original article

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# Phase III trial comparing intensive induction chemoradiotherapy (60 Gy, infusional 5-FU and intermittent cisplatin) followed by maintenance gemcitabine with gemcitabine alone for locally advanced unresectable pancreatic cancer. Definitive results of the 2000–01 FFCD/SFRO study

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**Background:** The role of chemoradiation with systemic chemotherapy compared with chemotherapy alone in locally advanced pancreatic cancer (LAPC) is uncertain.

**Patients and methods:** One hundred and nineteen patients with LAPC, World Health Organization performance status of zero to two were randomly assigned to either the induction CHRT group (60 Gy, 2 Gy/fraction; concomitant 5-fluorouracil infusion, 300 mg/m$^2$/day, days 1–5 for 6 weeks; cisplatin, 20 mg/m$^2$/day, days 1–5 during weeks 1 and 5) or the induction gemcitabine group (GEM: 1000 mg/m$^2$ weekly for 7 weeks). Maintenance gemcitabine (1000 mg/m$^2$ weekly, 3/4 weeks) was given in both arms until disease progression or toxicity.

**Results:** Overall survival was shorter in the CHRT than in GEM arm [median survival 8.6 (99% confidence interval 7.1–11.4) and 13 months (8.7–18.1), $P = 0.03$]. One-year survival was, respectively, 32% and 53%. These results were confirmed in a per-protocol analysis for patients who received 75% or more of the planned dose of radiotherapy. More overall grades 3–4 toxic effects were recorded in the CHRT arm, both during induction (36 versus 22%) and maintenance (32 versus 18%).

**Conclusion:** This intensive induction schedule of CHRT was more toxic and less effective than gemcitabine alone.

**Key words:** chemoradiotherapy, 5-fluorouracil, cisplatin, gemcitabine, maintenance, overall survival, pancreatic cancer, randomized phase III trial

## introduction

The prognosis for locally advanced pancreatic cancer (LAPC), which accounts for 29% of initial cases, lies between those for metastatic and resected disease [1]. The Gastrointestinal Study Group (GITSG) randomized trial (194 patients) suggested a survival benefit for patients who had received CHRT compared with radiotherapy alone (60 Gy): median OS of 5.3 months with radiation alone, 9.7 months with 60 Gy (split course) + i.v. bolus 5-fluorouracil (5-FU), and 9.3 months with 40 Gy (split course) + i.v. bolus 5-FU [2]. This has been partly confirmed by a second GITSG study (43 patients), comparing CHRT (54 Gy with 5-FU) followed by systemic chemotherapy (SMF: streptozocin, mitomycin C, and 5-FU) to SMF alone: median OS, respectively, 42 weeks and 32 weeks [3]. In contrast, the Eastern Cooperative Oncology Group failed to demonstrate any benefit of CHRT (40 Gy with 5-FU) versus 5-FU-based chemotherapy alone (median OS, 8.2 versus 8.3 months) [4]. All these trials used outdated imaging techniques, outdated methods of irradiation, and bolus 5-FU (or short infusion) as chemotherapy. Despite these limitations, CHRT has been regarded for a long time as the mainstay therapy for patients with locally advanced disease, and no recent randomized trials have compared CHRT using more

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modern techniques (new imaging techniques, modern irradiation, infusional 5-FU) with gemcitabine, which may be considered the best drug for advanced/metastatic pancreatic cancer.

We report on behalf of the Fédération Francophone de Cancérologie Digestive (FFCD) and the Société Francophone de Radiothérapie Oncologique (SFRO) the final results of a randomized trial that compared an intensified induction phase with CHRT combining infusion FU and cisplatin, followed by maintenance gemcitabine with gemcitabine alone in histologically or cytologically proven LAPC.

