

## The management of pancreatic cancer. Current expert opinion and recommendations derived from the 8th World Congress on Gastrointestinal Cancer, Barcelona, 2006

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This article summarizes the expert discussion on the management of pancreatic cancer, which took place during the 8th World Congress on Gastrointestinal Cancer in June 2006 in Barcelona. A multidisciplinary approach to a patient with pancreatic cancer is essential, in order to guarantee an optimal staging, surgery, selection of the appropriate (neo-)adjuvant strategy and chemotherapeutic choice management. Moreover, optimal symptomatic management requires a dedicated team of health care professionals. Quality control of surgery and pathology is especially important in this disease with a high locoregional failure rate. There is now solid evidence in favour of chemotherapy in both the adjuvant and palliative setting, and gemcitabine combined with erlotinib, capecitabine or platinum compounds seems to be slightly more active than gemcitabine alone in advanced pancreatic cancer. There is a place for chemoradiotherapy in selected patients with locally advanced disease, while the role in the adjuvant setting remains controversial. Those involved in the care for patients with pancreatic cancer should be encouraged to participate in well-designed clinical trials, in order to increase the evidence-based knowledge and to make further progress.

**Key words:** adjuvant treatment, chemotherapy, pancreatic cancer, radiotherapy

Pancreatic cancer represents just 2% of all cancers, but accounts for 6% of all cancer deaths. Nearly 90% of pancreatic tumors are ductal adenocarcinomas. The pancreatic cancer incidence of 10 cases per 100 000 individuals equals mortality, which highlights the poor prognosis of this condition. Pancreatic

cancer is rare before the age of 45 years and the majority occur >60 years. Aging of the population in the Western world will lead to an increase in absolute numbers. Nowadays, it is still more common in men than women [1, 2].

The cause of pancreatic cancer is unknown. Many authors believe that once the genetic material of a pluripotent stem cell in the adult pancreas is damaged and (epi)genetic changes accumulate, preneoplastic lesions (pancreatic intraepithelial neoplasia) may appear, which ultimately evolve into pancreatic cancer. There are only a few established risk factors for the

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disease; age, cigarette smoking and body mass index stand out as the most important [3]. More recently, we are beginning to appreciate the role of genetic factors in this devastating disease. Of patients with pancreatic cancer up to 10% have a family history of pancreatic cancer in >2 first-degree relatives. Some of these cases are related to well-known genetic syndromes that comprise familial atypical multiple mole melanoma syndrome, familial adenomatous polyposis syndrome, Peutz–Jeghers syndrome, breast cancer familial syndrome and hereditary nonpolyposis colorectal cancer syndrome [4]. The identification of a family with pancreatic cancer may open the perspective for genetic counseling and early detection.

Surgical resection remains the primary curative treatment option in pancreatic cancer. Recurrences are frequent following surgery, leading to 5-year overall survival (OS) rates of 10%–25%, depending on disease stage [5]. Interestingly, a Japanese study demonstrated a postoperative 5-year survival rate of 100% for patients with pancreatic cancer <1 cm. In most series though it is unusual to detect pancreatic cancer at such an early stage [6]. Seventy percent of these cancers are located in the head of the pancreas. Those that arise in the body or tail of the pancreas are almost always unresectable. Most patients are not operable at the time of diagnosis, have rapid ‘tumor’ progression and are in a poor general condition.

Several excellent clinical guidelines are available [7]. However, in this rapidly evolving field, new data are available focusing on the extent of pancreatic resection and on the additional treatment post- or preoperatively, which offer hope for improved outcome for patients with pancreatic cancer.

This article summarizes the expert discussion on the management of pancreatic cancer, which was organized during the 8th World Congress on Gastrointestinal Cancer in June 2006 in Barcelona, Spain. Opinion leaders and experts from different nationalities, selected on scientific merit, participated in the discussion. In preparation of this expert discussion, a detailed survey and questionnaire was sent to all participants and the questions, answers and conclusions were rediscussed at the meeting.

Expert committee reports reflect clinical experience on top of evidence-based medicine. As such, agreement or consensus was not always reached. The main strength, however, of this approach is that we hope to offer more than minimal guidelines, in order to help clinicians in the difficult task of making treatment choices in daily clinical practice.

## diagnosis and staging algorithm

### general remarks

In order to offer patients a curative treatment option, it is of paramount importance to detect the tumor at an early stage. However, patients are usually asymptomatic until the tumor has reached an incurable stage. Painless jaundice may be present in 50% of resectable tumors in the pancreatic head, but it may equally be caused by hilar or hepatic metastases. Common symptoms and signs are weight loss, abdominal discomfort (‘dyspepsia’-like symptoms such as nausea or early satiety), epigastric pain (back pain equals most often an

inoperable tumor), diabetes mellitus and venous thrombosis [8]. Acute pancreatitis may be a presenting feature of pancreatic cancer. A careful clinical examination is essential and supraclavicular palpable lymph nodes or umbilical metastases should not be overlooked. Performance status and a detailed family history should be recorded.

