**Cancer of the pancreas**

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**Introduction**

Only exocrine pancreas cancer (ductal adenocarcinoma) is treated herein, excluding other malignant tumors of the pancreas, notably ampullomas, endocrine tumors, and cystadenocarcinomas, which pose different problems. This work is based on “Les standards, options et recommandations de la Fédération Françophone de Cancérologie Digestive (FFCD) [2] and the GERCOR (Groupe d’Etude et de Recherche Clinique en Oncologie Radiothérapie), and their updates (Medline, January 1999 to January 2005).

**TNM classification (UICC 2002, 6th version)**

**Tumor (T):**

- Tx: insufficient information to classify primary tumor
- Tis: carcinoma in situ
- T1: tumor limited to pancreas <2 cm in its largest diameter
- T2: tumor limited to pancreas ≥2 cm in its largest diameter
- T3: tumor extended to one of the following organs: duodenum, common bile duct, peripancreatic tissue but no vascular invasion.
- T4: tumor extended to celiac trunk or superior mesenteric artery (primary tumor nonresectable).

**Adenopathies (N):** Examination of at least 10 lymph nodes is desirable.

- Nx: insufficient information to classify regional adenopathies
- N0: no regional lymph node metastasis
- N1: invasion of regional lymph nodes

**Visceral metastases (M):** M0: no metastasis, M1: presence of distant metastases

**Stages**

- Stage 0: Tis N0 M0
- Stage I: T1, N0, M0
- Stage IIA: T2, N0, M0
- Stage IIB: T1–3, N1, M0
- Stage III: T4, any N, M0
- Stage IV: M1 any T and N.

**Pretherapy explorations**

**Suspicion of cancer**

In cancers of the pancreas head, the diagnosis can be suspected by cost-effective means. In a patient who has cholestatic jaundice (jaundice, pale stools, with or without pruritus), often deteriorated general condition, palpation of a large gallbladder suggests the diagnosis of pancreatic cancer or cholangiocarcinoma of the lower bile duct. In absence of enlarged gallbladder (one out of two cases), ultrasound showing dilatation of biliary ducts can differentiate pancreatic cancer from hilar cancer. If there is no jaundice, in cancers of the body or the tail of the pancreas, more rarely cancers of the pancreatic notch, pain usually motivates ultrasound examination. The same holds true for rarer discovery circumstances (alteration in the general condition, metastases, etc.) [4]. If ultrasound does not show the pancreas clearly (20% of cases) or does not allow visualization of the tumor, radiological diagnosis is based on spiral CT with injection or echoendoscopy (EE). Spiral CT should be preferred in first intention to echoendoscopy because it is noninvasive and provides better exploration of the entire abdomen (in particular the liver) when searching for metastases. Its sensitivity is 90% for pancreatic cancer diagnosis. However, 20%–30% of pancreatic cancers of a diameter ≤20 mm are not recognized by this examination. If there is strong clinical suspicion, echoendoscopy should then be done because its sensitivity at 95% is independent of the tumor size [5,6]. In the hands of skilled operators, the normality of an echoendoscopy can eliminate with near certainty the diagnosis of pancreatic cancer. Anglo-MRI with ultrarapid sequences is an alternative to spiral CT [7,8]. FDG scintigraphy (PET scanner) is currently less accessible and still being evaluated; it has an advantage in cancer resectability assessment rather than in initial diagnosis.

**Diagnosis of metastatic extension**

The search for metastases, other than clinical examination, is based on abdominal ultrasound and chest x-ray or better yet, on fine-slice thoracoabdominal CT. Laparoscopy can be used to screen for peritoneal metastases and small liver surface metastases that are not visualized on imaging. Its results are all the more useful if preoperative imaging was limited, notably if there was no echoendoscopy. When imaging included thoracoabdominal CT and echoendoscopy, laparoscopy demonstrates a cause for nonresectability in 13% of cases [10].

**Proof of cancer**

Histological diagnosis should be obtained when nonsurgical treatment is planned because 10% of malignant tumors of the pancreas are not exocrine and all tumors of the pancreas are not malignant.

