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CLINICAL INVESTIGATION **Pancreas**

FEASIBILITY OF PREOPERATIVE COMBINED RADIATION THERAPY AND CHEMOTHERAPY WITH 5-FLUOROURACIL AND CISPLATIN IN POTENTIALLY RESECTABLE PANCREATIC ADENOCARCINOMA: THE FRENCH SFRO-FFCD 97-04 PHASE II TRIAL

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Purpose: More than 80% of patients who undergo a potentially curative resection for pancreatic cancer develop local or distant recurrence. Neoadjuvant chemoradiotherapy might offer potential benefits regarding local and systemic control and survival. This multi-institutional Phase II trial explored the feasibility of preoperative chemoradiation in this situation.

Methods and Materials: Treatment consisted of concurrent radiotherapy (50 Gy within 5 weeks), and chemotherapy with 5-fluorouracil (300 mg/m^2/day, 5 days/week, 5 consecutive weeks) and cisplatin (20 mg/m^2/day, Days 1–5 and 29–33), followed by surgical resection of the pancreatic tumor in patients without progression.

Results: A total of 41 patients were enrolled. Of these, 38 (93%) received ≥47 Gy; 30 patients (73%) received ≥75% of the prescribed doses of chemotherapy. Surgical resection was performed in 26 patients (63%). Because of local or metastatic progression, 5 patients (12%) did not undergo surgery and 10 underwent surgery without resection of the pancreatic tumor. Operative mortality was 2.8%. Among 40 evaluable patients, 27 were successfully treated (67.5%; 95% CI, 50.9–81.4%).

Conclusions: Pancreatic cancer is chemo-radiosensitive. The proposed pre-operative scheme is feasible, does not prevent successful surgery, and must be tested on a Phase III setting. Yet, the large proportion of tumor progression during and after chemoradiation justifies the use of more efficient drugs such as Gemcitabine, and optimized radiotherapy including new techniques such as intensity-modulated radiation therapy.

Pancreatic adenocarcinoma, Neoadjuvant treatment, Chemoradiation, Chemotherapy, Radiotherapy, Surgery.

INTRODUCTION

Pancreatic cancer is a leading cause of mortality in developed countries and accounts for approximately 30,000 deaths each year in the United States (1). Only 10% of patients presenting with pancreatic adenocarcinoma can undergo a potentially curative surgical resection (1). Moreover, the results of surgery alone are poor, with a >80% rate of local or distant recurrence and 5-year survival around 10% to 24% in cases of complete resection (1).

Recent trials have demonstrated that adjuvant chemoradiation with 5-fluorouracil (5-FU) and external beam radiotherapy improved survival and reduced local recurrence rate (2–4); however, in those studies, about 25% of the patients did not receive the planned adjuvant treatment because of a lengthy postoperative recovery period (4, 5). The neoadjuvant approach is recent and includes several interesting aspects: first, beginning the multimodality treatment with chemoradiation so that all patients will receive all its components (6); second, providing an observation period to exclude from surgery those patients with rapidly progres-

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sive disease (6); third, obtaining a sufficient tumor downstaging to reduce positive margins, reported to be one of the more significant prognostic factors after resection (7); and fourth, reducing the propensity of the cancer to spread along perineural and vascular structures, and sterilizing the adipose peripancreatic tissues (6).

In 1998, the Société Française de Radiothérapie Oncologie (SFRO) and Fondation Francophone de Cancérologie Digestive (FFCD) initiated a multi-institutional Phase II trial to evaluate the feasibility of a preoperative 5-FU– and cisplatin-based chemoradiation regimen for treatment of potentially resectable pancreatic cancer. Efficacy of chemoradiation was defined in terms of chemoradiation sensitivity, complete resection rate, and locoregional control rate.