Diagnostic pancreatic imaging has evolved markedly in recent years. Ultrasound, endoscopic ultrasound (EUS), computed tomography (CT), magnetic resonance imaging (MRI), endoscopic retrograde cholangiopancreatography (ERCP) and 2-[fluorine-18]fluoro-2-deoxy-D-glucose positron emission tomography (FDG–PET) may indicate a diagnosis of pancreatic cancer. The question emerges which tests are necessary and in what combination. The choice of diagnostic imaging, supplemented by laboratory tests and laparoscopy, should be based on the efficacy, availability and cost–benefit of the test. Based on randomized comparisons, spiral CT, MRI and EUS yield similar accuracy (>90%) in diagnosing pancreatic cancer >15 mm [9, 10].

### obtaining pathological proof

Not all tumors in the pancreas are ductal adenocarcinomas. The differential diagnosis of a pancreatic mass include a neuroendocrine tumor, a metastasis of other cancer (e.g. breast, colon or renal cell carcinoma) or even an inflammatory pseudotumor. It was therefore stressed by the expert panel that pathological confirmation of the tumor should be obtained at some time point in the course of the disease. Obtaining a pathological proof of malignancy is necessary in advanced cases or when neo-adjuvant therapy is planned. It is not mandatory preoperatively inoperable tumors when resection can be carried out with an acceptable morbidity. Preoperative percutaneous sampling should be avoided. It may be challenging, but often possible, to obtain a specimen by EUS-guided fine needle aspiration of the primary tumor. The sensitivity and specificity of this approach may reach 80%–95% and 100%, respectively [11]. Alternatively, a metastatic lesion can be biopsied under ultrasound or CT guidance.

### primary staging of pancreatic cancer

- A spiral contrast-enhanced CT is considered the cornerstone of the diagnostic and staging algorithm of pancreatic cancer, provided that contrast is administered in the arterial, portal and venous phase. Pancreatic cancer appears as hypodense mass during the pancreatic parenchymal phase; an important desmoplastic reaction may artificially increase the size of the tumor. There may be a dilated pancreatic duct (or bile duct) and atrophy of the gland proximal to the mass. The CT scan is the definitive test in the majority of cases due to the additional yield of staging information (including the detection of liver metastases and/or vascular invasion) [10].
- MRI is especially useful in the differential diagnosis of cystic pancreatic lesions.
- EUS is largely dependent on availability and is used for detection of small tumors if uncertainty exists with CT or MRI. It may be especially useful to include EUS in family screening protocols for pancreatic cancer, as these programs

are set up to detect very small tumors or preneoplastic changes in the pancreas. EUS can help for determining blood vessel invasion or to obtain cytology specimens by fine needle aspiration in tumors.

- A chest X-ray (some experts advocate CT) is necessary to exclude pulmonary metastases.
- Laparoscopy is very useful to detect small peritoneal and/or small liver metastases, which may be missed by current imaging modalities. According to several studies, laparoscopy may change the therapeutic plan in up to 25% of patients. Diagnostic laparoscopy can be recommended before resection [especially in left sided large (>3 cm) pancreatic cancer] or if a neo-adjuvant treatment is considered. The timing of the procedure is dependent on the local organization [12].

### additional investigations

- ERCP is not routinely done for diagnosis. The procedure has a therapeutic purpose in case of obstructive jaundice for the placement of a biliary endoprosthesis.
- The place of FDG–PET is considered very limited in the staging algorithm of pancreatic cancer. FDG–PET certainly allows earlier detection of recurrence than classical imaging [13]. It is not clear, however, to what extent this diagnostic superiority translates into a clinical benefit for the patient.
- Tumor markers such as CA19.9 (and carcinoembryonic antigen) are of limited diagnostic value, although they are often taken as a baseline, in order to guide treatment follow-up [14]. It is well known that in case of cholangitis or liver failure, very high values of CA19.9 may be encountered in the absence of malignancy. In case of suspicion of a neuroendocrine pancreatic tumor, serum chromogranin A should be determined.
- Molecular markers are not yet available that may be of any help in routine clinical practice.

### different stages: decision on resectability

The decision on resectability requires a multidisciplinary decision. A distinction should be made between tumors that are resectable, borderline resectable, those that will never become resectable (truly locally advanced) and metastatic. The diameter of the tumor, as such, does not influence the decision on resectability. However, it is unlikely that a tumor >5 cm is resectable. Regional lymph nodes are not taken into account for nonresectability; lymph nodes distant from the tumor (such as celiac and para-aortic nodes) make surgery a futile act. Patients should be classified in one of the following groups, which are clearly correlated to survival (Tables 1 and 2) [15, 16].

