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Simultaneous Distal Pancreatic Resection and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for Peritoneal Carcinomatosis in Adenocarcinoma of the Pancreas - A Case Report

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Rezumat

Rezecție pancreatică distală și chimioterapie hipertermică intraperitoneală (HIPEC) simultane pentru carcinomatoza peritoneală în adenocarcinomul pancreasului - prezetare de caz

Cancerul pancreatic rămâne una dintre cele mai mari provocări în oncologie, deoarece majoritatea pacienților sunt diagnosticați într-un stadiu de diseminare limfatică regională sau sistemică a bolii. 10% dintre pacienți prezintă carcinomatoză peritoneală la diagnostic. În ultimele decenii, a fost dezvoltată chirurgia citoreductivă (CRS) combinată cu chimioterapia intraperitoneală intraoperatorie hipertermică (HIPEC), ce reprezintă o nouă opțiune de tratament individualizat pentru pacienții cu cancer diseminat peritoneal. Această prezentare descrie cazul unui bărbat de 39 de ani diagnosticat inițial cu carcinom al cozii pancreatice şi carcinomatoză peritoneală localizată. Ca abordare individualizată, a fost recomandată chimioterapia neoadjuvantă. Stadializarea ulterioară a relevat o reducere a dimensiunii tumorii. Chirurgia citoreductivă (CRS) ce a inclus splenopancreatectomia distală a fost efectuată şi urmată de HIPEC. Postoperator, pacienta a dezvoltat o fistulă pancreatică relevantă clinic, însă remisă, şi a primit chimioterapie adjuvantă. În cancerul pancreatic cu carcinomatoză peritoneală localizată, asocierea dintre CRS şi HIPEC este o opțiune valabilă în cazurile extrem de selective, cu o supraviețuire globală potențial extinsă şi o calitate a vieții acceptabilă.

Cuvinte cheie: cancer pancreatic, adenocarcinom pancreatic, carcinomatoză peritoneală, HIPEC, chirurgie citoreductivă

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Abstract

Pancreatic cancer remains one of the biggest challenges in oncology, as most patients are diagnosed in a stage of regional lymphatic or systemic spread of the disease. 10% of the patients present with peritoneal carcinomatosis upon diagnosis. In the past decades, cytoreductive surgery (CRS) combined with hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC) has been developed and presents a new, individualized treatment option for patients with peritoneal disseminated cancer. This case report presents the case of a 39-year-old male with the initial diagnosis of a carcinoma of the pancreatic tail with localized peritoneal carcinomatosis. As an individualized approach, neoadjuvant chemotherapy was recommended with an option for a second exploration. Re-Staging revealed a reduction in tumor size. Cytoreductive surgery (CRS) including a distal splenopancreatectomy was performed and followed by HIPEC. Postoperatively, the patient developed a clinically relevant pancreatic fistula, however recovered and was able to receive adjuvant chemotherapy. Taken together, in pancreatic cancer with localized peritoneal carcinomatosis CRS and HIPEC are a valid option in highly selective cases with potential extended overall survival and an acceptable quality of life.

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

Introduction

With steadily increasing incidence, pancreatic cancer remains one of the biggest challenges in surgical oncology. Despite significant improvements in diagnostics and awareness of the importance of early detection, most patients with pancreatic cancer are diagnosed in a stage with regional lymphatic or systemic spread of the disease. Survival rates remain poor; whereas 5-year survival is about 40% in patients with limited disease, long-term survival across all stages is reported to be as low as 10.8%. (1).

Surgical resection combined with systemic chemotherapy is the only curative treatment. However, R1-resections are not uncommon and affect up to 70% of patients undergoing surgery, ultimately resulting in high rates of disease recurrence (2-4). While treatment strategy for the limited disease is of curative intent, palliative management is recommended for patients with advanced, e.g., metastatic or recurrent disease.

In palliation, chemotherapy with FOLFIRINOX or NAB-paclitaxel combined with gemcitabine has been shown to be efficient in delaying disease progression (5-7). However, under these circumstances, survival rates of 2% in 5 years and median life expectancy of less than one year from diagnosis remain very poor (8,9).

Besides hepatic metastasis being the primary site of disseminated pancreatic cancer, peritoneal carcinomatosis (PC) is present upon diagnosis in at least 10% of cases (10). As R0-status and thus curation cannot be achieved in patients with PC, a surgical treatment used to be off limits making palliative systemic therapy the only possible treatment option.

