

## ORIGINAL ARTICLE

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# Cytoreduction and HIPEC for peritoneal carcinomatosis of pancreatic cancer

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## Summary

**Purpose:** Peritoneal carcinomatosis of pancreatic cancer is generally considered for palliative treatment. The purpose of this study was to report the outcome of cytoreductive surgery and hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC) in patients with pancreatic cancer and peritoneal carcinomatosis.

**Methods:** Patients with documented resectable peritoneal carcinomatosis of pancreatic cancer underwent cytoreductive surgery in combination with HIPEC from 2008-2016 by the same surgical team.

**Results:** Six patients underwent 8 cytoreductions. Complete

or near-complete cytoreduction was possible in 7 cases, and palliative surgery in one case. Gemcitabine was used in 5 cases during HIPEC, and cisplatin+mitomycin-C in 2 others. All patients received adjuvant chemotherapy with gemcitabine. Four patients survived without evidence of recurrence for more than 12 months.

**Conclusions:** Cytoreductive surgery with HIPEC may be considered a treatment option in highly selected patients with pancreatic cancer and peritoneal carcinomatosis.

**Key words:** cytoreductive surgery, HIPEC, pancreatic cancer, peritoneal carcinomatosis

## Introduction

Pancreatic cancer is one of the non-gynecological cancers that frequently presents with peritoneal carcinomatosis [1]. The prognosis of pancreatic cancer is poor. The median survival of patients with pancreatic cancer and peritoneal carcinomatosis or other metastatic disease rarely exceeds 3 months [2-4]. In the presence of synchronous metastatic disease, the resection is contraindicated even if radical resection of the primary tumor is feasible because the prognosis has not been shown to improve survival [5]. In addition, a recent study does not favor palliative resection of the pancreas [6].

Cytoreductive surgery combined with intraperitoneal chemotherapy has been used in properly selected patients with primary or secondary peri-

toneal surface malignancy. Cytoreductive surgery combined with HIPEC is considered the standard of care in patients with peritoneal carcinomatosis of colorectal or appendiceal origin because it has been proved to be safe with acceptable morbidity and low mortality rates [7-9]. Recently, complete cytoreduction combined with HIPEC has been reported to offer long-term survival in one patient with an intraductal papillary mucinous tumor (IPMN) of the pancreas and peritoneal carcinomatosis [10].

The purpose of this study was to present our experience on treating pancreatic cancer patients with peritoneal carcinomatosis performing cytoreductive surgery and HIPEC.

## Methods

### Patients

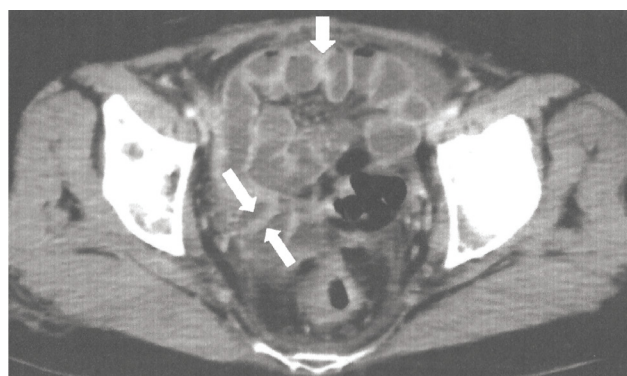
The study is a case series of pancreatic cancer and peritoneal carcinomatosis. The data of the patients were retrospectively reviewed in a prospectively maintained database. The research has been reported in line with the PROCESS criteria [11]. All patients were treated in designated Peritoneal Surface Malignancy Program by the same surgical team and gave written informed consent in a statement that the treatment was individualized, not within routine practice and without proven benefits.