METHODS AND MATERIALS

Eligibility criteria

This study was approved by the Biomedical Research Promotion Consultative Committee of Lyon. Patients were recruited from 10 participating institutions from January 1998 to March 2003. Inclusion criteria included the following: (*1*) newly diagnosed and histologically or cytologically proven American Joint Committee on Cancer Staging clinical Stage I, II, or III ductal pancreatic adenocarcinoma (8); (*2*) age from 18 to 75 years; (*3*) Eastern Cooperative Oncology Group performance status ≤2 (9); (*4*) complete history and physical examination, staging evaluation requiring abdominal ultrasound, chest radiography, thoracic and abdominal–pelvic computed tomography (CT) and/or magnetic resonance imaging (MRI); Celio-mesenteric arteriography and endoscopic ultrasound were optional; laparoscopy was initially optional but became mandatory in January 2001 to avoid any inclusion of patients with peritoneal undetectable occult metastases; (*5*) no distant detectable metastases; (*6*) initial tumor considered as potentially resectable by the surgeon; (*7*) no previous antitumoral treatment except placement of a biliary stent; (*8*) adequate hematologic, hepatic, renal, and cardiopulmonary functions.

All patients were fully informed about the nature and the purpose of the study, and gave written informed consent. Excluded were patients with any other previous or concurrent malignant disease or with any infectious or other medical condition (especially liver failure with a prothrombin time <60%, and digestive occlusion requiring surgical bypass) that would have precluded chemotherapy or radiotherapy.

Treatment and follow-up

As shown in Fig. 1, treatment started with concurrent chemoradiation. Radiotherapy target volumes were established by CT scan and/or MRI. The target volume included the pancreatic tumor and the potentially involved nodes (>1 cm on CT scan), with a 3-cm field margin. All treatments were delivered through 3 to 4 fields of 15 MV to 20 MV photons. Total dose was 50 Gy in 25 daily 2 Gy -fractions over 5 weeks. Chemotherapy started the same day as radiation therapy and consisted of 5-days/week cycles of 120 h continuous infusion of 5-FU (300 mg/m^2) combined with a daily cisplatin, i.v. bolus of 20 mg/m^2 (with prior hydration) on Days 1 to 5 and Days 29 to 33.

Chemotherapy dose modifications for hematologic toxicities were made as follows: full doses of 5-FU and cisplatin were given for absolute neutrophils count (ANC) ≥1500/mm^3 and platelets count ≥75,000/mm^3; when ANC was between 1,000/mm^3 and 1500/mm^3, doses were reduced to 50%; if ANC was <1000/mm^3 or platelets count <75,000/mm^3, chemotherapy was delayed until normalization and was reinstituted at 50%. Chemotherapy was completely stopped after a second interruption caused by hematologic toxicity.

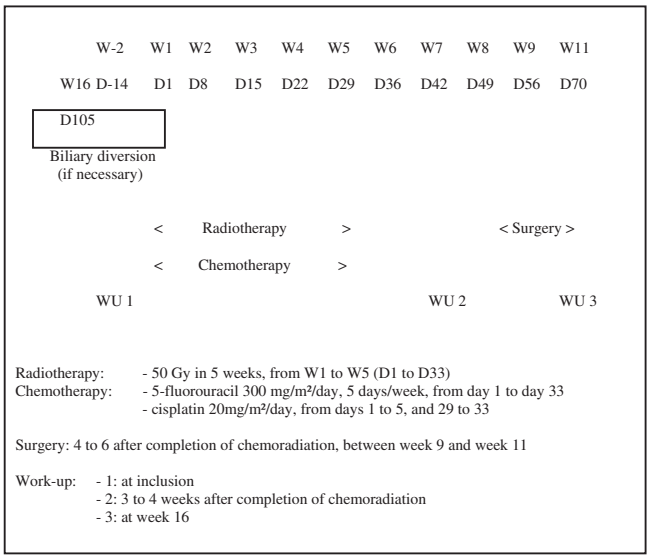

Fig. 1. Treatment scheme for the Société Française de Radiothérapie Oncologie and Fondation Francophone de Cancérologie Digestive (SFRO-FFCD) 97-04 Phase II trial. D = day; W = week; WU = work-up.

A preoperative work-up was performed 8 weeks after the beginning of the treatment to assess the resectability of the pancreatic tumor. Surgical resection was performed 3 to 6 weeks after completion of concurrent chemoradiation in patients who remained free of disease progression leading to an unresectable status, prohibitive decline in performance status, and distant metastasis. Pancreatectomy had the objective of achieving complete resection of the tumor with extended peri-pancreatic and celio-mesenteric lymph node sampling.

