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Original article

Intra-arterial chemotherapy with MMC, CDDP and 5-FU for nonresectable pancreatic cancer – a phase II study

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Abstract. In 26 patients with non-resectable pancreatic cancer, intra-arterial infusion with mitomycin C, cisplatin and 5-fluorouracil was performed. Twenty-four patients were classified as UICC stage IV, 1 as stage III and 1 as stage II. In 7 patients, invasion of the duodenum or bile duct was noted; 4 had tumor invasion of the stomach. Twenty-one patients had concomitant liver metastases; 4 had carcinosis of the peritoneum in the upper abdomen. Jaundice at the start of treatment was noted in 7 cases. Drugs were infused over 60 min on 5 consecutive days in a median of four cycles. Of 26 patients, 21 received treatment via celiac axis catheters placed angiographically. In 5 patients, Jet Port (PfM, Cologne, FRG) celiac axis catheters were placed surgically. Seven of 26 patients were treated for local recurrences after a Whipple resection; 19/26 patients had i.a. therapy for primarily non-resectable metastasized tumors. The response rate was estimated according to the stage indicated by tumor markers: 1 CR, 16 PR, 2 MR, 1 SD, 4 NR in stage IV, 1 PR in stage III and one NR in stage II. The overall response was 77%. In 14 patients receiving i.a. infusion via angiographic catheters, the median survival was 9 months. In 5 stage IV patients with implanted catheters, the median survival was 13.8 months (range 8–24 months).

Key words: Pancreatic cancer – Regional chemotherapy – Celiac axic infusion – Mitomycin C

Introduction

The prognosis of pancreatic cancer has not improved during the last decades [6, 9, 13]. Despite improved diagnostic facilities the diagnosis is most commonly made when the disease is already too advanced and the tumor has invaded adjacent structures. New treatment modalities such as irradiation [10, 18, 19] or various chemotherapy schedules [5, 8, 11, 17, 20, 21], as well as invasive surgery [4, 23, 24], have not changed the dismal outlook.

In an attempt to overcome the general nihilism in the management of pancreatic cancer we felt that it is nonetheless appropriate to focus further endeavors on the chemosensitivity [14] of cancer cells by means of increasing the dose intensity [2, 12, 16] in the target field. This can be achieved with intra-arterial application of anticancer drugs. In order to obtain a prompt answer within a short period of time as to whether or not regional chemotherapy is suitable for inducing an active response in pancreatic cancer, patients with far advanced, locally metastasizing disease, and thus a poor life expectancy, were treated intra-arterially.

Material and methods

Patients. Twenty-six patients with non-resectable pancreatic cancer underwent regional chemotherapy through celiac axis infusions. One patient was classified as UICC stage II, 1 as stage III and 24 patients as stage IV. Seven patients had tumor invasion of the bile duct and the duodenum and 4 patients showed penetration into the stomach (Table 1). Twenty-one patients had liver metastases, 3 had bulky peritoneal carcinosis in the upper abdomen, and 1 had a metastasis at the sigmoid colon, which was resected. Histologically, only 1 patient had papillary carcinoma. In 20/26 cases the tumor was located in the head of the pancreas.

Previous ineffective systemic chemotherapy had been performed in 3 patients, and 1 patient had had irradiation and 1 interferon. Seven of 26 patients had had Whipple resections, followed by local recurrences, and 19/26 patients had only had diagnostic laparotomies and tumor biopsies. In 5 of these 19 patients arterial infusion was performed via surgically implanted Jet Port celiac axis catheters, and 14 patients had chemotherapy via angiographically placed catheters. Of 26 patients, 17 had palliative treatments before they underwent regional chemotherapy (Table 2).