## patients and methods

### population

Patients were eligible if they had histologically proven ductal adenocarcinoma of the pancreas, no distant metastases at computed tomography (CT) scan, and zero to two World Health Organization (WHO) performance status (PS). Tumors were judged as nonresectable due to extension to regional lymph nodes and/or vascular structures such as the superior mesenteric artery or the celiac trunk or the existence of a portal or superior mesenteric–portal venous confluent thrombosis. Adequate organ function was required (absolute granulocyte count ≥1500/mm$^3$, platelet count ≥100 000 /mm$^3$, serum bilirubin ≥50 mM/l, if indicated after biliary drainage; serum creatinine <130 mM/l; prothrombin rate >80%). Patients signed an informed consent form submitted to an ethical committee ('Comité de Protection des Personnes' de Bourgogne). Patients were randomly allocated 1 : 1 to either the CHRT or gemcitabine alone (GEM) group using a minimization technique with stratification according to the center, the WHO PS (0–1 versus 2), prior exploratory surgery and/or biliary drainage.

### design and procedures

A conformational approach was recommended for radiotherapy in the CHRT induction arm. The gross target volume (GTV) included the tumor and the probably positive lymph nodes. The clinical target volume (CTV) included the tumor and peripancreatic lymph nodes and the celiac and hepatic hilar areas. The planning target volume, taking into account the movement of the tumor and setup uncertainties, was defined by the CTV plus a 2-cm margin in all directions. The dose distribution to organs at risk was evaluated using a dose volume histogram. The maximum dose delivered to the spinal cord was limited to 40 Gy. The total planned dose was 60 Gy to the GTV delivered in 30 fractions of 2 Gy per day, five fractions per week. All fields were treated every day. Concomitant 5-FU was given as a continuous infusion at a dose of 300 mg/m$^2$/day administered from days 1 to 5 of each week throughout the irradiation, and cisplatin was given in a short i.v. infusion with hydration at a dose of 20 mg/m$^2$/day, from days 1 to 5 only during weeks 1 and 5. An oral proton pump inhibitor was recommended. In the GEM induction arm, gemcitabine 1000 mg/m$^2$ was given weekly in 30 min for 7 weeks [5]. Maintenance treatment in both arms used gemcitabine (1000 mg/m$^2$ weekly in 30 min for 3 weeks every 4 weeks) until disease progression or excessive toxicity. In case of progression, second-line treatments were allowed and left to the discretion of the investigators.

Evaluation and follow-up including weight, WHO PS, and a CT scan were done every 2 months. The toxicity was assessed using the National Cancer Institute—Common Toxicity Criteria (version 3:0). Disease progression was determined by CT scan using the response evaluation criteria in solid tumors criteria and defined by an increase of >20% in the largest tumor diameter or by the discovery of new tumoral lesions.

### statistical considerations

The study was designed as a phase III trial. The primary objective was to detect an expected change in median overall survival (OS) from 6 months in the GEM arm to 12 months in the CHRT arm (bilateral $\alpha = 1\%$ and $\beta = 10\%$). It was required to observe 127 deaths and to include 176 patients over 2 years. For each arm, follow-up was calculated using the reverse Kaplan–Meier estimation. OS was calculated from the date of randomization until death from any cause or censored at the last follow-up. Secondary end points were progression-free survival (PFS) (time interval between randomization and progression or death) and WHO PS grades 3–4 free survival (time interval between randomization and date of first occurrence of WHO PS grade 3 or 4 or death). The Kaplan–Meier method was used to estimate survival. Log rank and stratified log-rank tests (according to randomization stratification criteria) were used to assess differences between arms. A univariate Cox model was used to calculate the hazard ratio (HR) with a 99% confidence interval (CI). A multivariate Cox model was applied to calculate the treatment HR independently of the stratification criteria and main clinical factors at inclusion (gender, age, weight, tumor location, lymph nodes >1 cm, and total bilirubin serum level <50 μmol/l). Either the chi square or Fisher's exact test was used to compare maximal toxicity grades 3–4 during induction and maintenance treatment and levels of treatment compliance. Mann and Whitney tests were used to compare continuous variables. The analysis was on the basis of a strict application of the intention-to-treat (ITT) principle (all randomized patients). To confirm the results, a per-protocol analysis was carried out among patients without major protocol deviations who received >75% of the planned dose of induction radiotherapy or >75% of the induction dose of Gemcitabine. All analyses were carried out using Stata V9; a $P$ value ≤0.01 was considered significant.