Evaluation of the primary outcome was performed at Week 16. Patients were then monitored every 4 months during the first year and every 6 months thereafter.

Toxicity and response assessment

Toxicity of the treatment were evaluated using the early toxicity criteria of the World Health Organization (WHO) (10) as well as the scale for late effects by the European Organization for Research and Treatment of Cancer and the Radiation Therapy and Oncology Group (11). Surgery-related morbidity and mortality events were those occurring within the first 30 postoperative days or during the hospitalization after the procedure.

The current WHO standard criteria were used to assess the response to preoperative treatment (12). Final response evaluation was performed by 1 experienced radiologist (P.J.V.).

Study design

The primary endpoint was determination of the proportion of patients having received (16 weeks after inclusion) all the components of the preoperative treatment. Success consisted of a patient being alive, having received the entire dose of radiation, and ≥75% of the

chemotherapy dose, without extra-hematologic toxicity >Grade 3. Centralized evaluation of the primary endpoint was performed by a multidisciplinary independent committee. All surgical specimens were reviewed by a single experienced pathologist (J.Y.S.) (13).

Secondary endpoints evaluated the efficacy of the proposed chemoradiation scheme in terms of response and resectability rates, locoregional control rate, and global efficiency of the therapeutic strategy (defined by the completion of the primary endpoint and surgical resection, and 1-year, 2-year, and 5-year survival).

Statistical analysis

Concerning the primary endpoint, for a treatment feasibility rate of 75% with a 5% α risk, and a 10% β risk, 31 patients were required to reject the null hypothesis of a feasibility rate of 50%. Survival was calculated as the time from inclusion to death or date of final analyses (March 31, 2003). Because subgroups corresponding to the completion of surgery have been constituted at the time of surgery, survival analysis was also calculated from the effective or theoretical time of surgery (Week 8), to avoid any analysis bias. Disease-free survival in resected patients was calculated as the time from effective and theoretical time of surgery to recurrence or death or date of final analyses. Survival was estimated by the Kaplan-Meier method (14). Statistical analysis was performed using the STATA software program, version 7.0. (Statsoft Inc., College Station, TX).

RESULTS

Patient characteristics

A total of 41 patients were included in the trial; 25 were male and 16 female. Mean age was 59.3 years (range, 33 to 75 years). Performance status was 0 in 21 patients (51%), 1 in 17 patients (42%), 2 in 2 patients (5%), and not recorded but ≤2 in 1 patient (2%). Fourteen patients (34%) underwent a laparoscopy at initial staging, and 21 (51%) a biliary stent placement before inclusion. Initial mean tumor diameter was 3.2 cm (range, 1.2–7.3 cm). The initial mean carbohydrate antigen 19–9 (CA 19-9) value in 35 patients was 599 UI (range, 0–4300 UI). The median time from tumor biopsy to inclusion was 18 days (range, 11–56 days).

Chemoradiation treatment

A total of 38 patients (93%) received ≥47 Gy (94% of the target dose). With regard to chemotherapy, 30 patients (73%) received at least 75% of the prescribed 5-FU and cisplatin doses. Eleven patients (27%) received <75% of the dose for the two drugs; 7 of these patients had actually received 74.6% of the theoretical dose for one of the two drugs (Fig. 2). The main reasons for stopping radiotherapy and/or chemotherapy were infection and hematologic toxicities (Table 1).

In the 40 assessable patients for tumor response, 4 patients (10%) presented with partial response, 26 (65%) with stabilization, and 10 (25%) with local progression.