- Potentially resectable disease is defined by (i) the absence of extrapancreatic disease, (ii) a definable tissue plane between the tumor and regional arteries [celiac axis (CA), superior mesenteric artery (SMA), common hepatic artery], (iii) a patent superior mesenteric vein (SMV), portal vein (PV) and their confluence (taking into consideration the technical ability to resect and reconstruct partially invaded venous structures). This definition corresponds to stage I and II in the tumor–node–metastasis (TNM) classification.

**Table 1.** Stage grouping of exocrine pancreatic carcinoma [15]

|   | M0        | M1              |
|---|-----------|-----------------|
|   | N0        | N1 <sup>a</sup> |
| Tis (severe ductal dysplasia/carcinoma <i>in situ</i> ) | Stage 0   |                 |
| T1 (≤2 cm), limited to pancreas                         | Stage I   | Stage IIB       |
| T2 (>2 cm), limited to pancreas                         | Stage IIA |                 |
| T3 (beyond pancreas, no involvement SMA or CA)          |           |                 |
| T4 (stomach, spleen, colon, involvement of SMA or CA)   | Stage III | Stage IV        |

<sup>a</sup>N1 are regional lymph nodes which are located superior and inferior to head and body of pancreas, anterior and posterior pancreaticoduodenal and proximal mesenteric, pyloric (tumors of head only) and common bile duct, hilum of spleen or tail of pancreas (tumors of body and tail only) and celiac (tumors of head only).

SMA, superior mesenteric artery; CA, celiac axis.

**Table 2.** Clinical and radiological staging of pancreatic cancer (adapted from [16]) and correlation with median survival

| Stage | Clinical/radiological criteria  | Long-term survival | Median survival           |
|-------|---|--------------------|---------------------------|
| I–II  | Resectable (T1–3, selected T4 <sup>a</sup> , Nx, M0)<br>No encasement of the celiac axis or SMA<br>Patent SMV–PV confluence<br>No extrapancreatic disease   | 20% <sup>b</sup>   | 13–20 months <sup>b</sup> |
| III   | Locally advanced (T4, Nx–N1, M0)<br>Tumor extension to involve celiac axis or SMA, or venous occlusion (SMV, SMPV confluence)<br>No extrapancreatic disease | Nil                | 6–10 months               |
| IV    | Metastatic (any T, any N, M1)   | Nil                | 3–6 months                |

<sup>a</sup>Resectable T4 include those with partial involvement of the SMV or PV.

<sup>b</sup>Following resection.

SMA, superior mesenteric artery; SMPV, superior mesenteric–portal vein; SMV, superior mesenteric vein.

- Borderline resectable disease is not described as such in the current TNM classification; it represents a stage between potentially resectable and truly locally advanced disease [17]. It may be defined by (i) the absence of extrapancreatic disease and (ii) the following tumor–vessel relationships, which can still be considered for resection and reconstruction: a short segment occlusion of the SMV–PV confluence with a suitable venous structure above and below the area of occlusion; a short segment encasement of the hepatic artery at the origin of the gastroduodenal artery; encasement of the SMA or CA ≤180° of the arterial circumference.
- Locally advanced disease which corresponds to stage III in the TNM classification when there is invasion in the arterial structures (encasement >180° of the circumference of the

- SMA or CA) or definite occlusion of above-mentioned venous structures (SMV, PV and their confluence).
- Metastatic disease (stage IV) is the presence of extrapancreatic disease. As the specificity of current imaging techniques is insufficient to diagnose enlarged lymph nodes as malignant, pathological proof of suspicious distant lymph nodes (on imaging) is considered mandatory before withholding potentially effective surgical therapy.

## treatment

At the time of diagnosis, 40% of patients have locally advanced or unresectable disease, 40% have visceral metastases, mainly liver and peritoneal implants, and 20% present with a possible resectable lesion. Patients with locally advanced disease are candidates for chemo(radio)therapy, whereas those with visceral metastases are candidates for chemotherapy. Resectional surgery is the only curative treatment, but is only an option in 10%–20% of patients with pancreatic cancer. Following resection, adjuvant treatment should be considered.