## results

### patients

From March 2000 to July 2005, 119 patients were recruited in 22 French centers (Figure 1). A negative celioscopy was initially required before the patient's inclusion. However, physicians, surgeons, and patients were reluctant to do this staging procedure and this requirement was given up following a protocol amendment approved by the ethics committee in October 2002. Only the absence of metastatic disease on the CT scan was required thereafter. The inclusion rhythm subsequently accelerated (33 inclusions from March 2000 to December 2002 and 86 from January 2003 to July 2005). Due to the low recruitment, an unplanned interim analysis was carried out at the request of both the ethics committee and an Independent Data Monitoring Committee (IDMC). According to IDMC recommendations, the study was stopped before the completion of recruitment due to a lower survival rate among patients in the CHRT arm.

The clinical characteristics were well balanced (Table 1). However, WHO PS grade 2 was more frequent in the GEM arm. Some patients presented minor protocol deviations regarding the serum bilirubin level: 10 patients in the CHRT arm and eight patients in the GEM arm had an initial value ≥50 μmol/l or the value was missing (Figure 1). One patient in the CHRT arm received induction gemcitabine instead of CHRT.

The final analysis was done in February 2007. Median follow-up was 31 months in the CHRT arm and 33 months in the GEM arm.

### treatment delivery

In the CHRT induction arm, seven patients (12%) did not receive at least one dose of radiotherapy and six (10%) did not

