussing the side effects of the systemic treatment (as she lived alone, had severe myopia, and was worried whether she could take care of possible skin lesions) decision was made to start chemotherapy FOLFOX (leucovorin, fluorouracil, oxaliplatin) and targeted therapy with bevacizumab. After 6 courses of systemic therapy CT scan showed a decrease in the size of the primary tumor and peritoneal dissemination but a second evaluation by a multidisciplinary team suggested prolonging systemic therapy. After 6 more courses patient underwent a third evaluation by a multidisciplinary team, at this time CT imaging showed a substantial decrease in peritoneal dissemination and size of the primary tumor, and the decision to perform CRS-HIPEC was taken.

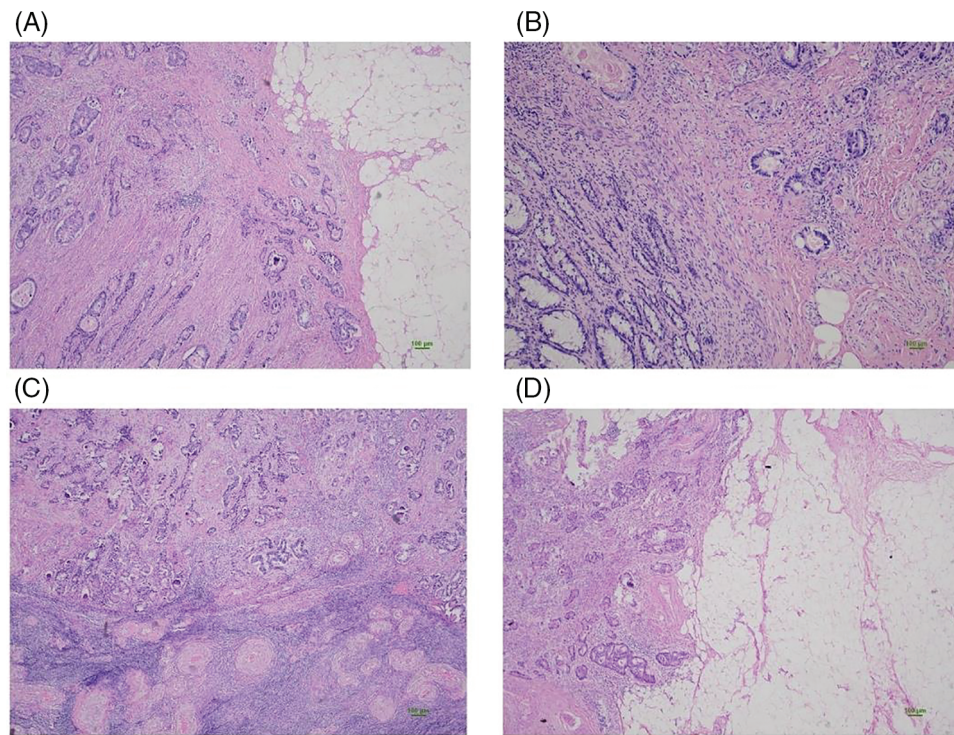


Fig. 1. Post-chemotherapy tumor regression in A and B–colon wall, C–ovary, D–omentum (hematoxylin and eosin).

The patient was operated on February 13, 2019. The duration of the operation was 8 hours. The procedure started with exploratory total laparotomy to assess the extent of peritoneal disease in an open setting. PCI was calculated by giving each of the 13 abdominal regions (0–12) a score ranging from 0 (no tumor seen) to 3 (tumor >5 cm or confluence) [18]. Visible disease was described as follows: diffuse small disseminates on right diaphragmatic peritoneum (right upper, region 1) PCI score = 3; omental disseminates (epigastrium, region 2) PCI = 3; right flank (region 8) PCI score = 2; pelvis (region 6) PCI score = 3 and small intestine disseminates PCI score 1. In total PCI reached 12.