### resectional and palliative surgery

Surgical resection of the primary tumors and regional lymph nodes is the treatment of choice for a patient with a potentially operable tumor. Surgery should be confined to an expert team of surgeons in high volume centers, in order to increase resection rates, minimize postoperative morbidity and mortality [18]. Any effort to achieve an R0 resection is mandatory. For tumors of the pancreatic head, a pylorus preserving pancreaticoduodenectomy is appropriate. In case of proximal duodenal involvement or location of the tumor close to the pylorus, a classical proximal pancreaticoduodenectomy with antrectomy (Whipple's operation) is indicated. Pancreatic body and tail tumors require a left (distal) pancreatectomy and involvement of the splenic vessels do not preclude resection. More radical and technically demanding procedures including PV or SMV excision or total pancreatectomy are sometimes necessary in order to obtain an R0 resection. Every procedure should include a locoregional lymph node resection, but the benefit of extensive lymphadenectomy has not been demonstrated. A randomized trial of standard versus extended lymph node resection failed to show a survival benefit [19]. Biliary drainage is mandatory in case of cholangitis; some experts require biliary drainage before resection, if surgery is to be delayed (>10 days).

In patients who are found irresectable during surgery (or laparoscopy), surgical bypass (hepaticojejunostomy and/or gastroenterostomy) is recommended and can also be carried out laparoscopically with minimal morbidity. There are no randomized comparisons of current expandable metal stents for biliary or duodenal obstruction versus laparoscopic bypass surgery.

### adjuvant treatment

Surgery is the only curative treatment for pancreatic cancer, but long-term survival after surgical resection of pancreatic cancer

is <20% [20, 21]. Patterns of relapse are important when considering adjuvant therapy. In a recent study, local recurrence with or without distant metastasis occurred in 41% of patients who underwent surgery alone and distant metastasis was diagnosed in 49% [22]. This failure pattern highlights the need for optimal surgery and evaluation of adjuvant treatment strategies, which include chemoradiation or chemotherapy.

A well-designed trial of adjuvant therapy should include only patients with pancreatic cancer who underwent a resection with adequate locoregional lymph node resection (>10 nodes retrieved). Patients should be stratified in trials according to the resection status (R0 versus R1). Quality control of surgery and pathology (evaluation of resection margins, including inking of retroperitoneal margin) is mandatory. At the start of the adjuvant treatment, metastases should be excluded by CT scan of the thorax and abdomen. Many trials have been carried out or are currently evaluating different treatment options aiming at decreasing local relapse as well as distant metastases. However, several of these studies lack the proper design as delineated above. The first trial was initiated in the United States by the Gastrointestinal Tumor Study Group (GITSG) in 1974 [23], which was slow to accrue and was terminated early following an analysis of the first 43 patients that demonstrated a statistically significant median survival advantage to adjuvant chemoradiation and 1 year maintenance chemotherapy [bolus 5-fluorouracil (5-FU)] in patients with resected pancreatic cancer. Patients who were treated with a split-course radiotherapy schedule (40 Gy) and chemotherapy (bolus 5-FU) during first and last week of radiation therapy, and continued later on) had a median survival of 21 months, a 2-year survival of 43% and a 5-year survival of 19%. This was significantly better than those who did not receive adjuvant therapy and who showed a median survival of 11 months, a 2-year survival of 18 months and 5% 5-year survival ( $P = 0.03$ ). This suboptimal, low-powered trial represents the basis for the adoption of adjuvant chemoradiotherapy (CRT) as standard of care in the United States and Canada over the last 20 years. However, the observed benefit may have been due to the maintenance chemotherapy and not to the radiotherapy component.

Norwegian investigators randomized 61 patients between combination chemotherapy (fluorouracil, doxorubicin, mitomycin C) and no postoperative therapy. Median survival was longer in treated patients (23 versus 11 months,  $P = 0.02$ ) [24].

An European Organization for Research and Treatment of Cancer (EORTC) trial randomized 218 patients between chemotherapy (5-FU) in combination with split-course radiotherapy and no postoperative treatment in patients with pancreatic carcinoma and ampulloma. In contrast with the GITSG study, no chemotherapy was given following completion of the CRT treatment. There was no benefit in terms of survival [25]. However, on reanalysis with more appropriate statistical methods, there is a statistically significant benefit to adjuvant chemoradiation for patients with pancreatic head cancers [26].

Patients with resected pancreatic cancer did not benefit from cisplatin and fluorouracil in a Japanese study [27].

The European Study Group for Pancreatic Cancer (ESPAC)-1 trial was a large study carried out in 541 patients, which was, however, heavily criticized because of randomization methodology and the lack of quality control for surgery and radiotherapy. Patients were treated with CRT, chemotherapy (5-FU) or no treatment. There was no benefit for CRT whereas an advantage for chemotherapy (5-FU) was indicated [28].