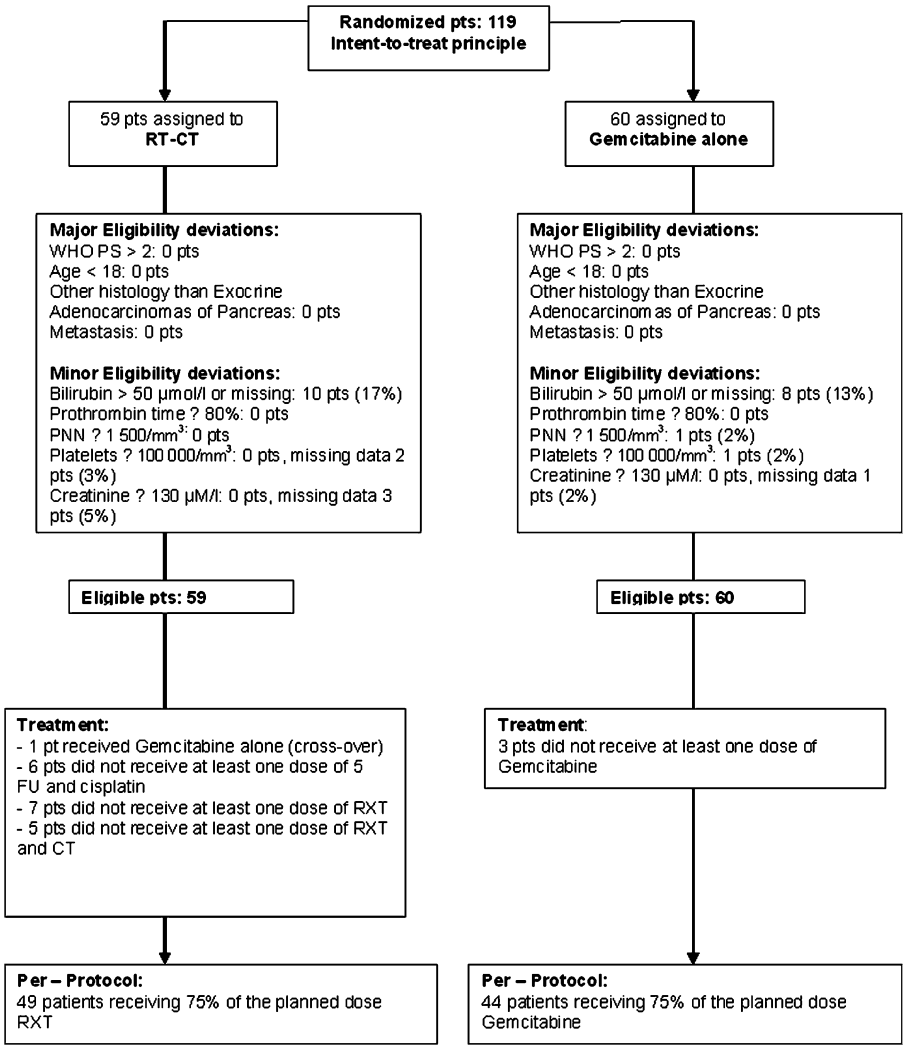



**Figure 1.** Flow chart.

receive at least one dose of 5-FU and/or cisplatin (Table 2), mostly due to early progression. Finally, 49 patients (83%) received at least 75% of the planned dose of irradiation, but only 25 patients (42%) received at least 75% of both the planned dose of irradiation and of concomitant chemotherapy. This reduction was implemented according to the planned dose reduction for hematological toxicity.

In the GEM induction arm, only three patients (5%) did not receive at least one drug dose. The median total dose administered was 6766 mg/m$^2$ for a theoretical total planned dose of 7000 mg/m$^2$, and 44 patients (73%) received 75% or more of the planned total dose of gemcitabine.

During the maintenance phase, there was no difference between the two treatment arms with regard to the number of patients who started at least one dose of gemcitabine (42 patients from CHRT and 46 from GEM) (Table 2). However, the median number of infusions and the median cumulated dose of gemcitabine were significantly higher in the GEM arm (Table 2).

## toxic effects

Grades 3–4 toxic effects are detailed in Table 3. During the induction phase, most of the grades 3–4 toxic effects were digestive and mostly reported in the CHRT arm, and they were more severe and more frequent compared with the GEM arm (65.5% versus 40%; $P = 0.008$) (Table 3). More treatment-related serious adverse events (four cases of severe digestive intolerance, three digestive hemorrhages, and two severe infections) were reported in the CHRT than in GEM group (one drug-induced microembolic disease of the toes). There was no difference between the two arms for hematological tolerance. No death was directly attributed to the induction treatments.

During the maintenance phase with gemcitabine, overall grades 3–4 toxic effects were more frequent in patients previously allocated to the CHRT arm (78% versus 40%; $P = 0.0001$). This difference was only due to hematological toxicity ($P = 0.0001$) (Table 3) and no death was related to the maintenance treatment phase.

## survival analysis

In the ITT analysis ($N = 119$), 54 (91.5%) and 52 (86.7%) patients had died in the CHRT and GEM arms, respectively. OS was shorter (stratified log-rank $P = 0.03$) in the CHRT arm than in GEM arm (Figure 2A). Median OS was, respectively, 8.6