In the past decades, cytoreductive surgery (CRS) combined with hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC) has been developed and presents a new treatment option for patients with peritoneal disseminated cancer. The rationale behind this procedure is the immediate effect of cytotoxic drugs in hyperthermic fluid on malignant cells in the abdominal cavity and thus intensifying regional dosage while reducing systemic toxicity (11). While having been proven effective for patients with PC due to ovarian or appendiceal malignancy, HIPEC as a treatment option for PC in colon carcinoma

has been abandoned at many centers as no significant survival benefit could be shown (12-15).

In the following, we present the case of a 39-year-old male with PC upon diagnosis of pancreatic cancer who received an individualized treatment regimen consisting of neoadjuvant chemotherapy, pancreatic resection, CRS, and HIPEC. This case report has been reported in line with the SCARE Criteria (16).

Case Report

A 39-year-old patient presented in our emergency department with ongoing upper abdominal pain, intermittent diarrhea, and weight loss of 6kg in the previous three months. Upon presentation, the symptoms had been present for about eight months. Prior medical consultation took place abroad, where intestinal steroids were administered following the endoscopic diagnosis of terminal ileitis. After the absence of improvement, an abdominal PET CT scan was performed and detected a suspicious mass in the pancreatic tail, prompting the patient to present at our institution.

So far, the patient's history included surgery for an umbilical hernia several years ago, no medication except occasional ibuprofen, and no significant allergies. The patient's mother had died aged 63, from unknown malignancy. Patient risk factors included heavy smoking with 20 pack years upon presentation.

Physical examination showed a 39-year-old male in good constitution with normal weight (69 kg, 170 m, BMI 23,88 kg/m^2), and no pathological findings were obtained. Laboratory diagnostics, however, revealed elevated tumor markers CEA and CA 19-9 with 47.6 µg/l and 560 kU/l, respectively. A review of the abdominal PET CT scan and interdisciplinary case discussion resulted in suspicion of malignancy of the pancreatic tail showing signs of the infiltration of the splenic vein and artery (*Fig. 1*). The consensus was reached for surgical exploration.

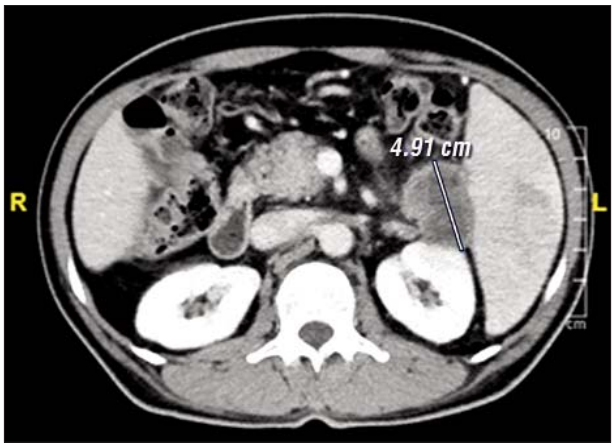

Figure 1. Staging CT scan prior to the neoadjuvant treatment showing the tumor mass at the pancreatic tail. The maximum diameter is 4.91 cm

Abdominal exploration revealed peritoneal carcinosis of the upper abdomen (bilateral diaphragm) and pelvic area resulting in a peritoneal cancer index (PCI) of 5. Parallel intraoperative histological examination of peritoneal biopsies confirmed adenocarcinoma cells. This finding formally established the diagnosis of peritoneal carcinosis due to pancreatic cancer leading to termination of surgery after implantation of a subclavian port system.

The final histological evaluation described a tumor originating from the biliopancreatic system. The tumor was tested for genetic alterations revealing no HER2 mutation. However, an activating mutation of KRAS was detected.

These additional findings were discussed in the interdisciplinary oncological board. With regard to the patient's young age and good condition (ECOG 0), chemotherapy with mFOLFIRINOX was recommended with an option for a second exploration in case of tumor regression or stable disease. Chemotherapy was initiated with mFOLFIRINOX approximately ten days after the surgery.

The patient received nine cycles of mFOLFIRINOX. After the second therapy administration, the patient developed relevant thrombopenia leading to dose reduction of Irinotecan and continuation without 5-FU for the remaining cycles. Other side effects

were polyneuropathy (grade I), diarrhea, weight loss, and nausea which, under sufficient supportive therapy, did not interfere with the therapy regimen.

Re-Staging after neoadjuvant treatment revealed a reduction in the tumor size and lymphatic nodes (*Fig. 2*). In line with the CT scan findings, the tumor markers CEA and CA 19-9 improved to 10.4 µg/l and 169 µg/l, respectively.

