CASE REPORT

# Repeated Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Peritoneal Carcinomatosis from Pancreatic Intraductal Papillary Mucinous Carcinoma

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## ABSTRACT

**Background** Pancreatic intraductal papillary mucinous carcinoma with peritoneal carcinomatosis is regarded as an unresectable disease for which only palliative chemotherapy or supportive care is recommended. Applying cytoreductive surgery with hyperthermic intraperitoneal chemotherapy on patients with intraductal papillary mucinous carcinoma with peritoneal carcinomatosis remains controversial. **Case Summary** A Fifty-four-year-old man with a past history of pancreatic tail intraductal papillary mucinous carcinoma post distal pancreatectomy and subsequent peritoneal carcinomatosis diagnosis after 13 months of primary surgery received neoadjuvant chemotherapy, complete cytoreductive surgery and hyperthermic intraperitoneal chemotherapy with mitomycin-C and cisplatin at 43°C for 40 minutes, followed by adjuvant chemotherapy with TS-1 (Tegafur and Gimeracil and Oteracil). Disease recurrence on positron emission tomography–computed tomography was noted after 8 months, and we performed a second complete cytoreductive surgery and hyperthermic intraperitoneal chemotherapy with mitomycin-C and cisplatin according to the report of histoculture drug-response assay. In the second recurrence, recurrent adenocarcinoma was impressed. No evidence of disease recurrence was observed at 15 months after PC diagnosis. **Conclusion** Compared with the poor prognosis for peritoneal carcinomatosis under conservative treatment, this aggressive repeated cytoreductive surgery-hyperthermic intraperitoneal chemotherapy may provide considerable life extension in selected patients. After surgery, regular follow-up for serum markers and positron emission tomography–computed tomography is recommended.

## INTRODUCTION

Intraductal papillary mucinous neoplasms (IPMNs) of the pancreas are neoplasms characterized by papillary growths in the pancreatic duct system, presenting with thick mucus secretion [1]. According to the sites of lesions and their distribution, IPMNs are classified as main-duct IPMN (MD-IPMN), branch-duct IPMN (BD-IPMN) and mixed. IPMNs have a wide range of neoplasms from dysplastic tumors with malignant potential to invasive malignancies. According to World Health Organization classifications, IPMNs comprise four categories: 1) slight dysplasia or intraductal papillary mucinous adenoma; 2) moderate dysplasia or borderline malignancy (borderline IPMN); 3) severe dysplasia or intraductal papillary mucinous carcinoma (IPMC) *in situ* (noninvasive IPMN); and 4) IPMC or invasive carcinoma (invasive IPMN) [2]. In a large long-term prospective cohort of 403 IPMN patients, 68 patients (18.6%) were found to have the invasive type, with a recurrence rate of 33.8% (23 patients), and the rate of peritoneal seeding was reported to be 11.8% (8 patients) [3]. The median disease-free survival of invasive IPMN is 18.1 months, ranging from 2.5 to 214.4 months. Peritoneal carcinomatosis (PC) at the time of initial diagnosis or recurrence after primary surgery is regarded as an incurable disease, and only palliative chemotherapy or supportive care is recommended.

PC is often regarded as an untreatable disease; however, a combined therapy strategy of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy

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**Abbreviations** CRS cytoreductive surgery; HIPEC hyperthermic intraperitoneal chemotherapy; IPMC intraductal papillary mucinous carcinoma; PC peritoneal carcinomatosis; PET-CT positron emission tomography–computed tomography
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(HIPEC) was developed to prolong patient survival in the 1990s. Numerous studies have demonstrated significant improvements in survival and prognosis through the use of CRS and HIPEC in patients with PC from appendiceal cancer, colorectal cancer, malignant peritoneal mesothelioma, gastric cancer, pseudomyxoma peritonei, and ovarian cancer [4, 5, 6, 7, 8]. Applying CRS-HIPEC in patients with pancreatic cancer and PC is controversial. Herein, we report our experience of repeated CRS-HIPEC for a 54-year-old male patient with invasive IPMN and PC recurrence after primary surgery.

