Original Article on Pancreas Cancer

Hyperthermic intra-operative intraperitoneal chemotherapy as an adjuvant to pancreatic cancer resection

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Background: Even after potentially curative resection the long-term survival of pancreatic cancer is poor. The local-regional failures are frequent. Previous studies have shown that adjuvant treatment with hyperthermic intra-operative intraperitoneal chemotherapy (HIPEC) may effectively control local disease. The objective of the study is to update the results of the prior publications by integrating data from recently accrued cases. Also, to revisit the clinical and pharmacological rationale for the intraperitoneal administration of chemotherapy in pancreatic cancer patients undergoing potentially curative resection.

Methods: This is a prospective study of pancreatic cancer patients that underwent R_0 resection in combination with HIPEC-gemcitabine. Morbidity and mortality were recorded. Survival was calculated and the sites for recurrent disease were recorded.

Results: The updated results for 33 patients that underwent treatment until 2016 and for 6 more patients that were included until 2018 were presented. The hospital mortality and morbidity rate were 5.1% (2 patients), and 28.2% (11 patients) respectively. The median and 5-year survival rate was 17 months and 24% respectively. With a median follow-up time of 13 months 23 patients (59%) were recorded with recurrence. Local regional failures were recorded in 4 patients (10.3%).

Conclusions: HIPEC following R_0 resection is a feasible and safe adjuvant treatment for pancreatic cancer. The local-regional failures appear to be significantly decreased and to result in an increased overall survival. Further studies with combined intraperitoneal and systemic perioperative chemotherapy may serve to supplement our data with an increased benefit for patients having pancreas cancer resection.

Keywords: Pancreatic cancer; hyperthermic intra-operative intraperitoneal chemotherapy (HIPEC); gemcitabine; intraperitoneal chemotherapy; perioperative chemotherapy; local recurrence; peritoneal metastases; r_0 resection

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Introduction

The incidence of pancreatic cancer increases in the Western world and is the 4th most common cause of cancer-related death in USA (1). By 2030 it is expected to be the 2nd most common cause of cancer-related death (2). Despite advances in imaging techniques the incidence of resectable pancreatic tumors does not exceed 10–15% (3-6). The majority of tumors are unresectable either because they infiltrate vital anatomic vessels or because they are associated with liver, retroperitoneal, or peritoneal metastases at the time of initial diagnosis. Five-year survival rate does not usually exceed 10%, although 20–25% has been reported from high volume centers (1,7-11).

The most frequent sites of recurrence after potentially curative resection are the liver in 50–60%, the peritoneal surfaces in 40–50%, and the bed of tumor resection in 50% (12). It is obvious that the incidence of local-regional failures is high and if it could be reduced the overall survival would apparently increase. The pathophysiology of local-regional recurrence remains somewhat an enigma. It may be the result of tumor progression that

has originated from undetected pre- or intra-operatively microscopic cancer emboli. It may also be the result of dissemination of cancer emboli that are implanted at the surrounding peritoneal surfaces as a result of surgical trauma during tumor resection (13). Intraperitoneal chemotherapy has shown to be effective by eradicating the microscopic residual tumor in diseases with peritoneal malignancy (14-18) and it could probably be effective in eradicating the residual microscopic cancer emboli after pancreatic surgery. Previous publications have provided evidence that HIPEC following R_0 resection of pancreatic carcinomas is quite effective in reducing the local-regional recurrences and increasing long-term survival (19,20).

The purpose of the study is (I) to describe the perioperative intraperitoneal methods of chemotherapy that are in use for the prevention of peritoneal metastases, (II) to update the results of the previously published studies by integrating recent cases into our database, and (III) to present the clinical and pharmacological rationale for the intraperitoneal administration of chemotherapy in patients undergoing potentially curative resection of pancreatic cancer.

Methods

From 2007 to 2018, 39 patients with resectable pancreatic carcinomas underwent R_0 resection of the tumor in combination with HIPEC-gemcitabine. The results of 33 of them had been previously analyzed (18) and updated. In the present study 6 more patients were included with the same criteria as before. The study was approved by the Hospital's Ethical Committee and all patients signed an informed consent.

