Subsequent resection of locally advanced pancreatic carcinoma after chemoradiotherapy

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SUMMARY

Objectives — The aim of this study was to evaluate the possibility of subsequent resection of locally advanced pancreatic adenocarcinoma after chemotherapy and external-beam radiotherapy.

Patients and methods — Between January 1996 and January 2001, 33 consecutive patients (18 males and 15 women, mean age 63 years) with locally advanced PA were treated with chemotherapy and concurrent external-beam radiotherapy. Radiotherapy delivered 45-50.4 Gy, in a classical manner (N = 27) or on a split-course (N = 6). Chemotherapy was made of 5FU by continuous infusion for 45-50.4 Gy, in a classical manner (N = 27) or on a split-course and concurrent external-beam radiotherapy. Radiotherapy delivered 10 to 15 Gy was delivered to the others. Tumor resectability was reassessed at the end of the chemoradiotherapy; surgical resection of tumour was attempted in patients whose tumor demonstrated reduction in size, and supplementary radiotherapy of 10 to 15 Gy was delivered to the others.

Results — Thirty-nine percent of patients experienced grade 3 acute toxicity. WHO criteria response to chemoradiotherapy four weeks after the end of treatment were: 4 partial responders (12%), 6 minor responders (18%), 14 stable disease (42%), 9 progression (28%). Ten patients underwent exploratory laparotomy, in one case vascular encasement did not allow for tumor resection, and in another patient, there was peritoneal carcinomatosis. In the 8 remaining patients, surgical (R0) resection was possible. In one patient histological examination showed fibrosis with no residual tumour. After a median follow-up period of 40 months, median survival was 16 months (66% and 37% of survival at 1 and 2 years respectively). In operated and non-operated patients, survival rates at 24 months were 73% and 12.5% respectively. At 1 year, 80% of the patients treated with radiochemotherapy developed recurrence, metastatic recurrence in 88%. Initial laparotomy, split course radiotherapy were poor outcome factors whereas chemotherapy appears to be a favorable outcome factor.

Conclusion — Subsequent resection of locally advanced pancreatic adenocarcinoma is possible after chemoradiotherapy allowing for a prolonged survival in some patients.

RÉSUMÉ

Traitement chirurgical après radio-chimiothérapie des cancers du pancréas localement évolutés

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Objectifs — Le but de cette étude était d’évaluer l’efficacité de la résection secondaire d’adénocarcinomes pancréatiques (AP) localement avancés après traitement par radiochimiothérapie (RCT) concomitante.

Malades et méthodes — De janvier 1996 à janvier 2001, 33 malades consécutifs (18 hommes, âge 63 ans) ayant un AP histologiquement prouvé, jugé non résectable au décours du bilan d’extension (TDM, IRM, échoendoscopie, exploration chirurgicale), ont été traités par une association radiothérapie-chimiothérapie. Le schéma thérapeutique combinait une irradiation de 45 à 50,4 Gy réalisée sur un schéma conventionnel (N = 27) ou Split course (N = 6), à du 5FU en perfusion continue (N = 33) durant 5 semaines et du cisplatine (N = 22) la 1ère et 5ème semaine. Une évaluation scansographique était programmée à la fin de la RCT. En fonction de la réponse, une laparotomie ou un complément d’irradiation à 10 à 15 Gy était proposé aux malades. Les critères de non résécabilité étaient un engainement vasculaire (N = 31) et la présence d’adénopathies régionales (N = 2).

Résultats — Une toxicité de grade 3 a été observée dans 39 % des cas. Après RCT, une réponse partielle était observée dans 12 % des cas, une réponse mineure dans 18 % des cas, une stabilisation dans 42 % des cas, une progression tumorale dans 28 % des cas. Une laparotomie était réalisée chez 10 malades. Pour 8 malades (24 %), une résection chirurgicale R0 était possible. Un malade avait une réponse histologique complète (pas de résidu tumoral sur la pièce opératoire). Avec un suivi moyen de 40 mois, la médiane de survie globale était de 16 mois (respectivement 66 % et 37 % de survie à 1 et 2 ans). À 24 mois, la survie était de 73 % dans le groupe des malades opérés et de 12,5 % dans le groupe des non opérés. À 1 an, 80 % des malades traités uniquement par RCT présentaient une rechute (métastatique dans 88 % des cas). Une laparotomie 1ère et une radiothérapie Split course étaient des facteurs de mauvais pronostic tandis qu’une chimiothérapie 1ère était un facteur de bon pronostic.