The results of the Charité Onkologie (CONKO)-001 randomized trial of adjuvant chemotherapy in resected pancreatic cancer patients were recently published [22]. A total of 368 patients with R0 or R1 resection of pancreatic cancer were randomized to adjuvant chemotherapy with six cycles of gemcitabine or observation. More than 80% of patients had a R0 resection. Median disease-free survival (DFS) was significantly better in the gemcitabine group (13.4 months) than in the control group (6.9 months). Estimated DFS at 3 and 5 years was 23.5% and 16.5% in the gemcitabine group, and 7.5% and 5.5% in the control group, respectively. Subgroup analyses showed that the effect of gemcitabine on DFS was significant in patients with either R0 or R1 resection. There was no difference in OS, but it is likely that the difference in OS between groups will become statistically significant with a longer follow-up and an increasing proportion of deceased patients. However, major drawbacks of this study were the lack of quality control of surgery, pathology and the participation of a large number of low-volume centers.

Preliminary results are available from the Radiation Therapy Oncology Group (RTOG) 9704 study [29], which included 442 patients, and was designed to determine whether the addition of gemcitabine to adjuvant fluorouracil-based CRT improves survival in patients with gross complete resection of pancreatic cancer. Chemotherapy with either gemcitabine or fluorouracil was given >3 weeks before and 12 weeks after chemoradiation that consisted of radiation therapy with fluorouracil (continuous infusion) as a radiosensitizer in both groups. In the subgroup of 381 patients with pancreatic head tumors, gemcitabine significantly improved OS [median 20.6 versus 16.9 months, 3-year survival 32% versus 21%, hazard ratio (HR) 0.79, 95% confidence intervals (CIs) 0.63–0.99,  $P = 0.03$ ], but median DFS was not improved (11.4 versus 10.1 months).

The use of neo-adjuvant strategies in the preoperative setting in potentially resectable tumors remains experimental. In a promising phase II study, 86 patients were treated preoperatively with gemcitabine plus radiotherapy  $10 \times 3$  Gy [30]. Seventy-one patients underwent surgery and 74% of them had a resectable tumor and 54% a pathological response. Median survival in resected patients was 36 months versus 7 months in nonresected cases. However, randomized studies are necessary to confirm these promising results.

Based on these studies and despite some shortcomings, adjuvant treatment is strongly recommended following pancreatic resection surgery. The agents used may be gemcitabine for 6 months or 5-FU. Although there is a good rationale for adjuvant CRT, the level of evidence that supports its systematic use is lower. It may be considered in case of positive margins or R1 resection, but there was no consensus among the experts on this particular point.

Due to the ongoing controversy about postoperative CRT, results are awaited from the current phase II/III EORTC 40013-

trial, in which patients are randomized following R0 resection between gemcitabine therapy (for 4 months) and CRT (two cycles of gemcitabine for a duration of 8 weeks, followed by weekly ( $\times 5$ ) gemcitabine in combination with 50.4 Gy radiation therapy). The phase II part of the study is currently under analysis.

### nonsurgical palliation

The majority of patients with pancreatic cancer present with either locally advanced, unresectable disease or with metastases. Median survival of these patients is extremely short. Therefore, all interventions in these patients should be carried out with a low morbidity and mortality, aiming at improving or maintaining quality of life (QoL). Endoscopic stenting, pain relief and pancreatic enzyme supplementation represent the mainstay of palliative care in advanced pancreatic cancer.

*endoscopic stenting of biliary and duodenal obstruction.* Biliary tract obstruction may lead to jaundice, pruritus, abdominal discomfort, nausea, malabsorption and hepatic dysfunction. As such, it seriously interferes with QoL [31]. In addition, biliary decompression is necessary before applying chemo(radio)therapy. Endoscopic biliary stent placement is the initial treatment of choice for patients with obstructive jaundice due to pancreatic cancer. It is certainly less invasive, as effective as surgical intervention in the treatment of cholestasis and is characterized by the same median survival as surgically treated patients [32–35]. However, endoscopic stenting requires much more late interventions because of stent dysfunction, and this may have a negative impact on QoL. The choice of therapy, either surgical decompression or endoscopic stenting, should be discussed with every individual patient, after a thorough discussion with the patient of the pros and cons related to both therapeutic procedures [36]. The choice between the more expensive metallic, self-expandable stent or the cheaper plastic, polyethylene stent should be based on the prognosis and the general condition of the patient and on his willingness to undergo repeated procedures. Once deployed, metal stents have a diameter of 30 French or 10 mm. They are characterized by a longer median patency rate of  $\sim 10$  months, as compared with 10 French plastic stents that have a median stent patency of  $\sim 4$  months [37–39]. The mechanism of stent occlusion is tumor ingrowth or overgrowth in metal stents and sludge formation in plastic stents. Although both types of stents have similar outcomes with regard to patient survival and early reduction of jaundice, the insertion of a metal stent seems advisable if the patient is likely to survive  $>4$ –6 months and who will never be candidate for a surgical resection [39–41]. Information about life expectancy can be derived from the general condition of the patient, from the presence of distal metastases and from the size of the primary tumor [42, 43]. Duodenal stents are indicated for duodenal of gastric obstruction caused by locally advanced or metastatic pancreatic cancer. Duodenal stents are of the self-expanding metallic type with diameters of 16–22 mm. The method is minimally invasive and has a low morbidity rate [44].