As has been emphasized only patients with resectable pancreatic adenocarcinomas that did not have distant metastases were included in the study. The preoperative work-up consisted of physical examination, hematological-biochemical examination, tumor markers (CEA, CA 19-9, CA-125), endoscopy combined with endoscopic ultrasound, CT-abdominal and thoracic scanning, or MRI, and bone-scanning.

Patients older than 16 years of age, with acceptable cardiopulmonary function, performance status >50% (assessed by the Karnofsky performance scale), normal renal function (blood urea level <50 mg/dL, creatinine level <1.5 mg/dL), satisfactory liver function (other than hepatobiliary obstruction), white blood cell count >4,000/mL, and platelet count >150,000/mL were included in the study.

Patients with evidence of distant metastatic disease (liver, osseous, brain, pulmonary or any other distant site), those with poor performance status (Karnofsky performance <50%), those who had been treated with systemic chemotherapy, those patients with prior malignancy at risk for recurrence (except for basal-cell carcinoma or in-situ cervical carcinoma adequately treated), those with psychiatric diseases or addictive disorders, and pregnant women were not included in the study.

Treatments

Patients with cancer of the head of the pancreas underwent subtotal pancreatoduodenectomy (Kausch-Whipple procedure), and those with tumor of the body or tail of the pancreas underwent distal (left) pancreatectomy. HIPEC was performed for 60 min at 42.5–43 ℃ with 1,000 mg/m^2 gemcitabine after tumor resection and before the reconstruction of the gastrointestinal tract with the Coliseum technique (open abdomen). A heater circulation with two roller pumps, one heat exchanger, one reservoir, an extracorporeal system of two inflow and two outflow tubes, and 4 thermal probes was used for HIPEC (Sun-Chip, Gamida Tech, France). A prime solution of 2–3 liters of normal saline was instilled prior to the administration of the cytostatic drug which was given as soon as the mean temperature in the abdominal cavity exceeded 40 ℃. Adequate fluids were administered during HIPEC in order to maintain diuresis at 500 mL/h and for 24 hours after surgery.

The reconstruction of the continuity of the gastrointestinal tract was always made after the completion of HIPEC. This was possible with an end-to-side pancreato-jejunal anastomosis, an end-to-side choledocho-jejunal anastomosis in continuity, and a Roux-en-Y gastro-jejunal anastomosis at 60 cm with a second jejunal loop after sub-total pancreatoduodenectomy. After distal pancreatectomy the pancreatic remnant was always sutured with 3.0 silk.

All resected specimens were sent for histopathological examination and staging. The intra-operative and post-operative complications were carefully recorded and treated. Stage III patients were scheduled to receive adjuvant systemic chemotherapy.

Follow-up

All patients were followed-up at 3-month intervals for the first year and at 6-month intervals later with physical

Table 1 Characteristics of 39 patients with pancreatic cancer

Characteristics	No. of patients	%
Performance status		
90–100%	29	74.4
70–80%	9	23.1
50–60%	1	2.6
Anatomic distribution		
Head	31	79.5
Body	2	5.1
Tail	5	12.8
Diffuse	1	2.6
Type of surgery		
Sub-total pancreatoduodenectomy	30	76.9
Distal pancreatectomy	7	17.9
Total pancreatoduodenectomy	2	5.1
pT		
T1	2	5.1
T2	5	12.8
T3	32	82.1
pN		
N0	17	43.6
N1	22	56.4
Degree of differentiation		
G1	6	15.4
G2	20	51.3
G3	13	33.3
pTNM		
I	4	10.3
II	9	23.1
III	26	66.7

examination, hematological-biochemical examinations, tumor markers (CEA, CA 19-9, CA-125), CT-abdominal and thoracic scanning or MRI. Recurrences and the sites of recurrence were recorded.

Statistical analysis

The gender, the anatomic distribution of the tumor, the age, the performance status, the pT, the pN, the pTNM stage, the degree of differentiation, and the use of adjuvant systemic chemotherapy were all correlated to survival. The proportion of patients with a given characteristic was compared by chi square analysis or by Pearson's test. Differences in the means of continuous measurement were tested by the Student's *t*-test. The survival curves were obtained using the Kaplan-Meier method. Cox's regression model was used for multiple analysis of survival. A two-tailed P value <0.05 was considered statistically significant.