**Table 1.** Baseline clinical and medical characteristics of patients

| | CHRT arm, $N = 59$ (%) | Gemcitabine-alone arm, $N = 60$ (%) | $P$ |
|---|---|---|---|
| Gender | | | |
| Male | 31 (52.5) | 34 (58.3) | 0.525 |
| Female | 28 (47.5) | 26 (41.7) | |
| WHO PS | | | |
| 0/1 | 54 (91.5) | 46 (76.7) | 0.027 |
| 2 | 5 (8.5) | 14 (23.3) | |
| Tumor location | | | |
| Head | 46 (78.0) | 40 (66.7) | 0.169 |
| Other location | 13 (22.0) | 20 (33.3) | |
| Lymph node > 1 cm | | | |
| No | 40 (67.8) | 37 (62.7) | 0.562 |
| Yes | 19 (32.2) | 22 (37.3) | |
| Unknown | 0 | 1 | |
| Vascular invasion | | | |
| None | 13 (22.0) | 12 (20.0) | 0.604 |
| Arterial | 11 (18.6) | 17 (28.3) | |
| Venous | 15 (25.4) | 17 (28.3) | |
| Mixed | 18 (30.5) | 12 (20.0) | |
| Not assessable | 2 (3.4) | 2 (3.3) | |
| Initial laparotomy | | | |
| No | 34 (57.6) | 35 (58.3) | 0.954 |
| Without derivation | 9 (15.3) | 8 (13.3) | |
| With biliodigestive bypass | 16 (27.1) | 17 (28.3) | |
| Peritoneal cytology | | | |
| Negative | 14 (26.4) | 12 (23.1) | 0.284 |
| Positive | 0 (0) | 3 (5.8) | |
| Not carried out | 39 (73.6) | 37 (71.1) | |
| Unknown | 6 | 8 | |
| Age in years, median (minimum–maximum) | 60 (41–79) | 62 (38–80) | 0.202 |
| Weight (kg), median (minimum–maximum) | 62 (40–105) | 62 (35–88) | 0.946 |

WHO, World Health Organization; PS, performance status.

(99% CI 7.1–11.4) and 13.0 months (8.7–18.1). One-year OS was, respectively, 32% and 53%. The risk of death in the GEM arm was lower, with a univariate HR of 0.69 (0.41–1.14). After adjusting for stratification criteria and other main clinical factors at inclusion, the multivariate Cox model highlighted the fact that only the treatment arm was significantly associated with OS (HR = 0.54, 0.31–0.96; $P = 0.006$).

At the data cut-off, 38 (64%) patients had tumor progression on the CT scan in the CHRT arm compared with 43 (72%) in the GEM arm. Nineteen (32%) and 14 (23%) patients had died in the CHRT and GEM arm, respectively, but disease progression was not documented by CT scan. PFS was shorter (stratified log-rank $P = 0.025$) in the CHRT than in the GEM arm (Figure 2B) and 1-year PFS was, respectively, 14% and 32%. The risk of progression was lower in the GEM group with a univariate HR = 0.72 (0.44–1.18). Progression was related to both failure in local control, often with peritoneal carcinomatosis as the recurrence pattern, and metastases, with numerous overlapping symptoms. As secondary surgery was allowed for patients who responded well and had good tumor control, five patients (4.2%) benefited from a secondary resection (two in the CHRT arm and three in the GEM arm) which resulted in prolonged OS (13.7, 20+, 22.3, 30.8+, and 65 months) after resection.

A per-protocol analysis was done among the 49 patients (83%) in the CHRT arm who received at least 75% of the planned dose of radiation and the 44 patients (73%) in the GEM arm who received at least 75% of the planned dose of gemcitabine. Respectively, 45 (92%) and 37 (84%) died in the CHRT and Gem arm. OS was shorter (stratified log-rank $P = 0.006$) in the CHRT than in the GEM arm (Figure 3). Median OS was 9.5 (99% CI 7.6–12.1) and 15.1 months (10.1–23.5), respectively. One-year survival was, respectively, 35% and 64%. The risk of death was lower in the GEM arm with a univariate HR = 0.58 (0.33–1.05).

### WHO PS of three to four free survival (ITT)

At the cut-off date, 30 (51%) patients had a WHO PS of three to four in the CHRT arm versus 19 (32%) in the GEM arm. Furthermore, 25 (42%) patients and 34 (57%), respectively, died without experiencing a reported WHO PS of three to four. WHO PS of three to four free survival was significantly shorter (stratified log-rank $P = 0.0024$) in the CHRT than in the GEM arm (Figure 4). Median survival was 7.2 (99% CI 5.0–8.4) and 11.6 months (7.7–16.1), respectively. The univariate Cox HR was equal to 0.58 (0.35–0.97).