*intractable pain.* The treatment of pancreatic cancer pain includes pharmacotherapy, chemotherapy and/or radiotherapy,

psychosocial support, celiac/splanchnic neurolytic blocks and epidural or intrathecal infusion of medications. The superiority of one method over the other, alone or in combination, has not been established so far [45]. Pain should be treated initially with a nonsteroidal anti-inflammatory drug-opioid sequence according to the World Health Organization recommended method. If pain is intractable, a celiac/splanchnic neurolytic block, either via EUS or percutaneous approach, should be considered. Overall, success rate is ~75% [46, 47], and the most prevalent complication being postural hypotension. These procedures are, however, nowadays carried out less frequently due to the venue of better medical relief with morphine and its analogues. In addition to pain, depression is a common problem in pancreatic cancer patients, which requires the necessary attention [48].

*pancreatic enzyme supplementation.* Obstruction of the main pancreatic duct may result in pancreatic exocrine failure and may be responsible for significant fat malabsorption. Enteric-coated pancreatic enzyme formulations may prevent weight loss and improve QoL in patients with pancreatic cancer [49]. However, there are no large studies in this field. It is important to administer sufficient dose of enzymatic activity, which should be at least 10% of the normal postprandial output of lipolytic activity (30 000 IU), to have some effect on steatorrhea.

### chemotherapy for advanced pancreatic cancer

The majority of patients with pancreatic cancer will develop metastases and are potential candidates for treatment with systemic chemotherapy. The median survival of patients treated with best supportive care (BSC) is ~3–4 months. However, many patients have a poor performance status and succumb to rapid tumor progression. Results obtained with chemotherapy failed to have a large impact on the final outcome and have been the reason for skepticism among clinicians and oncologists for many years. Accurate tumor measurements are often difficult to obtain (e.g. small peritoneal metastases), which represents a major drawback for many clinical studies carried out in pancreatic cancer. Moreover, the primary tumor is composed of a large amount of reactive fibrous tissue, which makes response evaluation in locally advanced tumors troublesome. However, a totally fatalistic approach is not justified because a significant proportion of patients do achieve benefit from chemotherapy.

Many studies have been carried out with 5-FU in pancreatic cancer. Early trials clearly overestimated the efficacy of 5-FU because of inadequate response criteria. The actual response rate is <10%. However, in these older studies, QoL was clearly improved in those patients who received chemotherapy in comparison with those who got only BSC [50]. Biochemical modulation of 5-FU with folinic acid and interferon did not show significant better results. Combination chemotherapy of 5-FU with mitomycin C, doxorubicin and streptozotocin (FAM and SMF regimens) has failed, despite some initial encouraging phase II studies [51]. A few studies have indicated that the activity of a protracted 5-FU infusion in combination with cisplatin was superior in terms of progression-free survival (PFS), but not OS [52, 53].

Gemcitabine is a nucleoside analogue with activity across a broad range of solid tumors [54]. The activity of gemcitabine in pancreatic carcinoma was assessed in early phase II trials. In a USA study of 44 patients, an objective response rate of 11% and a median survival of 5.6 months were found [55]. In a European study of 34 patients, a tumor response rate of 6.3% and a median survival of 6.3 months were found [56]. Both study groups reported symptomatic improvements in their patients that were greater than indicated by the objective tumor response rates. These improvements were seen with reductions in both pain severity and analgesic requirements as well as in performance status [57]. Therefore, 'clinical benefit response' was introduced as primary end point to evaluate the efficacy of gemcitabine [58]. In a randomized trial, 126 patients with advanced pancreatic cancer were treated with gemcitabine or with 5-FU. Gemcitabine (1000 mg/m<sup>2</sup>) was administered as a 30-min infusion weekly for seven consecutive weeks, followed by 1 week rest. Thereafter, the drug was given once weekly for three out of every 4 weeks. 5-FU 600 mg/m<sup>2</sup> was administered once weekly also as a 30-min infusion. Fifteen of 63 patients randomized to gemcitabine, experienced clinical benefit response (24%) with a median duration of 18 weeks versus three of 63 (5%) in the 5-FU-treated patients with a median duration of 13 weeks. In the gemcitabine group, 5.4% of the patients (three of 56) with measurable disease had a radiologic response versus none in the 5-FU group. Gemcitabine also showed a modest survival advantage over 5-FU (1-year survival 18% versus 2%; median survival 5.65 months versus 4.41 months) [58], which has been confirmed in many other trials where gemcitabine served as the control arm. As a result, the drug has been widely accepted as the standard first-line treatment of advanced pancreatic cancer. Some experts feel that it is not definitely shown that gemcitabine is superior to an optimal 5-FU or 5-FU/folinic acid schedule.