## CASE SUMMARY

The patient had a past history of fatty liver, dyslipidemia, and impaired glucose tolerance. In February 2015, a health check-up showed elevated carbohydrate antigen (CA) 19-9. Abdominal computer tomography revealed a 3-cm cystic lesion over the pancreatic tail **(Figure 1a)**. Endoscopic ultrasonography-guided fine-needle aspiration (EUS-FNA) of the cyst content revealed adenocarcinoma. Under the impression of pancreatic tail malignancy, he received a distal pancreatectomy with splenectomy, and pathological examination showed mixed-type IPMC, pathologic stage III, pT3N0M0. Adjuvant chemotherapy of TS-1 (Tegafur and Gimeracil and Oteracil) at a dosage of 120 mg/day was then initiated. In March 2016, elevated CA19-9 was again noted, and positron emission tomography–computed tomography (PET-CT) revealed peritoneal seeding at greater omentum, transverse colon and the left anterior abdominal wall **(Figure 1b)**. Salvage chemotherapy with gemcitabine and nanoparticle albumin–bound paclitaxel was performed. In July 2016, CRS and HIPEC were planned. During exploration, tumor recurrence over the greater omentum, transverse colon, ileum, and peritoneum were noted. The peritoneal cancer index, according to the principles described by Sugarbaker, was 3 [9]. Washing cytology of ascites showed adenocarcinoma. Complete cytoreduction was performed with peritonectomy, cholecystectomy, omentectomy, extended right hemicolectomy with side-to-side ileocolostomy, and resection of the small bowel segment (20 cm) with side-to-side anastomosis followed by HIPEC with mitomycin-C 20 mg (MMC) and cisplatin 40 mg perfusion in 4 L of saline at 43°C for 40 minutes. The operative time was 207 minutes, and the blood loss of 625 mL. The duration of ICU stay was 4 days, and the total hospitalization of surgery was 21 days. He recovered uneventfully after surgery. Afterward, he received adjuvant chemotherapy of TS-1.

In March 2017, elevated CA19-9 was again found, and PET-CT showed PC recurrence at left rectus muscle and Douglas' pouch of pelvic region **(Figures 1c, 1d)**. Surgical intervention was then performed, grossly revealing tumor recurrence over the left abdominal wall, sigmoid, rectum, left rectus muscle, and paraaortic lymph node. We performed a second complete CRS including completion total colectomy with reconstruction of ileorectal side-to-end anastomosis by EEA 25 mm, paraaortic lymph node dissection, and resection of the left gonadal vessels, right vas deferens, and partial rectus muscle with tumor involvement, followed by HIPEC with mitomycin-C 20 mg (MMC) and cisplatin 40 mg perfusion in 4 L of saline at 43°C for 40 minutes. This time, the specific choice of chemotherapeutic agents depended on the results of a histoculture drug-response assay, which showed that