## discussion

This trial was designed to determine whether intensified chemoradiotherapy combining infusional 5-FU and cisplatin as radiosensitizers and using modern irradiation techniques would result in longer survival than that obtained with gemcitabine alone, which is considered an acceptable standard in patients with locally advanced pancreatic adenocarcinoma. This is the first randomized trial comparing chemoradiation (followed by chemotherapy) with chemotherapy alone in ~20 years. Unexpectedly, and in contrast with the initial hypothesis, our study demonstrated that induction CHRT did not improve OS.

The reasons underlying the lower survival in the CHRT arm are not clear as all patients were treated in radiotherapy centers with experienced staff and benefited from modern and appropriate irradiation techniques. There were differences in dose intensity and this may in part explain the findings; 12% in the CHRT group versus 5% in the GEM group never started treatment. Only 42% in the CHRT group received at least 75% of the planned RT and CT, whereas 73% in the GEM group received at least 75% of the planned gemcitabine. These differences may be due to a longer delay before starting CHRT than before starting gemcitabine and to the greater toxicity of CHRT leading to early interruption of treatment in the CHRT group. However, after careful analysis of the serious adverse events and toxicity reports, increased toxicity during chemoradiotherapy only partly supports this hypothesis. Of course, CHRT was more toxic than gemcitabine, with more grades 3–4 digestive events, including three digestive hemorrhages and three severe infections. However, most of these symptoms were reversible and alleviated by symptomatic

**Table 2.** Description of treatment delivery at the induction and maintenance phase

| | CHRT arm, $N = 59$ (%) | Gemcitabine arm, $N = 60$ (%) | $P$ |
|---|---|---|---|
| Induction phase | | | |
| Received at least one dose of 5-FU | | | |
| Yes | 53 (89.8) | 0 (0.0) | |
| No | 6 (10.2) | 60 (100.0) | |
| Received at least 75% of planned dose 5-FU | 32 (54.2) | | |
| Median total dose of 5-FU (mg/m$^2$) (minimum–maximum) | 7214 (560–11524) | | |
| Received at least one dose of cisplatin | | | |
| Yes | 53 (89.8) | 0 (0.0) | |
| No | 6 (10.2) | 60 (100.0) | |
| Received at least 75% of planned dose cisplatin | 30 (50.9) | | |
| Median (SD) total dose of cisplatin (mg/m$^2$) (minimum–maximum) | 184 (19–596) | | |
| Received at least one dose of RXT | | | |
| Yes | 52 (88.1) | 0 (0.0) | |
| No | 7 (11.9) | 60 (100.0) | |
| Received at least 75% of planned dose RXT | 49 (83.1) | | |
| Median (SD) total dose of RXT (Gy) (minimum–maximum) | 60 (14–64) | | |
| Received at least one dose of CHRT | | | |
| Yes | 54 (91.5) | 0 (0.0) | |
| No | 5 (8.5) | 60 (100.0) | |
| Received at least 75% of planned dose CHRT | | | |
| Yes | 25 (42.4) | | |
| No | 34 (57.6) | | |
| Received at least one dose gemcitabine | | | |
| Yes | 1 (1.7) | 57 (95.0) | |
| No | 58 (98.3) | 3 (5.0) | |
| Received at least 75% of planned dose gemcitabine | – | 44 (73.3) | |
| Median total dose of gemcitabine (mg/m$^2$) (minimum–maximum) | – | 6766 (1000–8000) | |
| Maintenance phase | | | |
| Received at least one dose gemcitabine | | | 0.496 |
| Yes | 42 (71.2) | 46 (76.7) | |
| No | 17 (28.8) | 14 (23.3) | |
| Median number of infusions (minimum–maximum) | 6 (0–38) | 10 (0–58) | 0.02 |
| Median total dose of gemcitabine (mg/m$^2$) (minimum–maximum) | 6845 (294–33000) | 15000 (977–45066) | 0.003 |