Conclusion — En cas de réponse après RCT, une résection chirurgicale secondaire à visée curative d’AP non métastatique non résectable peut être discutée. Une survie prolongée peut être observée chez les malades opérés.
Introduction

Treatment of pancreatic adenocarcinoma is one of the most difficult challenges of medical care. Prognosis is very poor with survival rates of less than 5% at five years [1, 2]. Surgical resection offers the only chance of cure, but at diagnosis, more than 80% of patients present regional or metastatic dissemination dictating palliative care [3]. In addition, about 60-80% of operated patients experience local recurrence [4] and only 20% of them (without strafation) survive at five years [5]. The poor results obtained with surgery warrant the development of combined treatments.

Pancreatic cancer is defined as locally advanced when vascular extension reaches the celiac trunk, the superior mesenteric artery, or the portomesenteric venous junction (obstruction), or in the event of lymph node invasion reaching the 2nd and 3rd nodal relay.

Chemoradiotherapy has been found to be more effective than chemotherapy alone in one randomized study in patients with non-resectable non-metastatic pancreatic cancer [6]. It has also been demonstrated to be superior in terms of patient survival compared with exclusive radiotherapy [7]. Chemoradiotherapy can improve symptoms and control of locoregional extension, relapse after chemoradiotherapy generally being metastatic [8]. Tumor response has been observed in 6 to 42% of patients in phase II trials or retrospective series [9, 10]. 5-fluorouracil and cisplatin increase the radiosensitivity of the tissues and exhibit synergetic action [11].

The purpose of this retrospective study was to evaluate the efficacy of second-line surgical resection after first-line RCT or systemic chemotherapy followed by chemoradiotherapy in patients with non-metastatic non-resectable exocrine pancreatic cancer.

Patients and methods

Selection criteria and pretherapeutic work-up

From January 1996 to January 2001, 33 consecutive patients with histologically proven pancreatic adenocarcinoma considered to be non-resectable after the pretherapeutic work-up were treated with concomitant radiotherapy and chemotherapy. These 33 patients were selected among a cohort of 150 patients with pancreatic cancer seen between 1996 and 2000. The usual treatment for patients with locally advanced pancreatic cancer was chemoradiotherapy with or without prior chemotherapy. Resectability was assessed after the first-line treatment. Histological proof of pancreatic adenocarcinoma from surgical or radio-guided percutaneous biopsies were required for inclusion. Neuroendocrine tumors, cholangiocarcinomas, ampullomas and duodenal carcinomas were excluded.

Tumors were considered to be locally advanced when presenting vascular extension invading or encasing the celiomesenteric arterial trunk and/or the mesentericoporal junction (circumscribing tumor > 180°, venous contact > 2 cm), and/or with nodal extension reaching the 2nd or 3rd nodal relay. There were no detectable metastases.

An oncologist and a radiotherapy specialist assessed the patient’s general status using the WHO criteria. Surveillance during chemoradiotherapy included physical examination and weekly blood tests (cell counts, creatinine, liver battery). In the event of jaundice, patients were treated with a bile stent (endoscopic insertion) or biliodigestive bypass (surgery) before chemoradiotherapy.