If the patient is operated on, the histological diagnosis is...
obtained by pathological examination of the excision specimen, a lymph node, carcinoma nodes, or pancreatic biopsies, eventually transduodenal for the pancreas head. If there is no indication for surgery and there is accessible ascites or liver metastases, ascites needle biopsy with cytology or radiologically guided fine-needle liver biopsy (ultrasound or CT) should be proposed as first-line studies because they do not require general anesthesia.

In other cases, biopsy of the pancreatic mass with ultrasound or echoendoscopy is indicated [11-12], the alternative being CT-guided biopsy. A negative biopsy does not eliminate the diagnosis of cancer; in cases where malignant tumor is strongly suspected, a second attempt should be made. If excision surgery is planned (tests showing that the tumor is resectable and no operative contraindications), it is preferable not to do the biopsy so as to avoid the morbidity associated with the act and the theoretical risk of seeding along the needle trajectory, even though this risk and the prognostic impact of this act have not been established. In case of tumor that is judged to be resectable but for which the patient can be included in a therapeutic trial testing neoadjuvant treatment or in cases where there is a strong diagnostic doubt, for example a patient with a nodule of pancreatitis (normal CA19.9, preserved general condition), ultrasound- or echoendoscopic-guided needle biopsy should be done to reach diagnosis.

Operability and resectability criteria

Three questions should be asked: a) Are there any contraindications to surgery? b) Is the tumor resectable? c) If the tumor is not resectable during preoperative workup, should the jaundice treatment be surgical or endoscopic?

Surgical contraindications

There are two types of surgical contraindications: 1) a probability of postoperative mortality >10%; when there is visceral failure (cardiac, pulmonary, renal, etc.) [4]; 2) the presence of visceral metastases, given a probability of median survival of 3–6 months. Laparoscopy, which can detect peritoneal metastases or small liver metastases not detected on imaging (10%–15% of cases), can reduce the number of useless laparotomies [10].

Resectability workup

These tests should only be done if there are no surgical contraindications (patient's condition) and if the assessment of metastatic extension is negative. Distant local-regional, vascular, or lymph node extension are the three main elements to take into account for resectability.

Local-regional extension: posterior infiltration (hilar plate, invasion of the mesenteric artery of the aortic adventitia, etc.) do not allow curative resection.

Vascular extension: all vascular extensions are not synonymous with nonresectability: the splenic artery, the superior mesenteric vein, or the portal vein can sometimes be resected [4]. On the other hand, invasion of the superior mesenteric artery, the hepatic artery, or the celiac trunk contraindicate resection. The same holds true for invasion of the superior mesenteric vein or the portal vein if more than half of the venous axis is involved or if there is collateral circulation [4]. If the patient has received neoadjuvant treatment, resectability should be re-evaluated.

Lymph node extension: metastatic extension to the lymph nodes or the pancreatic loculus (adhering to the tumor) is not a criterion of curative nonresectability, because lymph node invasion is often known only after postoperative histopathological examination of the operative specimen. In addition, prolonged survival has been reported in this situation [4]. Lymph node invasion, however, is an independent prognostic factor in all the multivariate studies on survival factors [13].

On the other hand, documented distant lymph node invasion (originating in the celiac trunk, hepatic hilum, mesenteric, retroperitoneal, or between the aorta and cava vena areas) is a criterion of nonresectability for curative purposes.

As for positive diagnosis, spiral CT is the first-line examination for local-regional resectability testing. Results are excellent for assessing arterial involvement, less good for venous invasion, and mediocre for lymph node invasion [14]. Echoendoscopy is useful in patients with nonmetastatic tumor that appears resectable after spiral CT (30% of cases). It is better than spiral CT for detecting venous involvement when the tumor is small and in detecting distant adenomas, which makes it indispensable at this stage [6]. If there is doubt on the vascular or lymph node extension, surgical dissection remains the surest method for judging the lesion's resectability. The frequent extension to the superior mesenteric artery is an argument for approaching this artery first during attempts at excision [13].