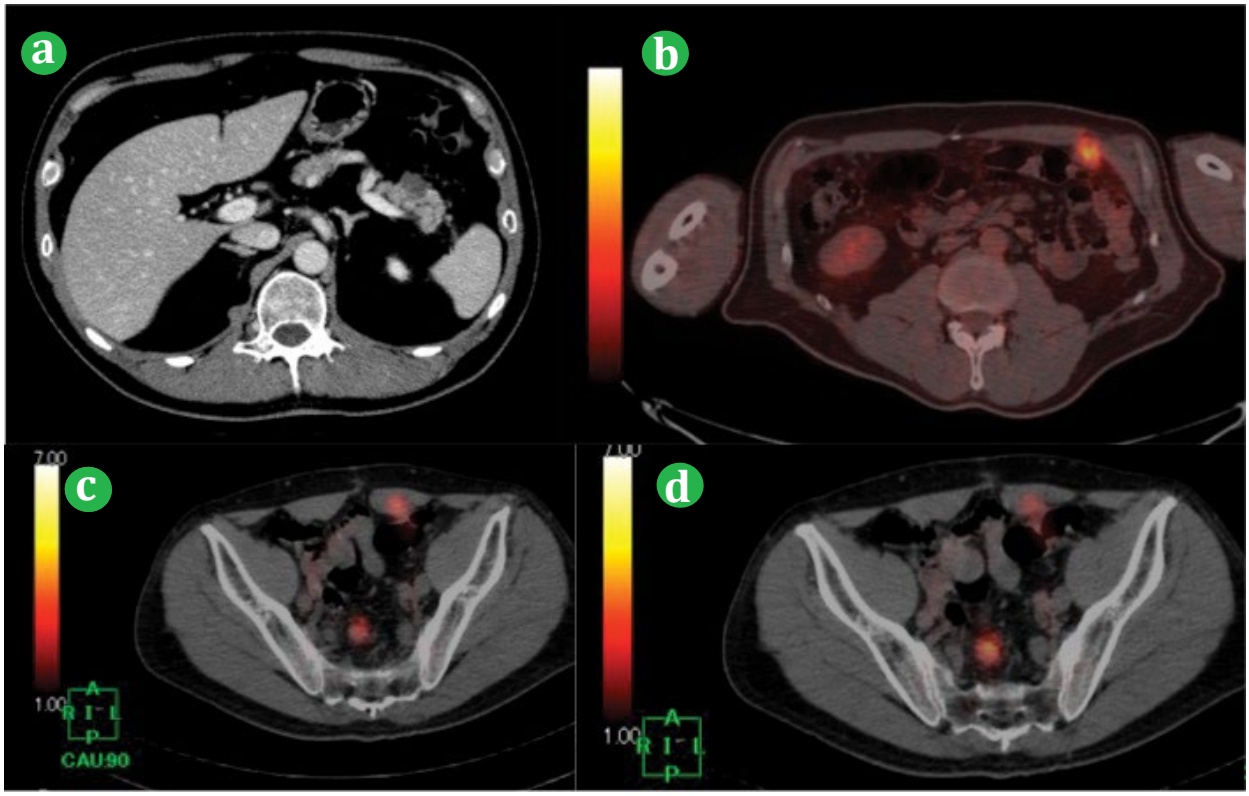


**Figure 1. (a).** Initially, CT showed a cystic neoplasm at pancreatic tail; **(b).** First recurrence over greater omentum and transverse colon; **(c, d).** Second recurrence at left rectus muscle and Douglas' pouch of pelvic region.

the antiproliferative ability was 65.1% for cisplatin and mitomycin-C 49.1% versus gemcitabine 12.7%. The operative time was 273 minutes, and the blood loss of 1095 mL. The duration of ICU stay was 4 days, and the total hospitalization of surgery was 20 days. After the operation, he experienced watery diarrhea about 10 times per day. The short-term parental nutrition and electrolytes monitor were supplied. This condition was gradually subsided and recovered at 2 month after discharge from hospital.

The pathological examination revealed tumor infiltration of mesorectum at Douglas' pouch in pelvic region, but without direct invasion to rectal wall **(Figures 2a, 2b)**. Hematoxylin and eosin-stained section showed the formation of irregular lumens by cuboid and cylindrical shape hyperchromatic cancer cells **(Figures 2c, 2d)**. The expression of MUC2 in first recurrent tumor tissue was positive, which concluded the diagnosis of recurrent IPMC. MUC2 stain is expressed in intestinal goblet cells of mucinous carcinoma from colon, breast, pancreas, ovary and stomach. However, in the second recurrence, recurrent adenocarcinoma was impressed because the expression of MUC2 turned to negative. It is possible that this IPMC had progressed to a pancreatic ductal adenocarcinoma (PDAC).

## DISCUSSION

The prognosis of IPMN or IPMC is relatively more favorable than that of pancreatic adenocarcinoma. The 5-year overall survival rate of IPMC is significantly higher than PDAC (31.4% *vs*. 12.4%) [10]. The 5-year survival of patients after surgical resection for noninvasive IPMN is reported to be at 77-100%, while for those with invasive carcinoma, it is significantly lower at 27-60% [1]. The median disease-free survival of invasive IPMN is 18.1 months [3]. Our aggressive repeat CRS-HIPEC achieved 28 months after initial diagnosis, and ongoing follow-up showed no evidence of disease recurrence at the time of this study. Although there are no available survival data specific to IPMC with PC, the median survival for pancreatic carcinoma with PC was reported to be only 6 weeks (95% confidence interval 5–7) without surgical management [11]. For the patient in the present study, preoperative chemotherapy with repeated CRS-HIPEC achieved more than 15 months of survival after PC diagnosis.

The management of IPMN depends on how malignant the presenting tumor is and the age of the patient. Resection is recommended for symptomatic tumors presenting with obstructive jaundice, epigastric discomfort or backache, diabetes, episodes of acute pancreatitis, and weight loss. Based on the high prevalence of malignancy in MD-IPMN and mixed-type IPMN, patients fit for surgery should undergo resection. The malignant features for consideration of surgical treatment include main pancreatic duct (MPD) dilatation >10 mm, enhanced solid component or mural nodules >3 mm, enlargement