Table 2 Complications of 11 patients with pancreatic cancer

Complications	No. of patients	%
Postoperative bleeding	1	2.6
Pulmonary failure	2	5.2
Anastomotic leak	4	10.3
Sepsis	1	2.6
Grade II neutropenia	2	5.1
Cerebrovascular accident	1	2.6

Results

From 2007 to 2018, 39 patients with resectable pancreatic adenocarcinomas were included in the study. There were 19 (48.7%) men, and 20 (51.3%) women. The mean age of the patients was 67.9±10.9 years (range, 38–86 years). The characteristics of the patients are listed in *Table 1*.

Ductal pancreatic adenocarcinomas were confirmed in all resected specimens and complete staging was possible (*Table 1*).

During the postoperative period (45 days), 11 patients (28.2%) were recorded with complications which are listed in *Table 2*. The patient with postoperative bleeding underwent immediate reoperation and hemorrhage was controlled successfully. Two patients with anastomotic leak required reoperation because of choledocho-jejunal anastomosis failure which were successfully controlled with T-tube insertion. The other 2 patients with choledocho-jejunal anastomotic failures were successfully treated conservatively. The rate of reoperation was 5.1%. One patient was recorded with stroke but 6 months after initial treatment was free of neurological symptoms. Two patients were recorded with grade II neutropenia that did not require any specific treatment.

The mean blood loss was 305±205 mL (range, 80–820 mL). The mean operative time was 399±106 min

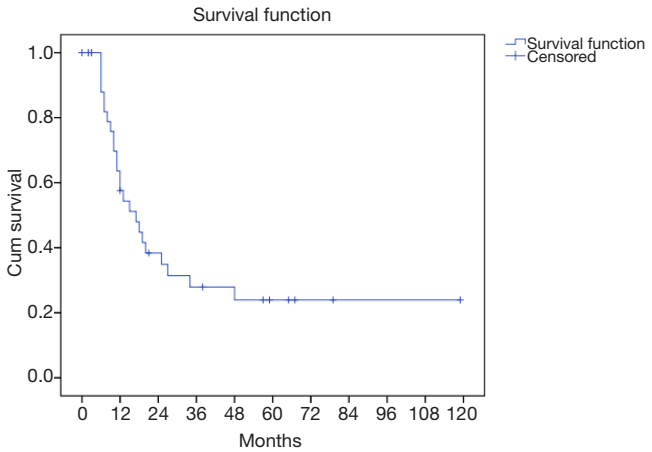

Figure 1 Overall survival of 39 patients with pancreatic cancer undergoing R_0 resection and HIPEC.

Table 3 Univariate analysis of survival

Variable	P value
Gender	0.758
Anatomic distribution	0.292
T	0.409
N	0.929
TNM	0.123
G	0.068
Adjuvant chemotherapy	0.226

(range, 185–592 min). The mean number of transfused blood units was 2±2 (range, 0–4), and the mean number of transfused FFP's was 3±1 (range, 0–8). The mean days of hospitalization was 17.7±7 (range, 9–45).

The hospital mortality rate was 5.1% (2 patients). One patient died as a result of sepsis from an unknown site and the other because of pulmonary failure.

Eighteen patients (46.2%) received systemic adjuvant chemotherapy.

The overall 5-year survival rate was 24%. The 1-, 2-, and 3-year survival rate was 64%, 38%, and 28% respectively. The mean and median survival time were 40.3±8.2 months, and 17 months respectively (*Figure 1*). No variable was found to be related to survival by univariate analysis of survival although the grade of the cancer was of border-line statistical significance (*Table 3*).

One patient with stage II and another one with stage I disease died during the immediate postoperative period. The median follow-up time was 13 months, and the median time to disease progression 11 months. During follow-up 23 patients (59%) were recorded with recurrence. Histopathologically, 2 of them were T_2N_1, 7 were T_3N_0, and 14 were T_3N_1. Nineteen patients (48.7%) were recorded with distant metastatic disease and 4 (10.3%) with local-regional. All patients with local-regional recurrences were T_3N_1.

Univariate analysis of time to recurrence showed that the degree of differentiation was related to recurrence (P=0.006). The degree of differentiation was prognostic for recurrence (P=0.003, 95% CI: 0.53–0.665).