Radiochemotherapy protocol

Twenty-seven patients (82%) were given classical radiotherapy (18 MV photon emission) delivering 45-50.4 Gy total dose in 1.8 (N = 7 patients) or 2 Gy fractions per day 5/7 days using 3 or 4 beams (figure 1). The radiation field was determined by outlining the regions of interest and organs at risk on the scan slices to include the tumor, visible nodes, duodenopancreatic nodes, the celiac region, the hepatic hilus for head tumors, the splenic hilus for body and tail tumors, and a 10-15 mm safety margin (due to variations in pancreas position and displacement). Conformal radiation was used. The concomitant chemotherapy included a continuous infusion of 5FU (300 mg/m²/d, 5/7 d) in combination with cisplatin (20 mg/m²/d, 5 / 7 d) delivered the first and fifth week of radiotherapy. Two patients had coronary artery disease contraindicating use of 5FU which was replaced with paraplatin given in a weekly infusion delivered during radiotherapy.

A split-course was used for six patients (18%) due to their poor general status (WHO 2). These patients underwent exploratory laparotomy. The radiotherapy protocol included three series of 20 Gy fractioned at 2 Gy per day separated by a 15-day rest period. The chemotherapy protocol used the same 5FU dose in continuous infusion with cisplatin also at the same dose and schedule delivered the first week of the first two series.

Ten patients (30%) were given first line chemotherapy combining 5FU and cisplatine for nine and gemcitabine and oxaliplatin in one (4 cycles). This treatment was started alone because of moderate asthenia due to jaundice or recent surgery for four patients who received four chemotherapy cycles or as induction treatment for six patients who received three (N = 4) or two (N = 2) cycles.

Response and toxicity

All adverse effects related to chemoradiotherapy were noted using the NCI criteria, considering only toxic effects above grade 2 requiring dose adaptation for chemotherapy, rehospitalization or interruption of treatment. A computed tomography scan was scheduled four to six weeks after the end of the classical radiotherapy or after delivery of 40 Gy for patients on a split course. The two criteria retained for surgical exploration were tumor response (WHO criteria) and decrease in mesenteric or celiac arterial encasement. Partial response corresponded to a 50% decrease or more in the sum of the products of the two largest diameters of the tumor, with minor response corresponding to a 25-49% decrease. If the tumor stabilized, complementary radiation was delivered on the pancreatic tumor. Therapeutic decisions were made on a case-by-case basis during multidisciplinary staff meetings.

Statistical analysis

Survival was determined from onset of treatment to date of death or last follow-up. The probability of survival was estimated using the Kaplan Meier method. Univariate analysis was used to search for factors influencing survival with an alpha risk set at 5% (P < 0.05). Survival curves were compared with the log-rank test.

Results

Patient characteristics

There were 18 men (55%) and 15 women (45%), mean age 63 years (range 37-79 years). The patient’s general health status was good in 27 (WHO 0/1) and moderately altered (WHO 2) in six. The inaugural symptom was pain in 19 patients (58%) and jaundice in 16 (48%).

Search for extension included a thoracoabdominal CT scan with injection (N = 33) with digestive endoscopic sonography and/or abdominal magnetic resonance imaging (MRI) as needed to detail vascular extension and rule out hepatic involvement. Certain CT scans performed in other centers for diagnostic purposes were insufficient to determine resectability. MRI was performed in 16 patients (49%) and endoscopic ultrasound in 10 (30%). This high rate of MRI explorations was related to equipment availability.

Pretherapeutic surgical exploration was performed in 22 patients (66%) to rule out peritoneal extension or when imaging had underestimated locoregional extension (allowing first-line surgical resection). Laparotomy was performed in 14 patients (42%) and laparoscopy in eight (24%). Histological confirmation was obtained on surgical specimens from 16 patients (48%), per-
cutaneous biopsies in 15 (45%) and endoscopic biopsies in two (7%). Jaundice was treated surgically in ten patients (62%) and endoscopically in six (38%).

The TNM classification was: T2 (N = 1), T3 (N = 1), T4 (N = 31), N0 (N = 21), N1 (N = 12).