The extent of surgery was anterior resection of the rectum, sigmoid resection, total hysterectomy with bilateral salpingo-oophorectomy, total pelvic peritonectomy, right diaphragmatic peritonectomy, radical omentectomy, excision of colostomy, right and left parietal peritonectomy and resection of the transverse colon (due to ischemic changes). Small peritoneal implants were either resected or coagulated and vaporized. After resection, HIPEC was performed for 30 minutes at a temperature of 42 °C by using a closed technique with oxaliplatin 400 mg. According to the residual disease classification after cytoreductive surgery: CC0 defined as non-visible was achieved. Formation of anastomoses was performed after HIPEC. The histological report showed Grade 2 adenocarcinoma ypT_{4b}N_{2a}M_xL₊V₊P₊R₀ with tumor regression variability from 0 to 2 (Dworak grading, Fig. 1).

The operation and postoperative period passed uneventfully, on February 18 she was referred from the intensive care unit to the surgical ward (5 days after surgery) and on February 26 discharged from the hospital (13 days after surgery). After the operation patient received additional courses of chemotherapy FOLFIRI (leucovorin,

fluorouracil, irinotecan). Changes in tumor markers over the course of the disease are shown in Fig. 2. In August 2019, CT scans showed complete remission, and adjuvant therapy was completed.

In May 2020, CT showed peritoneal dissemination. Chemotherapy with FOLFIRI was resumed; the patient still had Grade II neuropathy. The government policies in Latvia do not reimburse targeted therapies in the second line and beyond. After 6 courses of therapy CT scans showed disease progression and therapy with per-oral ftorafur (R, S-1-(tetrahydro-2-furanyl)-5-fluorouracil) was commenced and continued until February of 2022, when patients' performance status decreased to ECOG II and blood biochemistry tests showed elevated ALAT 343 U/l. The patient is receiving the best supportive care. The detailed course of the disease is shown in Table II. To summarize time from initial diagnosis until disease progression was 25 months, the time from the patient received second and third-line palliative treatment was 22 months, and OS time so far—was 48 months.

3. DISCUSSION

Patient selection for the CSR + HIPEC remains challenging. Several pre-operative and intra-operative prognostic scores have been proposed to address this problem.

Some of the scores that focus only on clinical data: Peritoneal Surface Disease Severity Score [19]; clinical data plus histology is incorporated in COREP and modified COREP scores [20] Other evaluation systems include radiological examination: CT predicted PCI [11] and Pre-operative Predictive Score [19] which combines clinical

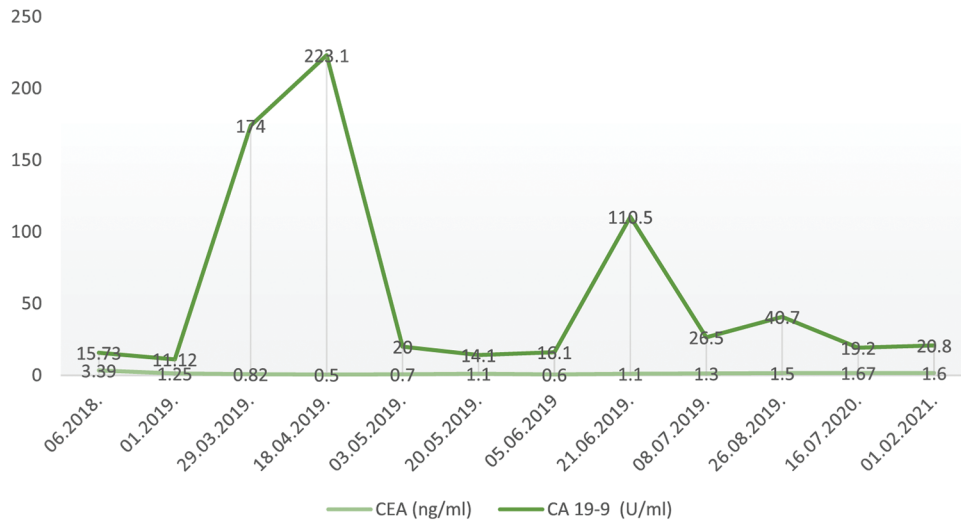


Fig. 2. Changes in tumor markers over the course of the disease.