Although a pharmacokinetic rationale exists for administering gemcitabine in a protracted infusion at 10 mg/m<sup>2</sup>/min (fixed dose rate, FDR) and a small clinical trial was promising, a randomized phase III study comparing the FDR regimen and the standard 30 min infusion failed to show superiority for the FDR gemcitabine regimen [59, 60]. Combination of gemcitabine with a variety of cytotoxic agents failed to show an increased survival in phase III studies [60–65]. Only one phase III study comparing the combination of gemcitabine and capecitabine with gemcitabine monotherapy has shown a significantly improved median (7.4 versus 6 months) and 1-year survival (26% versus 19%) in favor of the combination arm (HR for survival 0.80; 95% CI 0.65–0.98,  $P = 0.026$ ) with a good safety profile [66]. A previous Swiss study was underpowered to show a survival difference [67]. Other studies with gemcitabine ± 5-FU failed to show a difference between the two arms [68–70].

The individual studies combining gemcitabine plus cisplatin or oxaliplatin demonstrated a significant advantage in terms of response rates and PFS, but did not yield a significant OS advantage for the combination of these drugs, although there was a trend for an improved survival in several studies [60, 64, 65]. The individual trials were underpowered, which contributed to the negative outcome.

Two large meta-analyses of 3687 and 5561 patients, respectively, indicated a survival benefit for the combination of gemcitabine and the platinum analogue particularly for patients with a good performance status [71, 72].

The interest in targeted therapies and novel biologic agents has generated a wealth of clinical trials exploring combinations with gemcitabine [73–75]. Only one trial of 569 patients has shown a significant survival benefit of the combination of gemcitabine plus the epidermal growth factor receptor (EGFR) inhibitor erlotinib compared with gemcitabine alone [73]. Patients treated with the combination of gemcitabine and erlotinib had an 18% reduction in the risk of death or an overall 22% improvement in survival. The median survival and the 1-year survival were better for the combination treatment: 6.24 versus 5.91 months and 24 versus 19% (HR for survival 0.82; 95% CI 0.69–0.99,  $P = 0.038$ ). The excess toxicity of the combination with erlotinib was relatively limited. These numbers as well as the 1-year survival difference probably reflect better the impact of the treatment with erlotinib for an individual patient than the difference in median survival. Combination of bevacizumab with gemcitabine did not result in a survival benefit compared with gemcitabine monotherapy in a large phase III study [76]. The results of the randomized phase III study of gemcitabine with or without the chimeric anti-EGFR monoclonal antibody cetuximab are pending.

Based on all these clinical trial data, questions remain regarding the actual standard treatment for patients with advanced pancreatic cancer and the choice of the reference treatment for clinical trials. The answer to these questions remains controversial. From a clinical viewpoint, several standard options can be proposed. Gemcitabine monotherapy can certainly be defended, but the combination of gemcitabine plus erlotinib, gemcitabine plus capecitabine and perhaps—in patients with a good performance status—gemcitabine plus a platinum analogue may result in a small benefit [77]. The choice of a reference arm in clinical trials is even more difficult. In this setting, one is intended to use the most active combination that is also widely used and accepted. Cooperative groups and other investigators still have today the legitimate option of gemcitabine monotherapy, although the choice of the combination of gemcitabine with erlotinib or capecitabine might be a preferable option as a control treatment to which new treatment options and regimens should be compared [77].

Few studies have been conducted in patients who failed in first line to gemcitabine. There is some evidence that a combination of 5-FU and oxaliplatin may have some efficacy in selected patients [78], but there is an unmet need for studies in second line.

### **CRT for locally advanced pancreatic cancer**

The optimal therapy for patients with locally advanced, unresectable pancreatic cancer remains controversial. The majority of chemotherapy trials also included patients with locally advanced, unresectable disease. So, many of the conclusions drawn previously are applicable to locally advanced pancreatic cancer. The exact contribution of radiotherapy, however, is unclear. Radiotherapy to the pancreatic bed is limited by the proximity of radiosensitive structures. Several small trials have shown a significantly longer survival following

CRT (10 months) as compared with chemo- or radiotherapy alone (6–7 months) [79–81]. CRT should be reserved to those patients who have a good performance status and peritoneal metastases should be excluded by laparoscopy. Some patients with locally advanced disease have rapid tumor progression and develop metastases within a few weeks.