Radiochemical toxicity

Twenty-six patients (79%) completed the planned treatment protocol. Thirteen (39%) presented an acute toxic event (table I). Digestive toxicity was observed in eight patients with grade 3 vomiting (N = 5), grade 3 diarrhea, requiring parenteral rehydration, aphagia (N = 2), and severe mucitis (N = 1) requiring parenteral nutrition. Grade 3 hematological toxicity was observed in four patients (12%) and involved all three cell lines in two who were given packed red cell units. Treatment was discontinued for one week in these four patients. There were no cases of neutropenia with fever. One patient developed cardiac toxicity to 5FU with atrial fibrillation which was reversible after definitive interruption of the chemotherapy.

Five patients (15%) developed late severe toxic effect three to six months after the end of treatment. Four of these patients developed grade 4 radiation-induced gastritis revealed by digestive bleeding. These patients were given repeated blood transfusions and underwent endoscopic argon plasma coagulation procedures. One patient had a gastrectomy for hemostasis. Two had received 60 Gy and two others 50 Gy. One patient developed grade 3 radiation-induced ulcers of the antrum complicated by digestive stenosis. Revealing symptoms were repeated vomiting and pain late after treatment. This patient who had received 60 Gy underwent distal gastrectomy (antrectomy) (table I).

Radiologic response

The disease was considered stable at the CT examination before chemoradiotherapy in the ten patients given first intention chemotherapy. There were no cases of complete response among the 33 patients (table II). Four patients (12%) presented partial tumor response: no visible tumor contact with the mesenteric artery in one patient and in two others a significant decrease in the encasement on the superior mesenteric or celiac arteries (less than 25% of circumference). Six patients (18%) presented minor tumor response but with an unchanged vascular extension. The tumor was considered stable in 14 patients (42%). The disease progressed in nine patients (28%) (without histological proof), and was metastatic in all nine (7 with liver metastasis and 3 with peritoneal metastasis). Two patients also developed local progression with increase in the size of the pancreatic tumor. Among these nine patients, four had had laparotomy or laparoscopy (N = 1) before treatment which had not identified extrapancreatic spread (table II).

Subsequent resection

After multidisciplinary discussions, laparotomy was proposed for ten patients who had responded. Surgery was performed four to six weeks after the end of chemoradiotherapy. For two patients, resection could not be performed. The tumor was inextricable for one of them (extension to adjacent vessels, transverse mesocolon, metastatic nodes). The scan visualized

![Fig. 1](https://example.com/fig1.png)

**Fig. 1** – The radiochemotherapy protocol.

**Déroulement de la radio-chimiothérapie.**

<table>
<thead>
<tr>
<th>Toxic effect</th>
<th>Number of patients (%)</th>
<th>Number of patients Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic</td>
<td>4 (12)</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Thrombopenia</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Digestive</td>
<td>8 (24)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Nausea / Vomiting</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Mucitis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Radiation-induced</td>
<td>5 (15)</td>
<td></td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Gastrics</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Cardiac</td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td>Supraventricular arrhythmia</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
Table II. – Radiographic response to chemoradiation and pathologic findings in 8 patients who underwent pancreatectomy.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiologic response</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>33</td>
</tr>
<tr>
<td>Complete response</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>4 (12)</td>
</tr>
<tr>
<td>Minor response</td>
<td>6 (18)</td>
</tr>
<tr>
<td>Stability</td>
<td>14 (42)</td>
</tr>
<tr>
<td>Progression</td>
<td>9 (28)</td>
</tr>
</tbody>
</table>

| Histological results | |
| Total | 10 (30) |
| Complete response | 1 (3) |
| Stade TNM (UICC) | |
| T1, < 2 cm intrapancreatic | 2 |
| T2, ≥ 2 cm intrapancreatic | 1 |
| T3 / T4 extension extrapancreatic | 3 |
| N0 | 5 |
| N1 | 3 |
| M0 | 7 |
| M1 | 3 |
| Positive resection margins | 0 |
| - Pancreas | 0 |
| - Bile duct | 0 |
| Vascular emboli | 2 |
| Perinervous encasement | 1 |
| Vascular invasion | 2 |