Histological examination of the resection specimen

In series of patients who had curative resection, positive resection margins were an independent prognostic factor of local recurrence in several multivariate studies [13, 15-16] in which the retroperitoneal or hilar margin were described. The study of the classical margins (distal pancreatic, choledochal, and gastric or duodenal) do not suffice, and it is recommended to study this retroperitoneal margin representing the pancreatic tissue plate that terminates at the right edge of the posterior side of the superior mesenteric artery; the margin should be marked with ink on the excision specimen [13]. In addition, the study of the retroperitoneal margin will undoubtedly allow for better evaluation of the impact of adjuvant treatments.

Treatment

Surgical treatments and stents

RESECTION

Reference

Surgical resection of the tumor is the only curative treatment but is achieved in only 20% of patients operated on (level of evidence A). To what point is it beneficial to the patient? In cancers that are accompanied by adjacent lymph node invasion, the 5-year survival rate is 0% [4]. In cancers with lymph node invasion distant from the tumor or in cancers of the body and tail of the pancreas, there are almost no survivors at 5 years. In cancers head cancers, indications for total pancreatectomy are rare: the main indication is intraductal papillary and degenerated diffuse mucinous forms. The others are multiple foci or the existence of a particularly fragile pancreas.
Cephalic duodenopancreatectomy (Whipple procedure) is the reference surgery. The frequency of invasion of the pancreatic section slice, choledochal (20%) or of the hilar plate warrants extemporaneous pathological examination. One trial has shown that pancreatic-gastric anastomosis provides results that do not differ from those of pancreatic-jejunal anastomosis: the quality of the pancreatic parenchyma and the quality of the anastomosis count more than the part of the digestive tract to which the pancreas is anastomosed [4]. The advantage of preserving the pylorus has not been demonstrated and one randomized study has shown that this favors prolonged gastric stasis [19]. A trial of extended lymphadenectomy including celiac and lumboaortic removal during pancreatectomy showed no benefit in terms of survival [20]. Postoperative mortality after cephalic duodenopancreatectomy is less than 2% in specialized centers [4]. Elsewhere, it is 8%–12% [4, 21]. After resection of pancreatic head cancers, the 5-year survival rate is on the order of 10%. It is 20% when there are no lymphatic metastases. A comparative study showed that postoperative enteral feeding via jejunostomy prolonged gastric stasis and had no nutritional advantage [22]. Preoperative biliary duct drainage is not recommended in the absence of neoadjuvant treatment [23-24].

Nonresectable cancers of the pancreas head bring up the discussion of the choice of palliative treatment: surgical or nonsurgical. Several trials have shown that surgery led to higher mortality than palliative nonsurgical treatments, but less jaundice recurrence [4]. One trial showed that gastrojejunostomy sheltered from the consequences of duodenal stenosis, which arises in 15%–20% of cases [25]. The best biliary derivation is choledochojejunal anastomosis, simpler to perform and as effectual as choledochojejunostomy anastomosis. Biliary and duodenal stents are an alternative to palliative surgery. In biliary duct stenosis: when predictable survival is less than 3 months, a single plastic stent is preferable to a metallic stent for cost reasons [26]. If survival is greater than 3 months, a metallic stent is best because its median delay before obstruction is longer. Moreover, metallic stent obstruction is easily treated with endoscopic reintubation. If there is duodenal stenosis, a duodenal stent can be deployed in at least 90% of cases by experienced teams. In more than eight out of ten cases, these stents can maintain oral feeding until the patient’s death [27]. Before the duodenal stent is deployed, there must be no common bile duct dilatation, which would require draining first, because of the problems of biliary drainage with a duodenal stent in place.

The preference of the managing team between surgical or nonsurgical derivation(s) should guide investigations. If a surgical derivation is favored, preoperative diagnosis of resectability is useful. Indeed, if during the operation the tumor is resectable, it is resected, and if not, a double derivation is performed and possibly celiac alcoholization with antilucytic intent. If the operating team believes that bile duct and/or duodenal derivations can be performed with endoscopic or radiologic guidance, resectability should be evaluated to reserve this treatment for tumors that are clearly not resectable. In conclusion, if the probability of patient survival is less than 6 months (metastatic stage, general condition WHO 2), endoscopic or radiologic guidance (stenosis, biopsy/alcoholization) is indicated [27-28]. If the probability of survival is greater (locally advanced nonmetastatic stage, WHO general condition ≤1), operator experience, local technical equipment, and the patient’s opinion should guide the choice between endoscopic derivation (with metallic stent) and surgical double derivation [28].