Median doses were reported among patients receiving at least one dose of the considered treatment.
5-FU, 5-fluorouracil; SD, standard deviation.

treatment, including parenteral nutrition and transfusions. No death clearly related to CHRT was reported by the investigators, but two patients in the CHRT group and none in the GEM group died from digestive hemorrhage. This complication may have been caused by tumoral ulceration of the duodenum and/or local portal hypertension. Survival curves do not support the hypothesis of increased mortality directly related to the toxicity of CHRT since survival even seems to be slightly higher in this arm during the first 6 months, and the survival curves for the two arms only start to diverge after the eighth month. This late divergence between curves could be explained by the shorter duration and lower cumulative dose of gemcitabine administered during the maintenance treatment in the CHRT arm due to hematological toxicity, mostly with regard to neutrophils.

The choice of this intensified CHRT regimen for a phase III study could be criticized due to the lack of a previous phase II study with exactly the same drug regimen and radiotherapy dose. When this trial was designed at the end of nineties, the aim was to maximize the local antitumor effect by using the highest tolerated dose of radiotherapy with modern techniques to improve tolerance. One of the reference standards was the GITSG regimen which used 60 Gy and 5-FU bolus [2]. Using cisplatin and 5-FU-based radiochemotherapy regimens was considered as tolerable in LAPC in several pilot studies [6–9]. An identical 5-FU–cisplatin chemotherapy regimen, but with only 50 Gy radiation, was used by FFCD/SFRO in a phase II study as preoperative treatment of resectable pancreatic adenocarcinoma and was also considered as feasible [10]. So as not to alter the antitumor effect, the radiotherapy dose was not reduced from 60 to 50 Gy in the present trial. Interestingly, median OS in the CHTR arm in our study was 8.6 months compared with 9.7 months for GITSG, indicating that neither modern irradiation techniques nor using infusional FU, rather than a bolus, and cisplatin as a second radiosensitizing agent appears to be helpful. In recent trials, the dose of radiotherapy has been lowered from 45 to 50 Gy in LAPC. However, none of these phase II studies with 5-FU or gemcitabine, though less toxic, has reported median survival of more than ~9–11 months [11–19]. Our results indicate that the

**Table 3.** Grade 3/4 toxic effects during the induction and maintenance phases

| | Induction phase | | *P* | Maintenance phase | | *P* |
|---|---|---|---|---|---|---|
| | CHRT arm, *N* = 59 (%) | GEM arm, *N* = 60 (%) | | CHRT arm, *N* = 59 (%) | GEM arm, *N* = 60 (%) | |
| Hematological toxic effects | 17 (30.9) | 15 (27.3) | 0.675 | 29 (70.7) | 12 (26.7) | 0.0001 |
| Thrombocytopenia | 5 (9.1) | 0 (0) | 0.057 | 8 (19.5) | 5 (11.1) | 0.277 |
| Anemia | 2 (3.6) | 1 (1.8) | 0.558 | 18 (43.9) | 3 (6.7) | 0.001 |
| Leucopenia | 10 (18.2) | 7 (12.7) | 0.429 | 20 (48.8) | 5 (11.1) | 0.0001 |
| Neutropenia | 6 (10.9) | 14 (25.4) | 0.048 | 17 (41.5) | 5 (11.1) | 0.001 |
| Febrile neutropenia | 0 (0) | 1 (1.8) | 0.315 | 1 (2.4) | 0 (0) | 0.477 |
| Non-hematological toxic effects | 24 (43.6) | 10 (18.2) | 0.004 | 12 (29.3) | 11 (24.4) | 0.614 |
| Other infections | 2 (3.7) | 0 (0) | 0.495 | 2 (4.9) | 3 (6.7) | 0.723 |
| Stomatitis | 1 (1.8) | 0 (0) | 0.320 | 0 (0) | 0 (0) | – |
| Nausea vomiting | 12 (21.8) | 6 (11.1) | 0.132 | 4 (9.8) | 1 (2.2) | 0.187 |
| Diarrhea | 4 (7.3) | 0 (0) | 0.118 | 1 (2.4) | 0 (0) | 0.477 |
| Cutaneous | 0 (0) | 2 (3.7) | 0.243 | 0 (0) | 0 (0) | – |
| Renal | 0 (0) | | | | | |
| Neurotoxicity | 0 (0) | 0 (0) | – | 0 (0) | 0 (0) | – |
| Others | 11 (23.4) | 6 (12.0) | 0.140 | 6 (14.6) | 9 (20.0) | 0.512 |
| Overall toxic effects | 36 (65.5) | 22 (40.0) | 0.008 | 32 (78.1) | 18 (40.0) | 0.0001 |