Infusion technique and drug schedule. In order to cover the upper abdominal region, including the pancreas, liver, stomach, spleen and the lymphatic network, drugs had to be infused into the celiac axis. This was mainly achieved (21/26 patients) via catheters inserted angiographically through the femoral artery. These catheters were left in place for 5 consecutive days for each cycle. Prophylactic infusion of 20,000 U of heparin was given continuously daily over 23 h to avoid thrombosis. Chemotherapeutics were given as daily 1-h infusions consisting of a MMC, CDDP, 5-F U three-drug combination (Table 3) in 1 to 12 cycles (median 4), while care was taken not to exceed 70 mg

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Table 1. Local tumor invasion in 24/26 patients with non-operable pancreatic cancer

Local tumor invasion	Patients
Common bile duct	7
Mesocolon	2
Duodenum	7
Kidney	2
Stomach	4
Colon	1
Gallbladder	1

Table 2. Palliative treatments in 17/26 patients with locally invading pancreatic cancer prior to regional chemotherapy

Palliative treatment	Patients
Biliodigestive anastomosis	7
Biliary drainage	6
Gastroenterostomy	3
Sigmoid resection	1

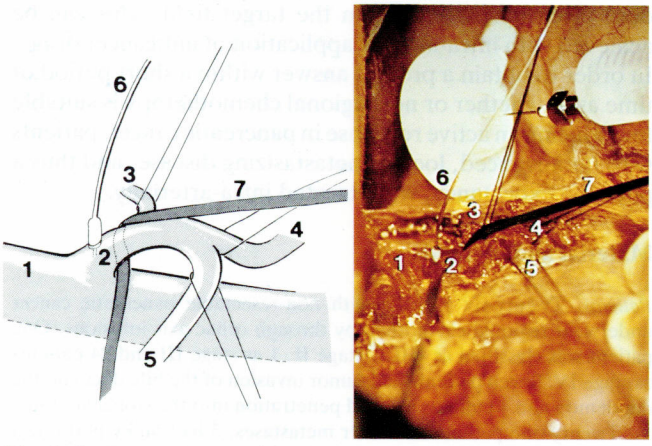

Fig. 1. Jet Port catheter implanted in celiac axis. *1*, Aorta; *2*, celiac axis; *3*, left gastric artery; *4*, splenic artery; *5*, common hepatic artery; *6*, Jet Port catheter; *7*, tape around celiac axis

total dose of MMC. In patients where this limit was reached, 30 mg of ADM was applied instead.

In patients undergoing surgical exploration to clarify resectability, when the celiac axis area could be exposed, a Jet Port Long (PfM, Cologne, FRG) catheter was inserted end-to-side into the celiac axis and fixed with a Prolene purse-string suture (Fig. 1). The catheter exited through the abdominal midline incision and the port was placed in a subcutaneous pouch. In one patient presenting with a bulky, infiltrating tumor mass in the head of the pancreas, extensive hepatomegaly due to disseminated liver metastases, and ascites, two arterial port catheters were implanted into the gastroduodenal artery in both directions – toward the pancreas and the liver. Injection of blue dye into the pancreatic line verified good infusion of the entire tumor-bearing region (Fig. 2).

Follow up controls. CA 19–9 levels were taken at the beginning of each cycle. CT scan controls were performed at the start of treatment and after the fourth cycle. If good remission was evident, CT controls

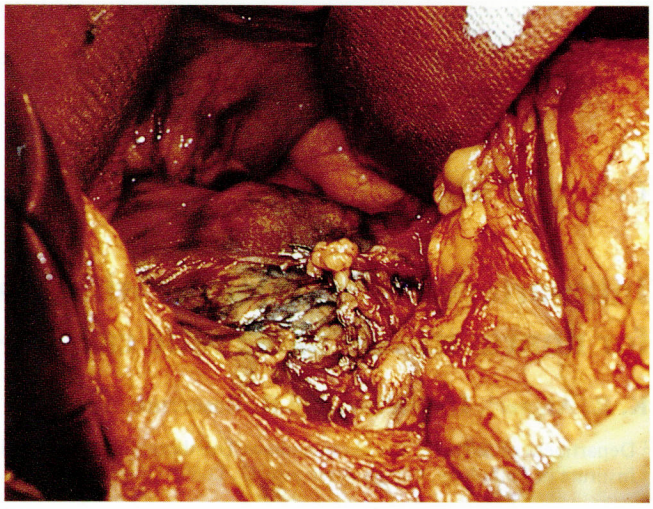

Fig. 2. Blue coloration of the pancreas after arterial injection of blue dye (Indigocarmin, Merck, Darmstadt, FRG)