Surgery

Surgical resection of the pancreatic carcinoma was performed in 26 patients (63%); this consisted of pancreaticoduodenectomy (Whipple procedure) in 22 cases and of distal splenopancreatectomy in 4 cases (Fig. 2). Ten patients (24%) underwent surgery but not resection despite a satisfying presurgical assessment: at the time of laparotomy, 4 patients were diagnosed with a vascular involvement, 2 with

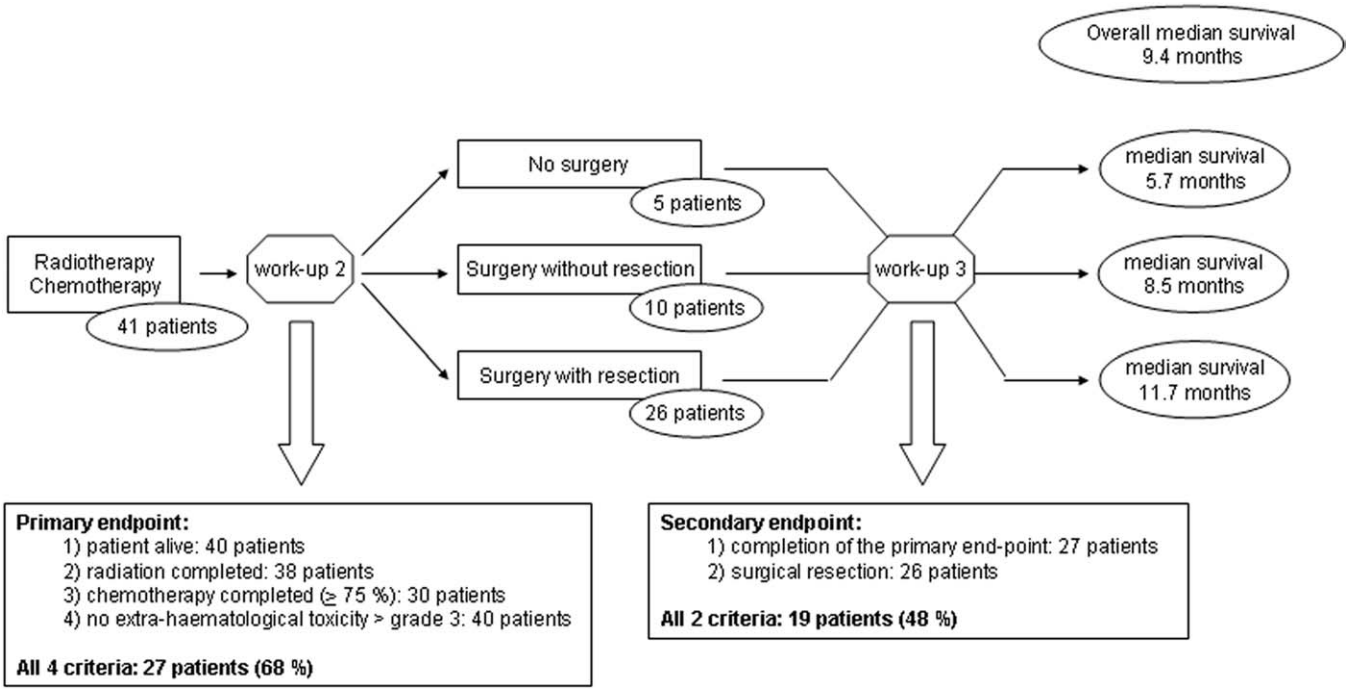

Fig. 2. Outcomes of the 41 patients included in the Société Française de Radiothérapie Oncologie and Fondation Francophone de Cancérologie Digestive (SFRO-FFCD) 97-04 Phase II trial.

Table 1. Early toxic events in the 41 patients included in the SFRO-FFCD 97-04 trial: at Week 8 (after chemoradiation) and at Week 16 (after completion of chemoradiation and of surgery if performed)

	Grade 3		Grade 4		Grade 5	
Complication	Work-up 2	Work-up 3	Work-up 2	Work-up 3	Work-up 2	Work-up 3
Hematologic						
Leukopenia	10	0	1	0	0	0
Granulocytopenia	6	0	2	0	0	0
Thrombocytopenia	2	1	3	1	0	0
Anemia	3	2	0	0	0	0
Digestive						
Nausea/vomiting	11	0	1	0	0	0
Diarrhea	1	1	0	0	0	0
Stomatitis	1	0	0	0	0	0
Infection	4	5	0	2	0	1
Other						
Skin	0	1	0	0	0	0
Neuromotor	2	4	0	0	0	0

liver metastases, 1 with a peritoneal invasion, 2 with both vascular involvement and liver metastases, and 1 with vascular involvement, liver metastases, and peritoneal invasion. Of these 10 patients, 6 had a palliative surgical digestive bypass.