### Methods

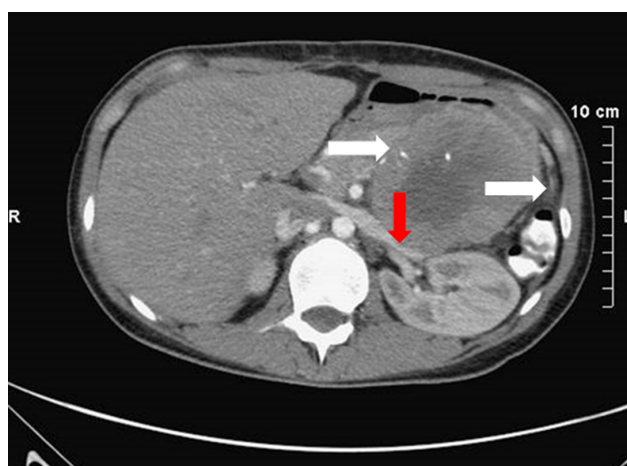
Preoperative investigation included abdominal and thoracic CT-scanning for the evaluation of possible unresectable metastases and gross estimation of the extent of the peritoneal carcinomatosis [12]. CT-enteroclysis or diagnostic laparoscopy was also used when CT scan was inconclusive for the assessment of the extent of the disease at the peritoneal surfaces of the small bowel. The precise extent of peritoneal carcinomatosis was calculated intraoperatively using the peritoneal cancer index (PCI) [13]. Standard peritonectomy procedures were performed with the intent of complete or near-complete cytoreduction [14] and the cytoreduction score (CC) was recorded at the completion of the surgical procedure [13]. HIPEC was given before the reconstruction of the continuity of the gastrointestinal tract with gemcitabine (1000 mg/m<sup>2</sup>) or cisplatin (50 mg/m<sup>2</sup>) + mitomycin C (15 mg/m<sup>2</sup>). Follow-up included physical examination, hematological-biochemical examinations, CEA and CA 19-9 levels, and abdominal CT scan every three months. A PET/CT scan was used when high CA 19-9 levels did not correspond to the imaging findings.

## Results

From 2008 until 2016, 6 patients with mean age 51.8±13.5 years (range 28-69), underwent 8 cytoreductive operations for pancreatic cancer with peritoneal carcinomatosis. All patients were in acceptable physical status (Karnofsky performance scale > 50%). The anatomic location of the primary site was the tail of the pancreas in all patients (Figure 1). There were 3 male and 3 female patients. The mean PCI was 12±8 (range 3-25). All patients had large volume tumor and ascites was present in 4 cases. Two patients presented with synchronous peritoneal carcinomatosis at initial diagnosis (Figure 2), while the others presented with metachronous carcinomatosis. Two patients received neoadjuvant chemotherapy because they had not been assessed as candidates for cytoreduction at initial diagnosis. After 4 cycles of chemotherapy the CT scan showed that the extent of peritoneal carcinomatosis was partially eliminated. In addition, two women had been previously treated with cytore-



**Figure 1.** Axial image of CT enteroclysis in the pelvis shows thickness of the small bowel wall due to accumulation of multiple cancerous implants (arrows). Inconclusive about the diagnosis.



**Figure 2.** Local recurrence occupying the tumor bed after distal pancreatectomy and splenectomy (white arrows showing the edge of the tumor) and invading the left renal vein (red arrow).

ductive surgery and systemic chemotherapy for ovarian cancer. The radiologic examinations were inconclusive about the origin of peritoneal carcinomatosis. In both cases the tail of the pancreas was enlarged but no obvious tumor was clearly visible. Complete (CC-0) and near-complete cytoreduction (CC-1) was possible in 5 and 2 cases respectively. Epigastric peritonectomy procedure (resection of the previous scar with the round and the falciform ligaments of the liver) was undertaken in 1 case. Right and left subdiaphragmatic peritonectomies were performed in 4 and 2 cases, respectively, greater and lesser omentectomy in 6 and 4 cases, respectively, and splenectomy in 4 cases. Cholecystectomy was performed in 3 cases and resection of the omental bursa in 4 cases. Right and left lateral peritonectomy procedures were required in 4 and 3 cases, respectively, while pelvic peritonectomy was necessary in 5 cases. In addition, subtotal gastrectomy was undertaken in