(1) Unmeasurable tumor in one patient due to difficulty in delimiting the tumor / pancreatic parenchyma after radiochemotherapy;
(2) Mean number of nodes analyzed : 9 (from 4 to 19);
(3) Tumor venous adherence.

decreased size of the pancreatic tumor, but with persistent mesentericoporal encasement covering more than 180° of the vascular circumference. Laparotomy was proposed in order to distinguish between tumor contact and fibrosis after chemoradiotherapy. One other patient developed peritoneal carcinomatosis which had not been detected on the evaluation scan where reduction in tumor size was noted, but with persistent celiomenteric encasement. This patient underwent pretherapeutic laparoscopy which did not detect extrapancreatic disease.

Subsequent resection was performed in eight patients (24%). Surgical procedures were: duodenopancreatectomy (N = 5), left splenopancreatectomy (N = 2), left pancreatectomy (N = 1). Vascular reconstruction (resection of the mesenteric vein without graft) was required in two patients. There were no preoperative deaths, reoperations or postoperative complications.

Histological examinations of the operative specimens demonstrated an exocrine adenocarcinoma in seven patients. One displayed complete histological response (no tumor residue in the operative specimen). Tumor staging was: pT1 (N = 2), pT2 (N = 1), pT3 (N = 1), pT4 (N = 2). Tumor dimensions could not be measured in one patient because the limit between the tumor and the normal pancreatic parenchyma could not be identified after radiotherapy. The resection margins were negative in seven patients (R0 resection). Among the eight operated patients, three presented invaded nodes. The presence of vascular emboli was noted in two patients with perinervous encasement on one operative specimen. For the two patients who had vascular reconstruction surgery, the venous adherence was tumoral (table II).

One patient who underwent duodenopancreatectomy had a centimetric liver metastasis in segment III (confirmed at peroperative pathology examination) which had not been detected at the preoperative evaluation. It was decided to continue the operation and associate resection of the liver nodule with the pancreatectomy. This patient had had a laparoscopy before chemoradiotherapy as well as intraoperative ultrasound exploration which had failed to identify any extrapancreatic disease. There was one minor tumor response on the evaluation scan and one persistent mesenteric encasement covering more than 180°.

Survival and recurrence

Median overall survival was 16 months, with a mean follow-up of 40 months. The rates of survival at one and two years were 66% and 37% respectively. The overall rate of survival in the eight patients operated after chemoradiotherapy was 87% at one year, 73% at two and three years. The overall survival rates for the 25 patients given chemoradiotherapy alone were 60%, 13% and 0% at one, two and three years respectively (figure 2).

Twenty-two patients (66%) died, all due to recurrent or progressive disease. Five patients who underwent tumor resection after chemoradiotherapy were living free of recurrence at 11, 18, 29 (N = 2) and 39 months after treatment onset. One patient given chemoradiotherapy alone (tumor considered non respectable at evaluation) was alive and free of disease progression 11 months after treatment onset.

Twenty-seven patients (82%) presented disease progression. Fifteen patients (56%) had metastatic dissemination, mainly to the liver and peritoneum (N = 13). One patient developed lung metastasis, another bone metastasis. Nine patients (33%) developed both local and metastatic dissemination, mainly to the peritoneum. There were also 11% of patients with unique locoregional extension.

The patient who underwent duodenopancreatectomy with resection of a liver metastasis in segment III developed recurrent metastasis 12 months later involving the peritoneum and the liver. This patient died 16 months after treatment onset.

Median progression-free survival for all patients was nine months. The rate of progression-free survival at one and two years was 32% and 13% respectively. In operated patients, the rate of progression-free survival at one, two and three years was 75%, 56% and 56% respectively. The rate of progression-free survival at one and two years for patients given chemoradiotherapy alone was 19% and 0% respectively.

Survival prognostic factors

In order to determine factors influencing survival in this series of 33 pancreatic adenocarcinomas treated by chemoradiotherapy, we examined eleven variables with univariate analysis: age, gender, general health, tumor size, tumor site, tumor differentiation, laparotomy or laparoscopy, primary chemotherapy, type of chemotherapy, mode of radiation.