Chemotherapy and radiotherapy

Adjuvant and neoadjuvant treatment

Combining radiotherapy and chemotherapy (RT–CT) with 5FU cannot be considered a therapeutic standard. A single randomized trial, the GITSG trial [29] was positive (40 patients). The EORTC trial (218 patients), which included pancreatic cancers, but also ampullomas and extrapancreatic biliary duct cancers, did not show a significant benefit for adjuvant RT–CT [30]. However, analysis of the pancreatic cancer group (114 patients: 60 patients in the RT–CT arm, 10 of whom did not receive treatment) showed a tendency toward improvement in the treated group (median survival: 17 vs 13 months, survivors at 2 years: 37% vs 23%; p=0.099). The ESPAC 1 trial (European Pancreatic Cancer Study Group), included 289 patients in 2X2 factorial design with observation, CT, RT–CT, and RT–CT then chemotherapy [31]. In addition to the factorial design, 192 patients were randomized to chemotherapy vs observation and 69 RT–CT vs observation. Analysis of all 550 patients showed that RT–CT was harmful and that chemotherapy alone with 5FU and folic acid, according to the Mayo Clinic protocol (folic acid 20 mg/m² in 1.5 min followed by 5FU 425 mg/m² bolus for 5 days every 28 days) significantly improved survival (19.7 vs 14 months; p=0.0005). The final results of the trial on only the patients included in the 2X2 factorial design (289 patients; 1-year survival: 21% in the chemother- apy arm vs 8% in the no chemotherapy arm; p=0.009) confirmed the significant benefit contributed by this chemotherapy on operated patient survival [32]. Other than methodological criticisms, the main complaint on these three trials was that they used old radiotherapy protocols (split-course) with doses of 2x20 Gy, 5FU bolus (continuous 5FU only in the EORTC trial). The size of the irradiation fields was not specified in any of the three trials, which had no quality control. Phase II studies using radiotherapy totaling 45–60 Gy with 5FU in continuous perfusion, showed encouraging results, especially in reducing the local recurrence rate, one of the major problems remaining the onset of visceral or peritoneal metastases [33, 34]. In addition, in patients whose pancreatic cancer is a priori resectable, neoadjuvant induction RT–CT is an alternative, but only within a clinical trial [35-37]. In a phase III study, presented at the American Society of Clinical Oncology conference in 2005, surgical pancreatic cancer patients were stratified according to tumor stage, lymph node invasion, and microscopic invasion of the margins, then randomized to receive gemcitabine (gemcitabine 1000 mg/m² D1, D8, D14/4 weeks x 6) or were simply followed up. The main evaluation criterion was disease-free survival. The study randomized 356 patients. Disease-free survival (14.2 months) observed in the adjuvant gemcitabine arm was twice that of the observation arm (7.5 months); p<0.001 [38].

Reference

Alternative: adjuvant chemotherapy, 6 cycles of gemcitabine (1000 mg/m² in 30 min D1, D8, D15; D1=D28) (level of evidence B).

Clinical trials:

EORTC-FFCD 03-04 pancreas adjuvant (Phase II–III) trial: 4 cycles of gemcitabine (1000 mg/m² D1, D8, D15; D1=D28) vs 2 cycles of gemcitabine (idem) then continuous radiotherapy 50.4 Gy (28 fractions of 1.8 Gy) with gemcitabine 300 mg/m² weekly for 5 weeks of radiotherapy. International coordinator: JL van Laethem and coordinator for France: P Hammel (open in France in June 2005).