The 5 remaining patients (12%) did not undergo surgery: 1 patient presented with liver metastases and 2 with vascular involvement, 1 patient experienced a grade 4 hematologic toxicity precluding curative resection, and 1 patient died just after completion of the presurgical work-up.

Of the 22 tumors from the Whipple procedures, tumor stage was pT1 in 1 case, pT2 in 6 cases, pT3 in 9 cases, pT4 in 3 cases, and not given in 3 cases. Pathologic nodal status was pN0 in 11 cases, pN1 in 9 cases, pN2 in 1 case, and unknown in 1 case. One specimen showed complete pathologic response, and 12 partial responses. Surgical resection margins were free of tumoral involvement in 21 cases (80%). Detailed pathologic results are under publication (13).

Toxicity

Grade 3/4 toxicities occurred in 27 patients. All acute early Grade ≥3 toxicities of the treatment are listed in Table 1. Main toxicities of the preoperative chemoradiation program were hematologic (14 patients) and digestive (15 patients). Surgery complications occurred in 13 of the 36 patients (surgical morbidity rate: 36%), and 1 patient died from septic shock at Day 3 after pancreaticoduodenectomy (surgical mortality rate 2.8%). Other postoperative complications consisted of 1 case of eventually lethal portal thrombosis and fistula, 1 abdominal hemorrhage requiring surgery, 7 infectious episodes, 1 persistent gastroplegia, 1 conscious trouble at Day 2, 1 melena episode, and 1 renutrition difficulty.

Late toxic effects were Grade 3 lower limbs bilateral neuropathy (1 case, in which the patient had received an oxaliplatin-based chemotherapy at the time of recurrence), cachexia (1 case), persistent biologic hepatic changes (1 case), and Grade 4 neuropathy (1 case in which the cause, either toxic or paraneoplasic, was not clearly established).

Primary endpoint

In all, 27 of the 40 evaluable patients (68% of patients; two-sided 95% CI, 50.9–81.4%; lower bound of one-sided 95% CI, 53.4%) completed the primary endpoint of the study (*i.e.,* being alive, having received the entire dose of radiation and 75% or more of the chemotherapy dose, without extra-hematologic toxicity greater than Grade 3) (Fig. 2). Only 19 patients (47.5%) reached the primary endpoint and received surgical resection of the pancreatic tumor. In the 8 patients who succeeded to the preoperative treatment but did not undergo resection, surgery was precluded by local and/or metastatic progression, not by chemoradiation toxicity.

Patient outcomes

Among the 15 patients who did not undergo resection, 9 presented with metastatic recurrence during follow-up, mainly located in the liver (7 cases) (Table 2, Fig. 2). In the 26 patients who underwent surgical resection of the pancreatic tumor, 1 (4%) patient presented with an inaugural loco-regional recurrence and 15 with metastatic dissemination, mainly located in the liver (8 cases) (Table 2). Regarding the entire cohort, metastatic recurrence occurred in 31 patients (76%); main metastatic sites were liver (21 cases), and peritoneum (13 cases) (Table 2).

With a median follow-up of 11 months, median survival time from registration for the 41 eligible patients was 9.4 months, and 1-year and 2-year survival rates were 41%, and 20% (Fig. 3). Median and 1-year and 2-year survival rates in subgroups defined by the form of treatment after completion of preoperative chemoradiation were as follows: for the 26 patients who underwent surgical resection, 11.7 months, 48%, and 32%; for the 10 patients who underwent surgery without resection, 8.5 months, 20%, and 0%; and for patients who did not undergo operation, 5.7 months, 40%, and 0% (Fig. 3). From the effective or theoretical (in nonresected patients) time of surgery, median, 1-year and 2-year survival rates were 9.5 months, 42% and 33% in the 26