Interdisciplinary re-discussion resulted in a recommendation for subsequent surgical assessment. Intraoperatively, PC was still detectable; however, it improved and localized to the dome of the right side of the diaphragm alone (PCI 3). Distal splenopancreatectomy was performed with en-bloc resection of the left hemicolon flexure, the upper part of the left kidney, and adrenal gland completed by cholecystectomy and appendectomy as well as partial parietal peritonectomy and systematic lymphadenectomy. Histopathological examination of intraoperative specimen resulted in the TNM -classification: G2, ypT3, ypN1(3/17 lymphatic nodes), L1, V0, Pn 1, yM1 (peritoneal) with local R0 wide resection margins.

Given limited PC, the interdisciplinary consensus was reached for HIPEC as an individual treatment concept that was discussed extensively with the patient as an addition to adjuvant completion of treatment with mFOLFIRINOX. Three days after resection, HIPEC was performed with Gemcitabine (1000 mg/m^2 body surface) for 90 min as described before .

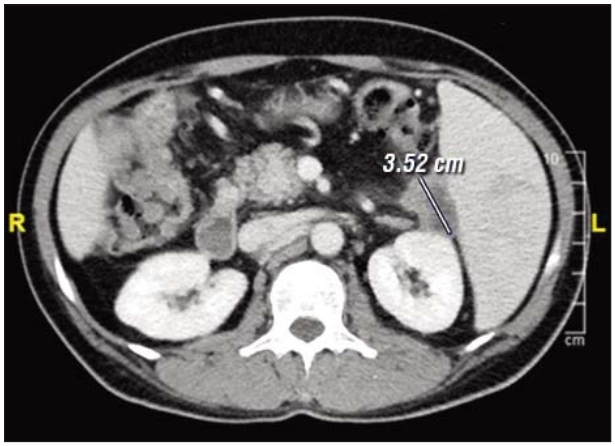

Figure 2. Staging CT scan after the neoadjuvant treatment showing the tumor mass at the pancreatic tail. The maximum diameter is 3.52 cm.

Over the postoperative course, the patient developed a type B pancreatic fistula according to ISGPS, which improved under continuous rinsing via the intraabdominal drains. The drains could then be removed. In addition, the patient presented with delayed gastric emptying type A according to ISGPS, resolved under prokinetic medication. Eight days after HIPEC, the patient presented with a dehiscent fascia revised on the same day. Later on, the patient showed signs of upper gastrointestinal bleeding. An endoscopic assessment revealed a Forrest IIb duodenal ulcer that was subsequently clipped. After full recovery, the patient was discharged after 25 days with a recommendation for three additional cycles of mFOLFIFINOX.

At the time of presentation for adjuvant chemotherapy, two months after surgery, the patient's overall condition was good (ECOG 0). Tumor markers CEA and CA19-9 showed normal values (2.0 and 14.9 respectively), chemotherapy was initiated, and the last cycle was completed four weeks later.

Approximately half a year after surgery, the patient presented to the emergency department with progressive abdominal pain for four days accompanied by nausea and vomiting. Diagnostic work-up revealed small bowel obstruction as a suspected result of tumor recurrence as indicated by elevation of tumor markers (CEA 8.5 µg/l and CA19-9 41.0 kU/l). After the failure of conservative treatment, the patient underwent surgical exploration. Intraoperatively small bowel obstruction due to PC was confirmed. In a multi-procedure approach, the patient underwent small bowel resection with terminal ileostomy complicated by 4-MRGN pneumonia. Ultimately the patient was discharged home and scheduled for reinduction of palliative chemotherapy.

Discussion

Current guidelines do not recommend

resection and HIPEC for PC in patients with pancreatic cancer due to a lack of evidence for its benefit (18). Standardized treatment includes palliative chemotherapy with FOLFIRINOX or nab-Paclitaxel plus gemcitabine (5-7). Thus, surgical procedures in patients with PC remain part of individualized treatment concepts and must be tailored according to tumor characteristics and biology as well as patient constitution and wishes.

Diagnostic workup in patients with suspected PC should include staging laparoscopy or explorative laparotomy to assess disease extent (as it is not always detected with diagnostic imaging) and resectability. Tumor size >3 cm and high levels of CA 19-9 and CEA are associated with advanced pancreatic cancer. In these cases, staging laparoscopy might be considered (19-21).

In the present case, re-laparotomy was performed after a good response to neo-adjuvant treatment with reduced levels of CEA and CA 19-9 and tumor size. The exploration revealed a locally resectable pancreatic tumor with persistent but decreasing limited peritoneal spread.

Given the young age of the patient and condition (ECOG 0) and the favorable tumor biology under systemic therapy, a radical resection, including cytoreduction, was performed. The surgical treatment was completed with a HIPEC three days after tumor resection and cytoreduction.

After completing systemic therapy, the patient experienced a period of 6 months without symptomatic disease recurrence and good quality of life. However, six months after surgery, the patient reported to the ER showing signs of mechanic bowel obstruction that ultimately was confirmed as a consequence of tumor recurrence. Surgery was indicated and resulted in bowel resection and terminal ileostomy.