NONRESECTABLE CANCER

For patients with nonresectable cancer of the pancreas, palliation of symptoms is the main therapeutic goal. Pain management with adapted antalgics (use of morphine derivatives and co-antalgics at sufficient doses, regular evaluation on a visual analogic scale, intervention of teams specialized in pain treatment, etc.) and treatment for anxiety and depressive syndrome are often indispensable. Chemotherapy and radiotherapy can sometimes contribute to reducing pain and improving quality of life.

Locally advanced nonmetastatic and nonresectable cancer

Two GITSG studies compared radiotherapy alone (40–60 Gy) with RT–CT (with 5FU bolus). Both showed significant improvement in median survival with RT–CT: 10 vs 5 months [39–40]. Two other studies compared chemotherapy alone (5FU, and streptozotocin, mitomycin, 5FU) with RT–CT (with 5FU bolus) similar to the preceding studies. The first [41], with substantial methodological bias, did not show a difference between 5FU alone and RT–CT, whereas the second [42] showed a significant difference with RT–CT. Therefore, RT–CT was considered the reference palliative treatment with radiotherapy of 40–60 Gy in two or three monthly series of 20 Gy, combined the 3 first days of each series with 5FU bolus at a dose of 500 mg/m².

All three trials were conducted with 5FU bolus; however, only one feasibility study of the maximum tolerable dose (MTD) of 5FU in continuous perfusion 7/7 days was done with radiotherapy of 60 Gy. MTD of 250 mg/m²/day was defined, at the time. Chemotherapy and radiotherapy can sometimes contribute to reducing pain and improving quality of life.

Metastatic cancer

For patients with metastatic cancer of the pancreas, chemotherapy, although moderately effective, has a palliative effect [46–48]. Studies that compared chemotherapy to supportive care have reported prolonged overall survival [46–48]. In a randomized phase III trial (5FUFOL ± VP16 vs symptomatic treatment), extended overall survival was accompanied by improvement in quality of life [47].

In a randomized investigation, weekly treatment with 5FU (600 mg/m² bolus) was compared to treatment with gemcitabine (1000 mg/m², 30-min perfusion, 7/8 weeks then 3/4 weeks) [48]. The study included 126 patients, 75% of whom had metastases. Results of treatment with 5FU vs gemcitabine were, respectively, clinical benefit: 48% and 24% (p=0.0022); objective response rate: 0% and 5.4%; survival medians: 4.4 and 5.6 months; 1-year survival rate: 2% and 18% (p=0.0025). This study led to gemcitabine obtaining its AMM in Europe (equivalent of the American FDA approval). Administration of gemcitabine in perfusion for 100 min (10 mg/m²/min) is superior in terms of overall survival than perfusion of 30 minutes in one phase II randomized study, but no phase III studies are available; consequently, administration of 100 min cannot be considered a reference [49].

One phase III study (207 patients) in patients with metastases compared 5FU bolus with the combination of continuous 5FU + cisplatin (5FU 1000 mg/m² in continuous perfusion from D1 to D5 combined with 100 mg/m² of cisplatin on D1 every 4 weeks) [50]. No objective response was observed with 5FU versus 10% with the combination (p<0.001). Survival medians were short and not different (59 vs 79 days for progression-free survival; 102 versus 112 days for overall survival). The 1-year survival rate increased with 5FU-cisplatin, but without reaching significance (17% versus 9%, p=0.08). Another phase III study, comparing no treatment to the 5FU-cisplatin combination did not confirm the benefit of this chemotherapy [51]. Combining 5FU and cisplatin cannot be considered a reference.

A phase II trial conducted by the GERCOR evaluated combining gemcitabine at a dose of 1000 mg/m² in perfusion of 10 mg/m²/min on D1 and oxaliplatin at a dose of 100 mg/m² in 2-h perfusion on D2 (GEMOX). The treatment was administered every 2 weeks. The results showed a 30% objective response rate and a survival median of 9 months [52], which led to conducting a phase III trial. The study randomized 313 patients between gemcitabine and GEMOX. The results confirmed the good tolerance and efficacy of GEMOX in terms of response rate, progression-free survival, and clinical benefit. The difference in overall survival was not statistically significant: 7.1 vs 9.0 months (p=0.13). This raises the question of the low statistical power and/or the impact of the second-line treatments ( crossover) [53]. Another phase III study showed that combining gemcitabine and cisplatin vs gemcitabine alone improved progression-free survival (4.6 vs 2.5 months; p=0.016) but not overall survival [54]. One phase III study presented at the ASCO 2005 conference compared, in 569 patients, gemcitabine with the combination of gemcitabine + erlotinib, a tyrosine kinase inhibitor of the EGFr [55]. The increase in survival with the combination was significant but low (6.37 months vs 5.91 months, p=0.025). The cost-benefit ratio still needs to be evaluated.