Table 2. Metastatic dissemination in the 41 patients included in SFRO-FFCD 97-04 trial: In patients with nonresected tumors (n = 15), after curative surgery (n = 26), and in the entire cohort (n = 41)

Metastatic dissemination	Nonresected tumors (n = 15)		Resected tumors (n = 26), during follow-up	Entire cohort (n = 41)
	After CT-RT	During follow-up		
Lung	0	0	5	5
Mediastinum, supraclavicular nodes, and peritoneum	0	0	1	1
Liver	5	5	3	13
Peritoneum	1	0	1	2
Liver and peritoneum	1	2	2	5
Liver, peritoneum, and subcutaneous tissue	0	0	1	1
Peritoneum and pleural effusion	0	1	0	1
Liver, peritoneum, and pleural effusion	0	0	1	1
Liver, peritoneum, lung, and pleural effusion	0	0	1	1
Peritoneum and ovary	0	1	0	1
Total	7	9	15	31

Abbreviation: CT-RT = chemoradiation.

patients with resection, and 5.6 months, and 29% and 0% in the 15 remaining patients. Median disease-free survival time for the 23 patients eligible for curative resection was 5.0 months, and the 1-year and 2-year disease-free survival rates were 44% and 22%.

DISCUSSION

This is one of the first large multi-institutional trials on preoperative chemoradiation exclusively dedicated to resectable pancreatic cancer. When the trial was designed, preoperative chemoradiation was mainly used for tumors that were judged to be unresectable by the surgeon (15–17). In those studies, obtaining a sufficient downstaging to undergo a curative resection of the pancreatic tumor after chemoradiation was fairly infrequent, with resection rates between 0% and 50%. However, induction chemoradiation had shown some efficiency in increasing disease control rates and survival in patients who have undergone resection (18).

Regarding the primary endpoint of our study, our results show that induction chemoradiation with 5-FU and cisplatin is feasible, with a completion rate of 68%, and acceptable hematologic and nonhematologic toxicities (Table 1, Fig. 2). The chemoradiation regimen does not prevent successful