**Table 1.** List of patients

Patients	PCI	CC	HIPEC	Site of failure	Overall survival	Neo-adjuvant chemotherapy
Female, 59y	23	CC-1	Cis-platin+Mit-C	Liver	36	No
Male, 59y	14	CC-0	gemcitabine	Head of the pancreas	12	Yes
Male, 59y	3	CC-0	gemcitabine	-	Hospital death	No
Male, 54y	16	CC-0	gemcitabine	Liver, peritoneum	4	Yes
Male, 54y	22	CC-3	-		1	No
Female, 28y	9	CC-0	gemcitabine	Liver	12	No
Female, 35y	3	CC-0	Cis-platin+Mit-C	NED	12	No
Female, 69y	13	CC-0	Cis-platin+Mit-C	-	4 months	No

NED: no evidence of disease. For other abbreviations see text

2 cases, subtotal colectomy in 2 cases, segmental intestinal resection in 3 cases, and in one case resection of the left kidney was required in order to achieve a CC-0 operation. Distal pancreatectomy was performed in 4 cases. In 2 cases, distal pancreatectomy had been previously performed and additional pancreatectomy was needed for a CC-0 surgery. In one case, only palliative surgery was possible (CC-3) because the small bowel was found to be extensively seeded by tumor nodules. The patient presented with complete obstruction of the small bowel and by-pass procedure was performed despite a previous CC-0 surgery. In this case intraperitoneal chemotherapy was not administered. The cytotoxic drug used during HIPEC was gemcitabine in 4 cases, and a combination of cisplatin+mitomycin-C in the remaining 3 cases. Postoperative systemic chemotherapy with gemcitabine was administered in 7 cases.

One patient died during the postoperative period after secondary cytoreduction because of liver failure. Another one, was re-admitted to the hospital and died 4 months after surgery because of delayed sepsis following intra-abdominal abscess adequately drained. One patient required prolonged mechanical ventilation, and in another case intra-abdominal abscess delayed the in-hospital stay. The intra-abdominal abscesses resulted because of pancreatic fistulas. In two other cases wound infection complicated the immediate postoperative course of the patients. No open re-operation was undertaken because of complications. The diagnosis of pancreatic adenocarcinoma was established in all specimens by histopathology.

Recurrence was recorded in 5 cases (62.5%), which was local-regional in 3 cases, and distant in 2. The mean time to recurrence was 11.8±6.8 months.

One patient survived 2 years, one survived 13 months, and two more patients survived 12 months, one of them without evidence of disease (Table 1).

## Discussion

Over the last decades pancreatic cancer surgery has advanced and improved, because postoperative morbidity and mortality have decreased [15]. Peritoneal metastases are present in approximately 40% of the patients, but free intraperitoneal tumor cells are detected in an additional one third of the patients without visible peritoneal surface metastases [16,17]. Peritoneal carcinomatosis of pancreatic origin is generally considered incurable, and patients receive systemic chemotherapy frequently in clinical trials. Until recently, the same general rule applied to most gastrointestinal cancers, as well as to primary peritoneal tumors. However, it has been proven that certain subgroups of patients with peritoneal carcinomatosis may be offered a significant survival benefit if treated with complete or near-complete cytoreduction and intraperitoneal chemotherapy [18-20]. This treatment has recently been used as an alternative in recurrent and persistent ovarian cancer and as upfront treatment in ovarian cancer, with its efficacy not yet clearly determined [21-23]. These findings have led surgical teams around the globe to adopt cytoreductive surgery in the setting of clinical protocols and offer this type of treatment to selected patients.

The resection of the entire macroscopically visible tumor has been shown to offer significant survival benefit in patients with peritoneal metastases, showing that completeness of cytoreduction is the most significant prognostic indicator for long-term survival [24]. Another prognostic indicator of survival is the extent of peritoneal carcinomatosis as assessed by the calculation of the PCI [8,13]. The tumor grade has also been shown to affect survival. Patients with low-grade tumors have significantly better long-term survival compared to patients with high-grade tumors, as is

commonly reproduced in pseudomyxoma peritonei [9,20,25].