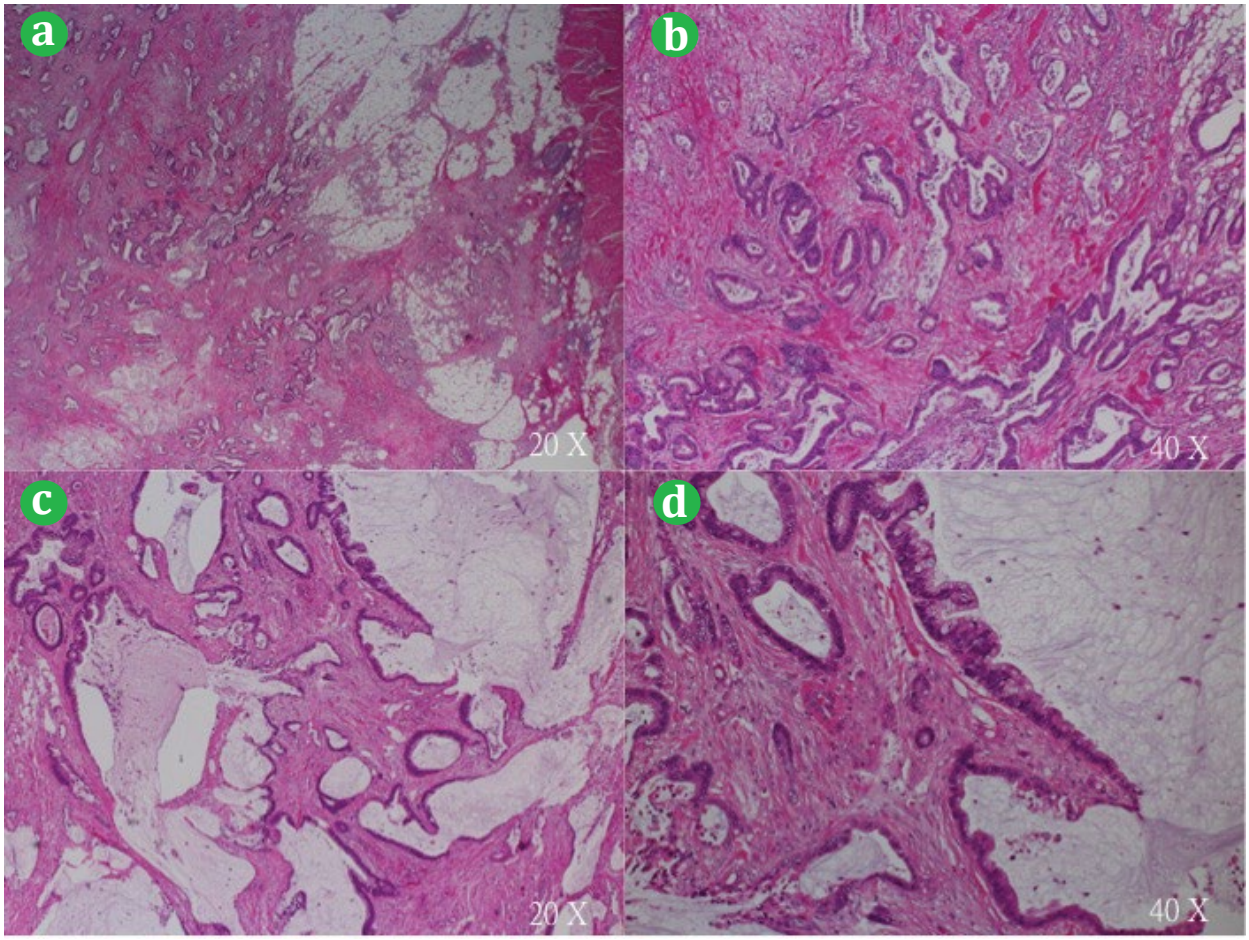


**Figure 2. (a, b).** Tumor infiltration of mesorectum of Douglas pouch in pelvic region, without direct invasion to rectal wall. Hematoxylin and eosin-stained section showed the formation of irregular lumens by cuboid and cylindrical shape hyperchromatic cancer cells. 20X and 40X; **(c, d).** Tumor infiltration of rectus muscle. 20X and 40X.