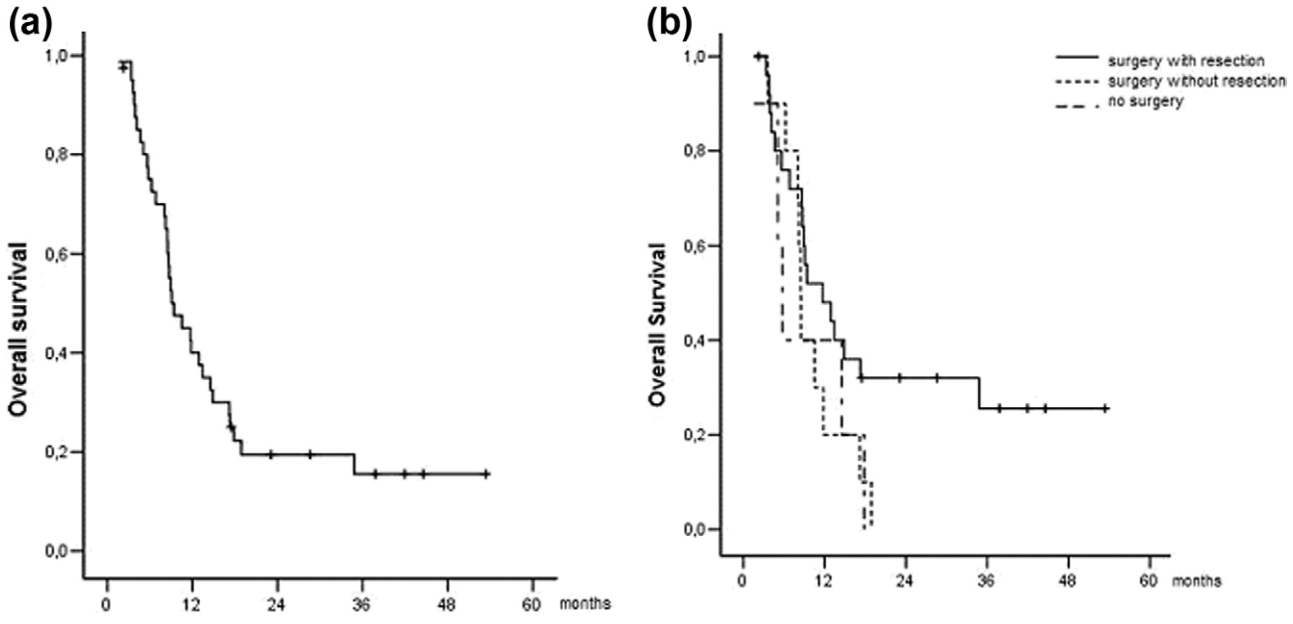

Fig. 3. (a) Overall survival for the 41 eligible patients by the Kaplan-Meier method from the time of registration to Société Française de Radiothérapie Oncologie and Fondation Francophone de Cancérologie Digestive (SFRO-FFCD) 97-04 Phase II trial. (b) Survival for the 41 eligible patients according to the treatment after completion of preoperative chemoradiation: Surgery with or without resection, no surgery.

Table 3. Studies of neoadjuvant chemoradiation therapy in resectable pancreatic cancer

First author, ref., year	*n*	Initial staging (*n*)	Chemotherapy	Radiation therapy	Toxicity of chemoradiation Grade 3–4 (*n*)			Radiographic response (*n*)	Resection (*n*, %)	Surgical morbidity (*n*)	Median survival from inclusion (mo)		
					Total	Hem	Non-hem				Global	Resected	Not resected
Evans *et al.* (19), 1992	28	L:14	5-FU	50Gy/S-IORT	6	0	6	5	17 (61%)	3	—	—	—
Yeung *et al.* (20), 1993	26		5-FU, MMC	50Gy/S	6	3	3	6	12 (46%)	2	8	—	—
Ishikawa *et al.* (21), 1994	23	L:0	No	50Gy/S	0	0	0	—	17 (74%)	6	15	15	9
Pisters *et al.* (22), 1998	35	L:11	5-FU	30Gy/R-IORT	3	0	3	23	20 (57%)	6	—	25	7
Hoffman *et al.* (23), 1998	53	L:24	5-FU, MMC	50Gy/S		30	75	8	24 (45%)	3	11	16	—
White *et al.* (17), 2001	53	L:30	5-FU, CDDP, MMC	45Gy/S	38	23	15	31	28 (53%)	11	22	—	—
Pisters *et al.* (24), 2002	35	L:0	Paclitaxel	30Gy/R-IORT	16	3	13	4	20 (57%)	5	12	19	10
Moutardier *et al.* (25), 2004	61		5-FU, CDDP	60Gy/SC-45/S	0	0	0	0	40 (66%)	7	13	27	9
Mornex *et al.*, present study	41	L:14	5-FU, CDDP	50Gy/S	27	14	20	4	26 (63%)	13	9.4	11.7	8.5

Abbreviations: L = laparotomy/laparoscopy; 5-FU = 5-fluorouracil; CDDP = cisplatin; MMC = Mitomycin C; S = standard fractionation regimen; R = rapid fractionation regimen; SC = split course fractionation regimen; IORT = intraoperative radiation therapy; Hem = hematologic; Non-hem = Non-hematologic.

* Combined with locally advanced pancreatic tumors.

surgery, given that our resection rate (63%), involved resection margins (20%), and morbidity rates (36%) favorably compare with previous studies that showed curative resection rates between 45% and 74% (Table 3) (17–25).

Tolerance to preoperative chemoradiation varies within the literature. Hematologic toxicity is higher, occurring in nearly 30% of patients, when combined-agents or potent radiosensitizer chemotherapy are used. On the other hand, gastrointestinal tolerance depends mostly on the delivered dose of radiation (Table 1). Preoperative chemoradiation with 5-FU and cisplatin has also been tested in a Phase II trial reported by Moutardier *et al.* (25), with a better tolerance than in our study (no reported Grade 3/4 toxicities), but at lower doses of chemotherapy and radiotherapy. Furthermore, their median survival in patients with resection was higher (26.6 months) than in the current study, even though the 2-year survival rates are similar.