Currently, 7 patients (17.9%) are alive without evidence of disease, 23 patients (59%) died because of the disease, 8 patients (20.5%) died because of reasons unrelated to disease, and 1 patient (2.6%) is alive with disease. Histopathologically, the disease-free patients are as following: one patient with T_1N_0, one patient with T_2N_0, one patient with T_3N_0, and four patients with T_3N_1 disease.

Discussion

The best and most effective adjuvant treatment after pancreatic cancer resection has not yet been identified. The Gastrointestinal Study Group trial showed in 1985 that patients receiving chemoradiotherapy were offered significant survival benefit after tumor resection compared to the observation group. The weak point of the trial was the small number of patients studied (21). The next trial (EORTC) that included a large number of patients showed that there was no survival benefit for patients treated with chemoradiation after tumor resection (22). The ESPAC trial showed in patients with pancreatic cancer undergoing potentially curative resection that only systemic chemotherapy offered significant survival benefit. In contrast, chemoradiotherapy or radiotherapy did not offer significant survival benefit (23). Other studies from the USA showed that chemoradiation was more effective than surgery alone (24). A recent retrospective publication including large number of patients showed that adjuvant radiotherapy significantly increased survival in pancreatic cancer patients undergoing surgical resection (25). An even more recent publication showed that adjuvant chemotherapy followed by radiotherapy is a better approach in patients undergoing upfront resection (26). There is evidence from one retrospective study with neo-adjuvant treatment that either chemotherapy or chemoradiotherapy is effective and provides significantly increased survival

compared to upfront surgery (27). Another comparative study shows the beneficial effect of preoperative treatment with chemoradiotherapy on both the rate of local-regional and distant metastases without any effect on overall and disease-free survival (28). It is apparent that there is much controversy about the most effective adjuvant treatment. Currently, in the USA chemoradiation is established as the preferred method while in Europe chemotherapy alone based on gemcitabine is the most frequently used popular adjuvant treatment. Newly developed chemotherapeutic regimens have been suggested to be more effective but the prognosis of pancreatic cancer still remains poor (29,30). More aggressive surgical operations (total pancreatectomy, extensive lymph node resection) have not shown to increase overall survival (31,32). The use of IORT (intraoperative radiation therapy) for the control of local disease has not convinced the medical community (33).

It is not possible to precisely determine the pathophysiology of local-regional recurrences. However, a reasonable hypothesis is to incriminate local-regional surgical treatment failure. One must assume that small volume local disease progression occurs in patients who have been left with positive margins of resection. The head of the pancreas, surrounded by vital anatomic structures has extremely narrow limits of resection and the interstitial tissues are frequently traumatized during surgery. The lymphatic vessels must be transected and venous blood is lost during surgical manipulations. As a consequence, cancer emboli disseminate in the peritoneal cavity. During wound healing, these emboli are entrapped in fibrin, inflammatory cells accumulate with local collagen, and this complex is stimulated by growth factors giving rise to recurrent tumor in 2–3 years after initial surgery. The cancer emboli are expected to efficiently implant at the resection site. The implantation of cancer emboli at the bed of resection causes a high-density local recurrence. In addition, distant peritoneal implants are expected to grow (13). Although systemic chemotherapy with gemcitabine has proved to be effective in high-risk patients with pancreatic cancer undergoing potentially curative resection, it has not been shown to be effective in the control of local-regional residual disease (34). The eradication of the residual microscopic tumor is possible with the use of intraperitoneal chemotherapy for those diseases that present with peritoneal carcinomatosis (14-18). Laboratory research has shown that the intraperitoneal administration of gemcitabine may effectively target local-regional control (35). Clinical studies have reconfirmed these same conclusions (19,20,36). The advantage of the intraperitoneal administration of chemotherapy is the high drug level that can be achieved loco-regionally with low systemic exposure (37). Another advantage is its effect on hepatic and lymph node micrometastases. Pharmacologic data have shown that the absorption of the intraperitoneally administered drug is possible in about 90% by the visceral peritoneum (38) and as a consequence the concentration of the drug in the portal circulation appears to be effective on micrometastatic disease. The high rate of distant metastatic disease (48.7% or 19 patients) implies that the intraperitoneal chemotherapy needs to be reinforced with a bolus of systemic chemotherapy. Therefore, we intend to change the protocol. Intravenous 5-FU (400–600 mg/m^2) in combination with leucovorin or isovorin (20 mg/m^2) during HIPEC will be added in the treatment. Other systemic agents or early postoperative intraperitoneal chemotherapy (EPIC) are also being considered.