Following the publication of the CONKO and ESPAC trials, gemcitabine has become one of the commonly used drugs in adjuvant chemotherapy, and it has been shown to improve survival in pancreatic cancer patients who have had potentially curative resection [26,27]. The drug has been used and tested for intraperitoneal use in animal studies which have shown that early postoperative intraperitoneal use of gemcitabine may reduce the extent or even prevent peritoneal disease [28]. Gemcitabine has been shown to concentrate at the peritoneal surfaces, while the plasma concentration remains low [29]. Laboratory pharmacokinetic studies have shown that the area under the curve ratio of intraperitoneal to systemic drug exposure is closely related to the intraperitoneal dose, while tissue samples have shown increased drug concentrations when administered with heat [30]. HIPEC as an adjuvant in resectable pancreatic cancer has shown that local-regional failures may be effectively controlled [31].

The long survival of the patient with pancreatic mucinous papillary carcinoma who underwent complete cytoreduction and HIPEC [10] hesitantly suggests that a highly selected population of patients with pancreatic carcinomas and peritoneal carcinomatosis may have a survival benefit if complete cytoreduction can be achieved. Our experience began by treating a patient with pancreatic adenocarcinoma who had an unexpectedly long survival without intraperitoneal recurrence despite a CC-1 operation and extensive peritoneal disease. The second patient survived for one year without disease on the peritoneal surfaces, as proven in re-exploration but had local recurrence at the pancreatic remnant. The patient died during the 5<sup>th</sup> postoperative day after a second cytoreduction because of liver failure. The third patient succumbed to massive disease early in the follow up period despite a CC-0 surgery. It should be noted that the manuscript is referred to patients with cancer of the tail of the pancreas. Involvement of the head of the pancreas in cases of cytoreductive surgery may prove to be an entirely different entity. The fourth patient developed distant metastases at the liver and died 12 months after cytoreduction despite a CC-0 surgery. The 5<sup>th</sup> patient remains disease-free 12 months following surgery and the 6<sup>th</sup> patient died 4 months postoperatively because of delayed complications.

The pathophysiology of the development of spontaneous peritoneal carcinomatosis in patients with cancer of the tail of the pancreas remains an enigma. It is certain that cancer emboli

are exfoliated from the tumor but the route of dissemination to distant peritoneal surfaces cannot be easily explained once the lesser peritoneal sac is a site of peritoneal fluid resorption and cancer emboli cannot be transported in the abdominal cavity, especially when the patient has not undergone surgery.

An important aspect that needs to be addressed is if cytoreduction should be more readily advised in cases of cancer of the tail of the pancreas compared to cancer of the head of the pancreas. It is known that cancer of the body and tail of the pancreas carries a worse overall prognosis, but it could be the only case in which cytoreduction may be indicated [32]. When upfront cytoreduction with concomitant resection of the primary site is considered, a Whipple's resection supplemented with peritonectomies would be far more technically demanding compared to distal pancreatectomy with any peritonectomy. If peritoneal carcinomatosis presents as a recurrence, it would also be very difficult, if not impossible, to clear the tumor bed deposits off, the mesenteric vessels and the areas of previous anastomoses. It seems reasonable to believe that if cytoreduction in pancreatic cancer will prove meaningful, it will be for cancer of the tail of the pancreas.

In a recent publication, it has been shown that cytoreductive surgery combined with HIPEC has been successfully performed for other rare tumors (rare ovarian cancer, neuroendocrine tumors, and sarcomatosis) with low hospital mortality, acceptable morbidity, and long-term survival. The report has confirmed that limited peritoneal carcinomatosis and complete cytoreduction have been documented as the most significant prognostic factors of survival for rare ovarian carcinomas and neuroendocrine tumors but not for sarcomatosis [33].

This report does not aim to draw conclusions or suggest that cytoreduction and HIPEC may be a choice for all patients with peritoneal carcinomatosis of pancreatic origin. In contrast, it covers controversial cases of patients and as a consequence, surgeons with similar anecdotal experience can provide their input. It also suggests that an international registry may be needed for the unfortunate patients with pancreatic cancer and peritoneal involvement. There is always a subgroup of patients waiting to be identified, and these patients will benefit from aggressive treatment.

### Conflict of interests

The authors declare no conflict of interests.

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