It is difficult to compare data from different authors for several reasons. Not only are patient selection criteria and induction treatment modalities inconsistent, but also survival is not calculated from the same date (from inclusion or from the effective or theoretical time of surgery). In addition, the definition of response and of resectability remains surgeon-dependent even in experienced centers, not only at the time of the diagnosis but also after induction chemoradiation. The quality of surgery and the examination of the pathologic specimens can also vary (25). In the prospective study of Snady *et al.* (18) reporting 159 patients (68 with an unresectable tumor at initial staging received preoperative chemoradiotherapy, and 91 with a resectable tumor were treated with surgical resection with or without adjuvant chemoradiation); despite a more advanced disease and a low resectability rate of 29%, the median survival rate was significantly higher in the induction treatment group (23.6 months vs. 14.0 months). Even patients in the induction treatment group who ultimately did not undergo operation had a higher median survival (21.2 months) than patients with a resectable tumor at initial staging. When compared with the series reported by the M.D. Anderson Cancer Center (5, 19, 22, 24), some patients would have been considered by this center to be candidates for resection and may have received induction treatment in this study.

Preoperative chemoradiation ultimately leads to patient selection, as patients who show a tumor progression during the induction period do not undergo surgery. In the literature, as many as 20% to 30% of patients initially presenting with resectable pancreatic tumors, but which had become unresectable at preoperative staging, were spared the morbidity of a futile pancreatectomy (5, 17, 22, 23, 24, 25).

The low local recurrence rate (4%) and the survival (2-year survival, 33%) after surgical resection of pancreatic tumors are encouraging. Local recurrence rates, reported to be as high as 50–80% in patients treated with surgery alone (6, 26), have been retrospectively reported to be decreased after neoadjuvant chemoradiation (7). Moreover, survival is clearly increased when compared with historical studies with surgery alone (5) and seems to be similar to those

observed in studies with adjuvant chemoradiation, between 11 and 27 months after diagnosis of the pancreatic cancer (2–4). In the large prospective database of the M.D. Anderson Cancer Center (5), local recurrence occurred in only 11% of patients treated with preoperative chemoradiation and surgery and in 21% of patients who received adjuvant treatment. Because a standardized approach to per-surgical histopathologic evaluation has not been universally adopted, determination of the overall efficacy of neoadjuvant chemoradiation in reducing resection margins remains difficult (7).

The toxicity of the induction scheme with 5-FU and cisplatin has been established as being acceptable, which makes this treatment feasible. However, it still remains difficult to evaluate its potential therapeutic value, as only a few trials have so far been published, most of which included fewer than 50 patients (Table 3). Pancreatic cancer appears to be more aggressive than other solid tumors, such as non–small-cell lung cancer, rectal cancer, or esophagus cancer, which may benefit from neoadjuvant treatments. The large proportion of tumor progression during chemoradiation precluding curative surgery (37%), of metastatic dissemination after resection (58%) and the increasable overall survival justifies the use of more efficient drugs and optimized radiotherapy including new techniques such as intensity-modulated radiation therapy. An improved selection process, based on optimal imaging and mandatory laparoscopy, should help define the best candidates for an aggressive neoadjuvant approach who might really benefit from surgery. Regarding those results, showing that pancreatic cancer is clearly chemo-radiosensitive, the same French groups as in the current study are preparing the next trial which will include more efficient drugs (such as gemcitabine), as well as a potential comparison between preoperative and postoperative approaches, a trial which will require the cooperation of several groups in Phase III randomized setting.

CONCLUSION

Pancreatic cancer is chemoradiosensitive. Preoperative chemoradiation with 5-fluorouracil and cisplatine is feasible, does not prevent successful surgery, and leads to low local recurrence rates. Regarding those results, the same French groups as in the current study are preparing a new trial which will include more efficient drugs (such as gemcitabine), as well as a potential comparison between preoperative and postoperative approaches, a trial which will require the cooperation of several groups in a “phase III randomized setting”.

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