Reference


Chemotherapy as for metastatic pancreatic cancer (level of evidence A).

Clinical trials


GERCOR trial. Nonresectable nonmetastatic cancers. Phase II study: 4 cycles of GEMOX then radiochemotherapy (5FU in continuous perfusion 250 mg/m²/day for the 5 weeks of radiotherapy and oxaliplatin, radiotherapy 45 + 10 Gy). Coordinator: L Moureau-Zabotto.
Another phase III study in 533 patients, presented at ECCO meeting n 2005 showed that combining gemcitabine and capetcitabine vs gemcitabine alone improved overall survival (7.4 vs 6 months, p=0.06, hazard ratio : 0.80, IC 95 % : 0.65-0.98) [56].

Reference

— Gemcitabine 1000 mg/m² in 30-min perfusion on D1 every week, 7/8 weeks, then 3/4 weeks [48] (level of evidence A).
— No chemotherapy and symptomatic treatment if the patient is elderly or in poor general health.

Alternative

— Combination of gemcitabine at a dose of 1000 mg/m² in perfusion of 10 mg/m²/min on D1 and oxaliplatin at a dose of 100 mg/m² in 2-h perfusion on D2 (GEMOX) [52, 53]. (level of evidence C).
— Combination of gemcitabine 1000 mg/m² in 30-min perfusion on D1 every week, 3/4 weeds and capectabine (1600 mg/m² d

Clinical trials

— GERCOR GEM-simplified GEMOX D04-1 trial. Phase II randomized study in metastatic adenocarcinomas of the pancreas: GEMOX and simplified GEMOX. GEMOX 1, gemcitabine 1000 mg/m² in 100 min on D1, oxaliplatin 100 mg/m² on D2; GEMOX 2, gemcitabine 1000 mg/m² in 100 min on D1, oxaliplatin 100 mg/m² on D1. Coordinator: C Louvet
— FFCD 03-01 trial: Strategic phase III study in metastatic adenocarcinomas of the pancreas: gemcitabine (1000 mg/m² in perfusion of 30 or 100 min on D1 every week, 7/8 weeks then 3/4 weeks) then LV5FU2-cisplatin second line (cisplatin 50 mg/m², folinic acid 400 mg/m², 5FU bolus 400 mg/m² then continuous 5FU 2400 mg/m² in 46 h; D1=D15) vs LV5FU2-cisplatin then gemcitabine in second-line treatment. Coordinator: JF Seitz
— FNCLCC ACCORD 11/0402 trial. Phase II/III randomized trial in metastatic adenocarcinomas of the pancreas: Folfirinox (oxaliplatin 85 mg/m², irinotecan 180 mg/m², folinic acid 400 mg/m², 5FU bolus 400 mg/m² then continuous 5FU 2400 mg/m² in 46 h; D1=D15) vs gemcitabine (1000 mg/m² in perfusion 30 min on D1 every week, 7/8 weeks then weeks) in first-line treatment. Coordinator: T Conroy

Monitoring

• After treatment with curative intent (surgical resection): clinical examination every 3–6 months and if there are symptoms. Paraclinical tests should be requested as symptoms require or according to protocols in therapeutic trials and/or to assess the efficacy of radiotherapy and/or chemotherapy.

Treatment of recurrences after surgery

In cases of recurrence after excision surgery

• local recurrence: treatment identical to that given for nonresectable locally advanced tumors
• metastatic recurrence: treatment identical to that given for initially metastatic tumors

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REFERENCES


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