The phase III study from the Fédération Francophone de Cancérologie Digestive randomly assigned 119 patients with locally advanced pancreatic cancer between CRT (60 Gy in 6 weeks, 2 Gy per fraction, concomitant with 5-FU, 300 mg/m<sup>2</sup> per 24 h as a continuous infusion, day 1–5 every week and cisplatin, 20 mg/m<sup>2</sup>/d, day 1–5 at week 1 and 5) and gemcitabine (1000 mg/m<sup>2</sup> weekly seven times every eight weeks) as induction treatment. Maintenance treatment was gemcitabine (1000 mg/m<sup>2</sup> weekly three times every four weeks) in both arms until progression or limiting toxicity. Those patients treated with first-line gemcitabine had a superior OS (51.4% at 1 year versus 24%; stratified log-rank  $P = 0.014$ ), which led to a premature stop of the study [82]. The reasons why this exposure to immediate CRT failed are currently under investigation.

The French Groupe Coopérateur Multidisciplinaire en Oncologie (GERCOR) proposes a different but attractive strategy of initial chemotherapy for at least 3 months, followed by CRT in patients whose disease had not progressed and who have a good performance status [83]. A retrospective analysis of 181 patients with locally advanced pancreatic cancer enrolled into prospective phase II and III GERCOR studies was carried out to compare the survival of patients who received CRT with that of patients who continued chemotherapy alone [83]. Fifty-three patients (29.3%) had metastatic disease after 3 months of chemotherapy and were not eligible for CRT. Among the 128 remaining patients (70.3%) who had no disease progression and who were, therefore, eligible for CRT, 72 (56%) received CRT (group A), whereas 56 (44%) continued with chemotherapy (group B). The two groups were balanced for initial characteristics (performance status, gender, age, type and induction results of chemotherapy). In groups A and B, the median PFS was 10.8 and 7.4 months, respectively ( $P = 0.005$ ), and the median OS was 15.0 and 11.7 months, respectively ( $P = 0.0009$ ). These results indicate that, following disease control by initial chemotherapy, CRT could significantly improve survival in selected patients with locally advanced pancreatic cancer compared with chemotherapy alone. This concept is explored in ongoing prospective phase III studies.

Outside clinical trials, it is therefore an interesting concept to start with chemotherapy (gemcitabine or gemcitabine plus erlotinib, capecitabine or cisplatin) and to consider the addition of radiotherapy after 3 months of chemotherapy and in the absence of disease progression, in patients with a good performance status. Following CRT, it remains controversial whether chemotherapy should be continued, as increased hematological toxicity may be an issue [84].

### **treatment duration and monitoring**

Following resection of pancreatic cancer and appropriate adjuvant therapy, there is no clear evidence that systematic follow-up is useful. An early detection of recurrence does not lead

to curative therapeutic interventions. The experts recommend limiting technical examinations to a minimum if the patient is asymptomatic, with surveillance visits every 3–6 months.

In metastatic pancreatic cancer, the majority of the experts continue chemotherapy until disease progression or toxicity. Monitoring of treatment is done by (bi)weekly clinical evaluation, serial measurements of serum CA19.9 and imaging procedures (CT thorax and abdomen) every 2–4 months. There is no place for routine PET or PET-CT.

Following chemo(radio)therapy for locally advanced pancreatic cancer and in case of a response (to be expected in 10% of patients), surgical resection should be reconsidered after the appropriate imaging examinations [85].

## future research

There are still many open questions for future research, which include the evaluation of diagnostic modalities in order to detect pancreatic cancer at an early stage. We need predictive and prognostic tools to better select patients with pancreatic cancer. This issue is becoming increasingly important in almost all cancers since the increasing therapeutic options lead to an increased economic burden to our health care system and also lead to more complex drug regimens with higher toxicity.

Much is expected from the study of new targets beyond EGFR and vascular endothelial growth factor, including Mammalian target of rapamycin (mTOR), sarc (Src) or insulin-like growth factor-1 receptor. The availability of intriguing mouse models which recapitulate the pancreatic carcinogenic process will undoubtedly lead to new insights in diagnosis and therapy [86].

## conclusions

The knowledge on the biology and on the management of pancreatic cancer is progressing. A multidisciplinary approach to a patient with pancreatic cancer is mandatory in order to guarantee an optimal staging, surgery, selection of the appropriate neo-adjuvant strategy and chemotherapeutic choice management. Moreover, optimal symptomatic management requires a dedicated team of health care professionals.

Quality control of surgery and pathology is especially important in this disease with a high locoregional failure rate. There is now solid evidence in favor of chemotherapy in both the adjuvant and palliative setting, and gemcitabine combined with erlotinib, capecitabine or platinum compounds seems to be slightly more active than gemcitabine alone in advanced pancreatic cancer. There is undoubtedly a place for CRT in selected patients with locally advanced disease, while the role in the adjuvant setting remains controversial and is subject to further research.

Those involved in the care for patients with pancreatic cancer should be encouraged to participate in well-designed clinical trials in order to increase the evidence-based knowledge and to make further progress.

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