or metastasis of the lymph nodes and rapidly increasing tumor size (particularly a growth rate over 2 mm/year) [1, 12, 13]. MPD dilatation of 5–9 mm and cyst size of >30 mm, thickened enhanced cyst walls, nonenhanced mural nodules, and abrupt changes in the MPD caliber with distal pancreatic atrophy are considered "worrisome" features, and, owing to the accumulating risk of cancer, resection is still recommended in fit patients with a high life expectancy. High-grade dysplasia or positive cytology and elevated carcinoembryonic antigen of cysts or mucins [14], and elevated serum CA19-9 are additional factors for considering resection. The aim of surgical intervention is to completely remove the tumor with a negative margin [12, 13]. Assessment of the resection margin through cryosection during the operation is essential, but no consensus has been reached regarding how a positive margin should be defined. The presence of high-grade dysplasia or invasive cancer at the resection margin warrants aggressive resection to completion pancreatectomy; however, obtaining a further negative margin when low-grade or moderate dysplasia is encountered is controversial [15]. The risk of local recurrence of the remnant pancreas with atypia or dysplasia on the resection margin is low, and it seems that a total pancreatectomy is not mandatory given the comorbidity that results from this operation [16].

PC is considered an untreatable disease and is associated with a short life expectancy. However, the development of comprehensive treatment with CRS-HIPEC has changed this view since the 1980s. Several reports have demonstrated that CRS-HIPEC has improved the survival of patients with appendiceal cancer, colorectal cancer, malignant peritoneal mesothelioma, gastric cancer, pseudomyxoma peritonei, and ovarian cancer. It remains questionable as to whether CRS-HIPEC also yields better outcomes for patients with more aggressive malignancies such as pancreatic cancer, duodenal cancer, and gallbladder cancer. Very few studies have reported the use of CRS-HIPEC for pancreatic cancer patients because of the high rate of liver metastasis in its advanced stage. Farma *et al*. reported a median survival of 16 months in 7 patients with pancreatic cancers when using CRS-HIPEC with cisplatin. However, in that cohort of aggressive pancreatic cancer, gastric cancer, and duodenal cancer patients, this strategy does not appear to alter the natural history of the disease and has a high incidence of complications [17]. Reports of applying CRS-HIPEC on invasive IPMN (IMPC), a less aggressive pancreatic origin malignancy, are also scarce. Alvaro reported a case of a 63-year-old woman with peritoneal mucinous carcinomatosis originating from IPMC treated by CRS-HIPEC with mitomycin C (30 mg) at 42°C for 60 minutes. The patient has lived without signs of the disease for at least 70 months after the procedure [18].

Though few case series reports suggested applying CRS-HIPEC for patients having pancreatic origin malignancies, larger studies and randomized-controlled studies are needed before this strategy can be recommended. A critical question is the indication of CRS-HIPEC in pancreatic malignancies with PC. Unfortunately, there are only few formal guidelines for the selection of patients for CRS-HIPEC in patients other than pancreatic origin malignancies. The generally accepted selection criteria are satisfactory cardiopulmonary, renal, liver, hematological function and profile; acceptable performance status with Karnofsky performance status >50% or Eastern Cooperative Oncology Group (ECOG) performance status of less than or equal to 2; absence of inoperable extraabdominal metastasis and reasonable life expectancy compared to recovery time after surgery. The bulky disease with bowel obstruction and unresectable pancreatic malignancy with biliary obstruction or major vessel invasion are also contraindicated. The limited peritoneal cancer index (ex: less than 10) and achievable completeness of cytoreduction score to 0-1 were also recommended [19]. Furthermore, based on the tumor biology and HIPEC rationale, mucinous adenocarcinoma, IPMC and solid pseudopapillary neoplasm are better indication than pancreatic ductal adenocarcinoma.

Patients with IPMC following resection must be closely followed up to observe for tumor recurrence or new lesions on the remnant pancreas. Serial serum tumor marker check-ups and regular image surveillance with pancreatic protocol CT or gadolinium-enhanced magnetic resonance imaging with magnetic resonance cholangiopancreatography are recommended. EUS-FNA can also be considered for more accurate characterization of the lesion. For advanced-stage IPMC, PET-CT is recommended for surveying metastasis throughout the whole body. The diagnostic value of PET-CT after CRS-HIPEC in detecting PC recurrence is superior to contrast-enhanced CT. However, imaging studies may underestimate the real severity of disease dissemination in the abdominal cavity. Klumpp *et al*. reported an assessment of relapse in patients with PC after CRS-HIPEC by using F-18-FDG-PET/CT. The author found relapses were missed in 4 patients of 44 examinations and significantly underestimated in 8 patients [20].

## CONCLUSION

CRS-HIPEC may provide considerable life extension in selected patients with IMPC and PC. After surgery, regular follow-up for serum markers and PET-CT is recommended.

## Conflicts of Interest

All authors have no conflicts of interest to disclosure. Neither research grants nor commercial financial supports were received for this study.

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