Table 3. Overall response in 26 patients with non-resectable pancreatic cancer treated with regional chemotherapy

Response	Patients	(%)
CR	1/26	(3.8%)
PR	17/26	(65.4%)
MR	2/26	(7.7%)
SD	1/26	(3.8%)
NR	5/26	(19.2%)

were also taken in between for documentation. In 10 patients second-look laparotomies were performed. Four turned out to be locally resectable after four courses of i.a. infusion.

Results

The response rates were estimated dependent on the stage, as determined by the tumor markers: stage II (1 NR), stage III (1 PR), stage IV (1 CR, 16 PR, 2 MR, 1 SD, 4 NR). A response was seen in 20/26 patients (Table 3). The overall response rate was 77% (3.8% CR, 65.4% PR, 7.7% MR). Stable disease was noted in 1 patient (3.8%), and 5 patients were classified as non-responders (19.2%).

In the group of 14 patients receiving celiac axis infusions via angiographic catheters the actual median survival is 9 months. Seven of 14 patients are still alive after 5, 6, 7, 8, 9, 11 and 13 months, respectively, with good quality of life. Therefore, further improvement of the median survival rate can be expected. In the group of 5 stage IV patients who had surgical implantation of celiac axis catheters, the survival ranged from 8 to 24 months (median 13.6 months). Seven patients, treated for locally invasive and metastasizing recurrences after Whipple resection survived for a median of 6 months (Table 4). Three of these 7 patients are still alive after 3, 5 and 9 months. In the 4 patients who underwent resection following celiac axis infusion, the survival is 8+, 9, 9+ and 10 months. The longest survival in a

PR patient, presenting with an invasive primary tumor, hepatomegaly from liver metastases and ascites, was 24 months, with transient resolution of the ascites and hepatomegaly for 1 year (Fig. 3a, b).

Histological findings in second-look biopsies

At second-look laparotomy, which was performed in 10 patients biopsy specimens from the tumor itself showed massive cytoplasmatic edema and marked tumor-cell degeneration (Fig. 4a, b). Biopsies from liver metastases after celiac axis infusional chemotherapy showed shrinking of the metastases and replacement of the parenchyma by collagen fibrous tissue. No more vital tumor tissue was observed (Fig. 5a, b). Parapancreatic lymph-node biopsies showed complete necrosis of the metastases with some intact tumor cells in transition to necrosis in the periphery of the node (Fig. 6a, b).

Table 4. Survival after cytotoxic celiac axis infusion, dependent on pretherapeutic invasive surgery (relapse after Whipple resection)

Pre-treatment	Median survival (months)
No resection (n = 19)	10.2
Infusion via angiographic catheters (n = 14/19)	9
Infusion via Jet Port catheters (n = 5/19)	13.6
Whipple resection (recurrence) (n = 7) (angiographic catheters)	6

Tumor markers and laboratory tests

The courses of CA 19–9 commonly showed a continuous decrease within the first two cycles, reaching minimal levels at about 4 months after the start of therapy (Fig. 7). It has recently been observed that the CA 19–9 decrease was steeper when the initial dose of MMC was increased to 30 mg/h and central venous drug filtration for systemic detoxification was used simultaneously.

The blood count showed no changes of importance. Chemical hepatitis was never observed and the transaminases remained stable. Alkaline phosphatase decreased in responders. One patient who had presented with elevated bilirubin of 12 U/l and had complete remission showed a decrease to 4 U/l within 7 days and had normal bilirubin at the start of the second cycle. Sclerosing cholangitis was never observed. Responders presenting with elevated lipase prior to therapy showed decreased lipase values at the beginning of the following course.