Factors of poor prognosis were: laparotomy before treatment (figure 3) (median overall survival 12 months versus 19 months;
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P = 0.02, split-course radiotherapy (figure 4) (median survival 7 months versus 18 months; P < 0.001). Patients given first intention chemotherapy had a significantly longer survival than those given chemoradiotherapy as first-line treatment (figure 5) (median survival 22 months versus 12 months; P = 0.03). Factors not associated with survival were: gender, age, general health, tumor site (head, body, tail), tumor size, degree of differentiation, laparoscopy, chemoradiotherapy with 5FU and cisplatin compared with monotherapy using para-platin.

**Discussion**

Keeping in mind the fact that this was a retrospective study, and although certain patients had received first-line chemotherapy, we observed that subsequent potentially curative resection of locally advanced pancreatic cancer after primary chemoradiotherapy can be achieved and that longer survival is observed in operated patients.

Surgical resection is the only curative treatment for pancreatic adenocarcinoma, with an objective of complete R0 resection and nodal stage N0. Surgery offers the best chances of long-term survival, but approximately 80% of patients have a non-resectable tumor and half of them have locally advanced disease [12]. Despite numerous innovations for medical care, the rates of tumor response and survival remain low. It is suggested that results could be improved by using a combined therapeutic strategy.

There remains a certain degree of uncertainty concerning the role for combined radiotherapy-chemotherapy for pancreatic tumors. For resectable tumors (for which surgical resection is used to improve prognosis), chemoradiotherapy appears to be beneficial when used as a neoadjuvant and adjuvant treatment [13, 14], even though following the ESPAC-1 study [15] there has been some question as to the appropriate indication. For non-resectable non-metastatic tumors, the problem is different: should chemoradiotherapy be used only as a palliative measure or is it a preoperative treatment for selected patients? The concept of preoperative chemoradiotherapy concerns cancers other than pancreatic cancers and has been suggested for locally advanced non-resectable gastric and esophageal tumors which have in certain cases responded well allowing subsequent surgery in some patients [16].
Theoretically, the success of such a therapeutic strategy depends on rigorous patient selection. A supplementary proportion of patients, about 20%, would have metastases missed on the evaluation scan [17]. The two key explorations are helicoidal CT and endoscopic ultrasound with needle biopsy. The latter enables the histological diagnosis in 79% to 93% of cases [18, 19] and limit the risk of dissemination. The CT scan provides best assessment of resectability for pancreatic tumors with reliability to the order of 100% [20]. The capacity of CT scan to predict resection varies from 70% to 90% [21]. In our study, among the ten operated patients, three developed metastatic progression non detected by the CT scan. Magnetic resonance imaging (MRI) does not improve results in this indication [22]. Laparoscopy is optional [23].