Gemcitabine (2, 2-difluorodeoxycitidine) is a pyrimidine analogue. The cytotoxicity of gemcitabine is quite consistent particularly against pancreatic cancer. The pharmacokinetics and tissue distribution of intraperitoneal administration of gemcitabine has been investigated in a rat model and has been shown that the AUC ratio after intraperitoneal administration is favorable for its intraperitoneal use (39). The use of normothermic intraperitoneal gemcitabine in advanced cancer has also been investigated (40-42). Also, a potential indication for heated intraoperative intraperitoneal administration of gemcitabine as an adjuvant to resected advanced pancreatic cancer with high risk of recurrence has been published (36). Although it has not been proved, it is assumed that the open abdominal technique (Coliseum) appears to be the most effective because the surgeon distributes heat and drug uniformly in all peritoneal surfaces, especially the pancreas resection site. In a small number of patients Sugarbaker has used long-term normothermic intraperitoneal chemotherapy (NIPEC-LT) targeting on additional control of the local-regional disease. The method is promising although the distribution of the drug at the peritoneal surfaces is restricted because of the adhesions (43).

Pancreatic cancer resection combined with HIPEC is a safe method, associated with low hematologic toxicity that does not require specific treatment. The preliminary results reported by Sugarbaker have not shown hematologic toxicity (43). There has been no evidence to incriminate HIPEC for the complications. The incidence of complication (28%) of the present study appears to be

comparable to the 41–46% complication rate following surgical resection only (19,20,44,45). Delayed gastric emptying and pancreatic leak are very severe and frequent complications after Whipple's procedure that have not been recorded in the present study. In contrast, biliary leak has been present in 10.3% of our patients, comparable to 9% leak reported after Whipple's resection without HIPEC (44,45). Intra-abdominal bleeding has been recorded to be 2.6%, comparable to 3% reported in other studies (44,45). Other severe complications are the intra-abdominal abscess 10%, and gastrointestinal bleeding 5%. None of them has been recorded in the present study. In contrast, sepsis of an unknown primary has been present in 2.6%, pulmonary failure in 5.2%, and stroke in 2.6% (*Table 2*). The hospital mortality of 5.1% is acceptable (19,20,44).

The up-dated results have shown that long-term survival remains high as previously reported and is comparable to survival reported from high-volume centers (10,11). The median follow-up time has been extended from 11 to 13 months. The median survival has also been extended from 13 to 17 months, and the median disease-free survival from 9 to 11 months. The overall survival has remained stable at 24% and the recurrence rate has slightly declined from 60.6% to 59%. In contrast with longer follow-up the rate of local-regional failure has slightly increased from 9.1% to 10.3%. Although these variations are not significant it is important to note that the survival has been stable despite the addition of new patients to our series.

HIPEC with gemcitabine has been used after extensive cytoreduction in 6 patients with peritoneal carcinomatosis of pancreatic cancer. Four of them survived more than 12 months. This limited experience shows that there is probably a group of patients with peritoneal carcinomatosis of pancreatic cancer in which the peritoneal metastases may be adequately eradicated with cytoreduction and HIPEC (46).

Conclusions

There is evidence that HIPEC as an adjuvant after pancreatic cancer resection is a safe and rationale treatment strategy that is effective in improving the local-regional failure. Additionally, HIPEC is probably an effective method in controlling micrometastatic disease. So far, it has been shown that local-regional failure is reduced and the overall survival is high. Building on these positive results, further studies that involve HIPEC-gemcitabine are indicated.

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Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Paul H. Sugarbaker and Kurt Van der Speeten) for the focused issue"Intraperitoneal Chemotherapy for Peritoneal Metastases: HIPEC, EPIC, NIPEC, PIPAC and More" published in *Journal of Gastrointestinal Oncology*. This article has undergone external peer review.

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jgo-20-46). The focused issue was sponsored by the Peritoneal Surface Oncology Group International (PSOGI). The author has no other conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Hospital's Ethical Committee and all patients signed an informed consent.

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