Side effects

Intra-arterial infusion of the celiac axis with the given dosage was tolerated without local toxicity requiring specific therapy, except that H_2-blockers were given routinely. In a few patients reporting slight abdominal discomfort, gastroscopy revealed mild gastritis. When blue dye was injected into the catheter during gastroscopy the areas showing gastritis turned blue. During therapy moderate elevation of the lipase occurs, indicating mild chemotherapy-induced pancreatitis. However, lipase was never elevated above 600

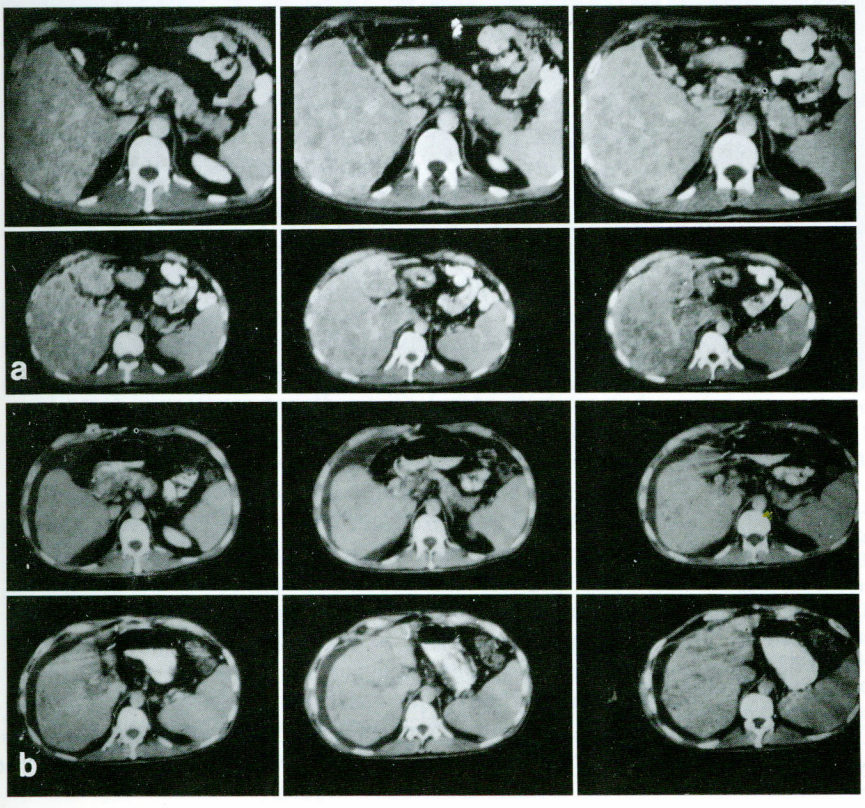

Fig. 3. a CT-scan of locally infiltrating carcinoma of the head of pancreas with disseminated liver metastases. **b** CT-scan of same patient 12 months after regional chemotherapy