This strategy is also dependent on tumor response to chemoradiotherapy, particularly in terms of arterial vascular extension, the only true contraindication for curative surgical resection. In our series, three patients whose operative margins were negative developed significant regression of the tumor in contact with the superior mesenteric artery or the celiac trunk. It is noteworthy that three of these patients had been given first-line chemoradiotherapy. Inversely, there were failures or early recurrences after surgery, with a slight decrease in tumor size on the evaluation scan but with a persistent vascular encasement. The chemoradiotherapy combination enables down staging in certain cases. The proportion of R0 resections and of N0 nodal staging is greater after chemoradiotherapy. In a retrospective series reported by Sohn et al. which included 616 pancreatectomies performed for potential tumor resection, 70% of the resections were complete (R0) with nodal invasion in 72% [5]. Results were better in the study by Breslin et al. which included 132 patients treated with chemoradiotherapy then pancreatectomy: 88% R0 resections and advanced nodal invasion in 48%; here again the tumors were potentially resectable [24]. Several phase II trials published in the 1990s reported tumor progression of locally advanced cancers in patients given chemoradiotherapy, allowing subsequent surgery [9, 10, 25]. In the study by Jessup et al. published in 1993 and including 16 patients with locally advanced non-resectable pancreatic tumors, resection was possible in two patients (13% of patients) after 45 Gy chemoradiotherapy with continuous 5FU. Recurrence-free survival was greater than 20 months in two operated patients [9]. Yeung et al. reported a rate of 38% secondary resections with ten R0 resections in their retrospective series of 26 non-metastatic non-resectable pancreatic tumors after 50.4 Gy chemoradiotherapy with continuous 5FU the 1st and 5th week and mitomycin C on day 2 [25]. Median overall survival was more than 24 months in the operated patients and eight months without resection. In the study by Khamtan et al., 35 patients were given two or three cycles (depending on observed response) of a polychemotherapy protocol combining 5FU, streptozocine and cisplatin associated with split-course radiotherapy with two 20 Gy fractions. Five patients (14%) underwent surgery after radiochemotherapy with R0 resection. Median overall survival of patients treated with radiochemotherapy was 15 months and 31 months in the subgroup of operated patients [10]. In the series reported by White et al., 25 patients with pancreatic carcinoma considered unresectable were given fractionated chemoradiotherapy with a total dose of 45 Gy (1.8 Gy) and concomitant chemotherapy with 5FU, combined for certain patients with mitomycin C (N = 12) or cisplatin (N = 10). In all, pancreatectomy was possible in five patients after chemoradiotherapy with only one R0 resection (5%). Median overall survival was not more than ten months in the nonoperated patients and reached 17 months in the event of curative resection [26]. Lower tumor stage after chemoradiotherapy for locally advanced pancreatic cancers remains a subject of debate and publications have been criticized on several points (non-comparative trials with few patients, inclusion biases, non-homogeneous criteria for non-resectability). For many authors, tumor response (upon which depends the surgical decision) is observed occasionally (10-20%) using current chemoradiotherapy protocols using 5FU with few tumor sterilizations [10, 26] and would only concern a limited number of tumors corresponding to the definition of locally-advanced tumors [26-28]. The lack of prognostic factors accentuates the difficulty in determining the appropriate approach for these locally-advanced tumors since about 20% of patients will develop metastasis after chemoradiotherapy. In our series, among the ten operated patients, one developed a secondary hepatic localization and another had peritoneal carcinomatosis. The preoperative laparoscopy had ruled out metastatic extension in these patients.

In recent years, most chemoradiotherapy protocols have used 5FU and/or cisplatin. There is hope for better results with more recent cytostatic drugs such as gemcitabine, a nucleoside analog which has demonstrated systemic activity in metastatic pancreatic adenocarcinoma and which is also a powerful radiosensitizing agent (requiring when used in a combination protocol to adapt the dose or the radiation volume [29, 30, 32, 33]. For example, a team from Munich treated 33 patients with chemoradiotherapy using four cycles combining gemcitabine-cisplatin with fractionated radiotherapy at 45-50 Gy; two supplementary chemotherapy cycles were administered after the radiotherapy. Secondary resection was possible in 14 patients (42%); there was an objective response (imaging) in 23 patients (70%) [31]. The current recommendations of the French Federation for Digestive Cancer (FFCD) appear more reasonable: “for non-resectable non-metastatic tumors, and when surgery is an option, treatment with chemoradiotherapy is possible with reevaluation of the possibility of secondary resection in the event of tumor response”.

In conclusion, since surgery must be included in any curative approach to cancer of the pancreas, use of a chemoradiotherapy combination which could improve the resection and the prognosis is an attractive possibility. Subsequent curative resection of locally-advanced pancreatic tumors after chemoradiotherapy can be discussed if there is an objective tumor response and notably significant regression of the celiomesenteric perivascular encasement. Prolonged survival can be observed in operated patients. Use of powerful radiosensitizing agents such as gemcitabine which also has a systemic effect could be interesting for this strategy.

REFERENCES