TABLE II: COURSE OF THE DISEASE

Events	Time
First hospitalization, initial diagnostic work-up, colonoscopy showing pathological sigmoid mass	March of 2018
Colostomy	April 14 th 2018
1 st course till 12 th course of systemic treatment	20.06.2018–17.01.2019
CSR + HIPEC	13.02.2019
1 st –10 th course of systemic treatment	29.03.2019–26.08.2019
Disease progression	May of 2020
1 st –6 th course of systemic therapy	16.07.2020–07.10.2020
Disease progression	October of 2020
Per-oral therapy with ftorafur (CT 04.2021. showed slow progression of the disease)	October 2020–February 2022
Best supportive care	From February of 2022

data and CT results. However, CT has a low sensitivity and specificity for the detection of PM [21]. Additionally, some scoring systems base their decision on intra-operative findings: Gilly peritoneal carcinomatosis staging [11], Verwaal Prognostic Score, Colorectal Peritoneal Metastases Prognostic Surgical Score (COMPASS) [19], and PCI [11]. The study, where 12 international experts provided their decision algorithms for CRS + HIPEC, provided only 1 scenario for which the consensus was reached 100%: treatment of young patients with complete cytoreduction and a peritoneal carcinomatosis index (PCI) of <16 in the presence of certain risk factors [22].

To address this problem, we extrapolated factors found in different prognostic scores. In our presented case patient was 70 years old, with no weight loss or ascites, mild abdominal pain; normal markers CEA, CA 19-9 (CA 125 was not evaluated) as well as C-reactive protein, albumin, platelet count, hemoglobin, white blood count and no signet cells in histology. Patients' selection evaluating preoperative CT scans by the team of radiologists and surgeons corresponded well with intraoperative PCI evaluation. In the described case it was 12 points within the range of desirable score <20 [11] (as well as <16 as described by experts [22]).

Regarding CSR + HIPEC procedure in the presented case, there were 5 regions affected by PM similarly as reported in the PRODIGE 7 trial (in CSR + HIPEC group 5; range 3–9) [15]. The time of the operation of our patient was 8 hours which is longer than the reported 280–460 min in the previously mentioned trial [15], which could be explained by a larger number of resected organs (in our case 5 vs. 3 in trial) and two anastomoses. Duration of ICU unit (5 vs. 1–8 in trial) and hospital stay (15 vs. 14–27 in trial) corresponds with PRODIGE7 trial. Similarly, as in the PRODIGE 7 [15] and COLOPEC [2] studies we utilized oxaliplatin for HIPEC in conjunction with adjuvant systemic chemotherapy, whereas the PROPHYLOCHIP [14] study administered varying regimens.

The recorded rise in tumor markers after CRS and HIPEC is not well understood. Guidelines recommended only the use of CEA for determining prognosis, surveillance after curative resection, and monitoring treatment. Monitoring of CA19-9 is still not recommended [23], [24].

Addressing the choice of systemic therapy, we guided our decisions based on the patient's preference and knowledge that additional bevacizumab and cetuximab lead to similar effectiveness outcomes in mCRC treatment [25] and restricted reimbursement policies. The possibility of a rechallenge with oxaliplatin was restricted due to persistent Grade II neuropathy and during the Covid-19 pandemic, per-oral therapy with ftorafur was considered to be optional.

In the presented case time from initial diagnosis until disease progression was 25 months, and overall survival so far 48 months. Our data fall within the range or median OS data calculated in retrospective trials mean weighted median OS of 27 months (range 15–63 months) [6], [7] and exceeds 41.7 months OS reported in PRODIGE 7 trial [15].

4. CONCLUSIONS

In light of this case, we affirm the importance of a multidisciplinary team in the patient selection, a small team of surgical oncologists experienced in multivisceral resection and interdisciplinary cooperation with anesthesiologists to minimize intraoperative and postoperative complications.

Hence, instead of discontinuing the utilization of CSR + HIPEC for managing patients afflicted with colorectal cancer accompanied by peritoneal carcinomatosis, the existing data appear to delineate a more specific patient population for whom this treatment modality is appropriate.

Achieving optimal cytoreduction stands as the foremost prognostic factor, while the need for incorporating HIPEC requires further elucidation.

DECLARATIONS

All procedures performed were in accordance with the ethical standards of the institution and with the 1964 Helsinki Declaration and its later amendments.

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CONFLICT OF INTEREST

Authors declare that they do not have any conflict of interest.

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