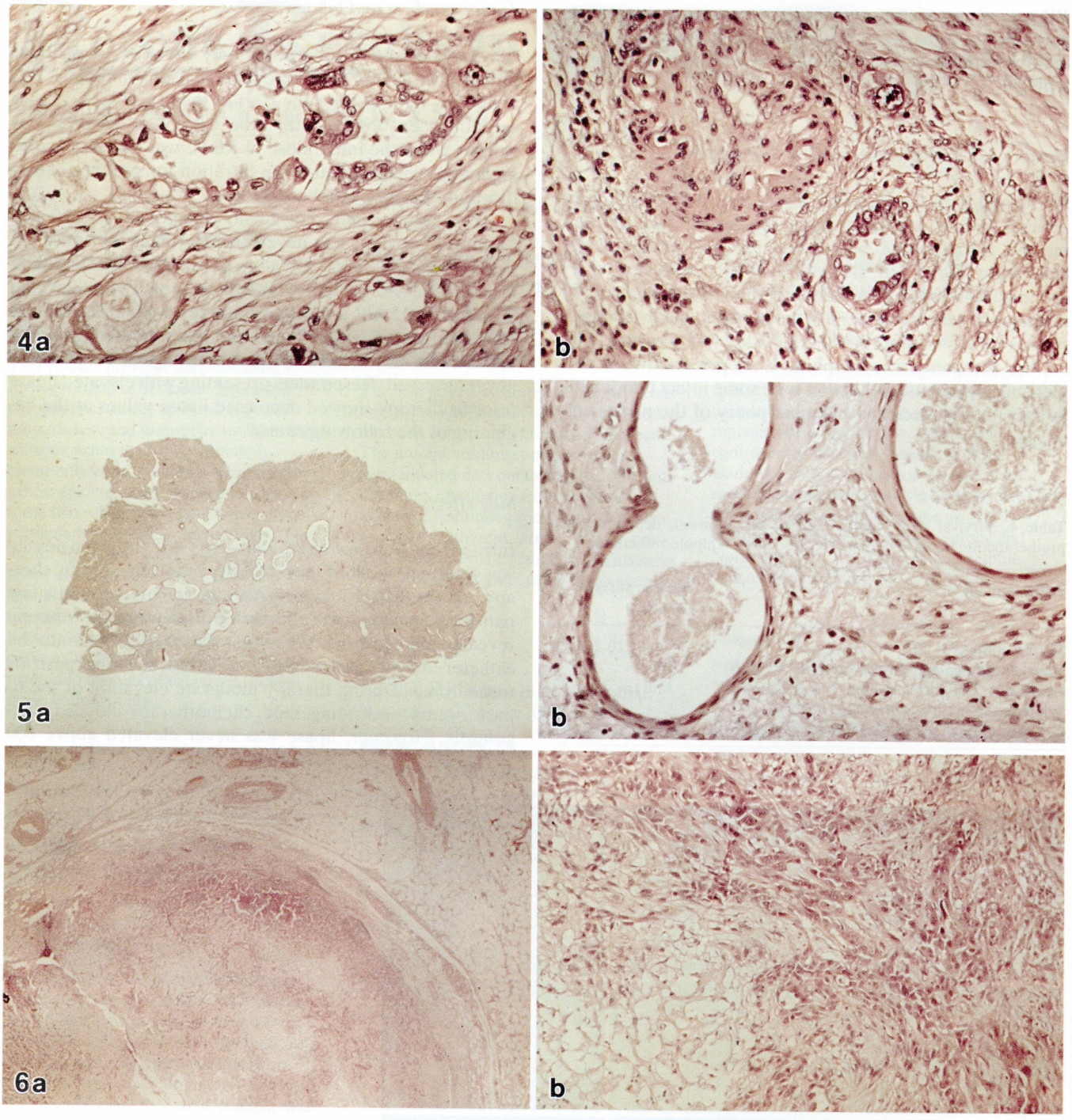

Fig. 4 a, b. Histology of pancreatic carcinoma after two courses of regional chemotherapy through celiac axis. **a** H&E, ×100; **b** H&E, ×100

Fig. 5 a, b. Histology of liver metastases from pancreatic carcinoma after two courses of celiac axis infusion. **a** H&E, ×20; **b** H&E, ×100

Fig. 6 a, b. Histology of lymphnode metastasis from pancreatic carcinoma after two courses of celiac axis infusion. **a** H&E, ×20; **b** H&E, ×100