When assessing patients with advanced pancreatic cancer with possible peritoneal spread, the following points need to be considered:

First, HIPEC does not present a curative treatment option in pancreatic cancer for patients with or without PC. In a prospective analysis, Tentes et al. monitored patients who received HIPEC after R0 resection of localized pancreatic carcinoma to find that the 5-year survival rate after tumor resection and HIPEC was 24% compared to an overall survival rate of 10-15% without HIP (22,23). However, in a study collective with PC, 4 out of 6 patients who received cytoreduction and HIPEC with additional adjuvant treatment showed no signs of tumor recurrence after 12 months - a period that exceeds median survival rates (24).

Secondly, intraperitoneal and systemic chemotherapy is most effective for patients with tumors with biological features rendering them susceptible to treatment. In patients with pancreatic adenocarcinoma resulting from BRCA-2 mutation, HIPEC presents a more suitable treatment option: Pancreatic adenocarcinoma due to BRCA-2 mutation results in a DNA repair defect rendering it susceptible to platin-based chemotherapeutic agents as well as Mitomycin C facilitating prolonged patient survival (25,26). Therefore, when considering CRS and HIPEC for advanced pancreatic cancer, preoperative histology, and genetic alterations should be assessed to gain insights into tumor biology and optimize the surgical and chemotherapeutic treatment approach.

Combining pancreatic resection with CRS followed by HIPEC is a procedure with a high risk for postoperative complications. Our patient developed fascial dehiscence requiring surgical management. Downs-Canner et al. compared the postoperative outcome of patients who underwent distal pancreatic resection in combination with HIPEC to those who only underwent surgical resection. While the rate of postoperative pancreatic fistula (POPF) did not differ between the two groups, patients who received CRS and HIPEC tended to have more severe POPF (grade B and C) compared to the resection-only group (27). The validity of this study on all over pancreatic resection is limited as it only observed patients

after distal pancreatectomy. Schwarz et al. could later demonstrate that the occurrence of POPF after distal pancreatectomies and simultaneous HIPEC does not impact the 90-day mortality (28). Further analysis revealed that the safety of HIPEC and CRS alone for patients with pancreatic malignancy is acceptable and should be considered as a treatment option (29).

The case at hand combines a complex resection of the pancreatic tail with simultaneous HIPEC and CRS in a palliative setting which so far has not been subject to investigation on a larger scale. The only study available on this topic was conducted by Tentes et al. in 2016. Yet the primary endpoint of this investigation was the overall survival rate in patients without PC who received HIPEC as an adjuvant treatment with curative intent. Complications were monitored, but there was no control group, and no valid conclusion regarding the procedure's safety could be drawn (21).

In patients with peritoneal carcinosis or locally advanced pancreatic cancer, neoadjuvant treatment with mFOLFIRINOX or gemcitabine/nab-paclitaxel presents a more frequently used opportunity to render initially unresectable tumors susceptible to surgery.

An interdisciplinary and individualized approach with perioperative chemotherapy, cytoreductive tumor resection, and HIPEC extended patient survival above the reported statistical median survival data in this patient (8,9). The role of neoadjuvant mFOLFIRNOX was crucial in this patient as it enabled tumor resection. Of utmost importance is the extensive neoadjuvant treatment that must be completed postoperatively and patient selection (relatively young, EGOG 0). In addition, HIPEC, after sufficient tumor resection (macroscopically no tumor residues), presents another treatment option in patients with a good response to neoadjuvant chemotherapy that needs further evaluation. Patients with solid organ metastasis should be excluded from cytoreduction and HIPEC due to a lack of treatment efficacy.

Up to now, the patient has survived 15 months, starting with the initial diagnosis of PDAC with PC. Despite multimodal treatment, tumor recurrence occurred 13 months after initial diagnosis leading to palliative treatment. During this time, the patient has spent 15 weeks hospitalized with several outpatient consultations. Regarding the quality of life under this regimen compared to palliative chemotherapy alone, it remains unclear if the surgical approach can be considered superior. Nonetheless, the temporary results of tumor resection allowed the patient to spend holidays in his home country with his family 12 months after the initial diagnosis of pancreatic cancer with peritoneal carcinomatosis. Retrospectively the patient expressed no regrets regarding the choice of treatment.

Conclusion

PC in patients with pancreatic adenocarcinoma remains challenging. Allover survival is poor. However, combined with HIPEC and CRS, tumor resection might be a valid option in highly selective cases with potential extended overall survival and an acceptable quality of life. Further research is required to identify patients who might benefit from HIPEC in pancreatic cancer.

Conflicts of Interests: None

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