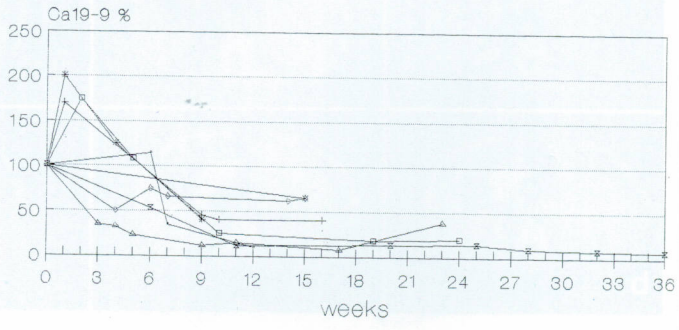

Fig. 7. CA 19-9 levels during regional chemotherapy of pancreatic cancer

U/l and the patients never complained of pain. One of the five patients with implanted catheters had temporary occlusion due to blood reflux. Viability of the system was achieved by an injection of urokinase.

Discussion

At the time of diagnosis the chances of achieving surgery are poor in pancreatic cancer. An increased effort to improve the screening techniques has had no substantial effect on early detection of the disease. This situation provides a rationale for focusing further endeavors on improving the therapeutic measures.

Since the pattern of metastatic spread is largely confined to the upper abdominal organs within the arterial supply of the celiac axis, aiming the total chemotherapy dose at this area is suggested to increase the locally active drug concentration. In our experience pancreatic cancer has turned out to be somewhat sensitive at higher drug concentrations, showing a clear dose-response behavior. It was therefore postulated that an improvement in celiac axis infusion techniques might result in better local tumor control. In far advanced cases, where diagnostic laparotomy reveals tumor invasion of the liver hilum and celiac axis, surgical catheter placement would demand separation of the tumor tissue in order to get a catheter implanted at the root of the celiac axis. As a consequence, in cases with unviable tumor masses, only biopsies are taken for staging and intra-arterial chemotherapy is performed through the angiographic route. Although the Seldinger technique generally provides satisfactory results, the drug may stream [7, 22] into one artery or side branch if the tip of the catheter moves a little bit in the celiac axis and may consequently cause inhomogeneous infusion of the target region. To avoid this situation, in patients where the celiac axis is exposable, we try to implant a port catheter during the first laparotomy. The tip of the catheter, which is advanced to about 2–3 mm into the celiac axis blood stream, causes some local turbulence and therefore keeps the risk of the "streaming phenomenon" to a minimum [7].

When a second-look laparotomy is performed to evaluate resectability, again catheter implantation should be taken into consideration, since further on the patient could be treated on an outpatient basis. In addition, second-look laparotomy provides reliable tumor staging after the treatment, giving information on the histological response, which is of great importance together with tumor markers and clinical screening. It has been observed in the past that the CT scan and tumor markers may show complete remission [1], but small nests of surviving tumor cells in the periphery of the metastases still remain a source of later recurrence.

The catheter technique and the intra-arterial chemotherapeutic schedule for pancreatic malignancies described herein actually induce a high rate of partial remissions with diminuation or even resolution of ascites and improved quality of life. However, it is suggested that the local therapeutic efficiency might be further improved by increasing the local drug concentrations. This can be achieved either by means of microembolization or by an increase in the total dose of cytotoxics and systemic detoxification, the so-called chemofiltration [3, 7, 15]. In a pilot study there is evidence of a more rapid decrease of tumor markers and increased response rates when such a modality is applied (to be published).

So far, regional chemotherapy of advanced pancreatic cancer cannot be considered curative therapy, mainly due to local variations of the chemosensitivity in the infused area, sites of poor vascular supply in bulky tumors, which cannot be eradicated completely, and the sometimes complicated vascular access to extended tumor masses.

Nevertheless, it should be taken into consideration that cytotoxic celiac axis infusion does not affect the quality of life to any significant extent. Patients usually report only mild side effects caused by moderate gastritis and fairly symptomless pancreatitis. With the given dosages of chemotherapeutics, bone marrow depression did not occur. When there is a response, the performance status generally improves.

There might be a well-defined indication for potentially resectable cases when intra-arterial infusion is given as induction prospective and maintenance chemotherapy to attain better resectability and improve long-term results by means of the eradication of micrometastases in the upper abdomen to prevent a relapse.

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