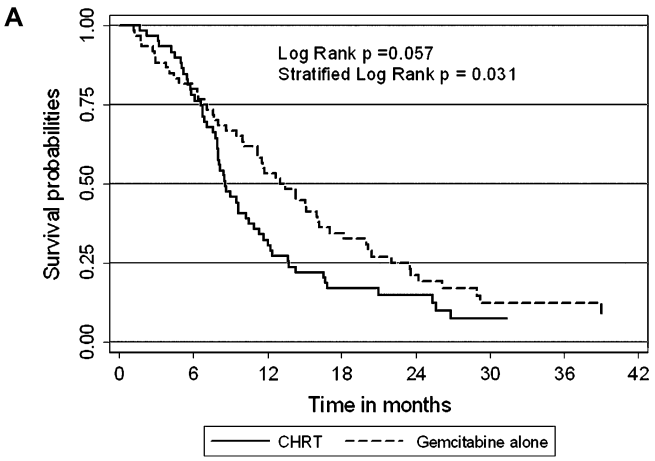
barrier of 1-year median survival cannot be broken through by using an intensified chemoradiotherapy regimen, even in the subgroup of patients who received >75% of the planned radiotherapy dose (median survival 9.5 months).

Gemcitabine alone, as used in metastatic pancreatic cancer, demonstrated some efficacy and was well tolerated in this trial. Systemic 5-FU-based chemotherapy produces a significant survival benefit over best supportive care [20], and gemcitabine is more efficient than a weekly bolus of 5-FU in metastatic pancreatic cancer [5]. In a retrospective study, OS among patients receiving 5-FU-based CHRT was 10.4 months compared with 11.3 months for those who received gemcitabine-based chemotherapy alone. Both groups showed a survival benefit compared with those who received supportive care (6.1 months) [21]. In an adjuvant setting, chemotherapy with a combination of 5-FU + folinic acid resulted in a significant survival benefit (19.1 months) in patients after resection of their pancreatic cancer, whereas adjuvant CHRT seemed to have a deleterious effect on survival (15.5 months) [22]. Postoperative gemcitabine significantly improved PFS, but not OS, after complete resection of pancreatic cancer compared with surgery alone (PFS 13.4 versus 6.9 months; OS 22.1 versus 20.2 months) [23]. In our trial in LAPC, median survival was 13 months in the gemcitabine arm and 15.1 months for those who received 75% or more of the planned drug dose in the induction phase. This is longer than in the pivotal study of Burris et al. [5] with gemcitabine (5.6 months), which, however, included mainly metastatic patients. The median survival in the gemcitabine arm seems relatively high in the present trial. In fact, LAPC is reported to have a better prognosis (median OS 6–10 months) compared with 3–6 months for metastatic cancer [24]. According to the adjuvant study by Oettle et al. [23], the use of gemcitabine after surgery prolongs the time to relapse by ~6 months. Combining these data, the 13 months median survival in the GEM arm is then plausible without any selection or bias. In our opinion, the toxicity of this intensive chemoradiotherapy regimen negated the small benefit due to gemcitabine.

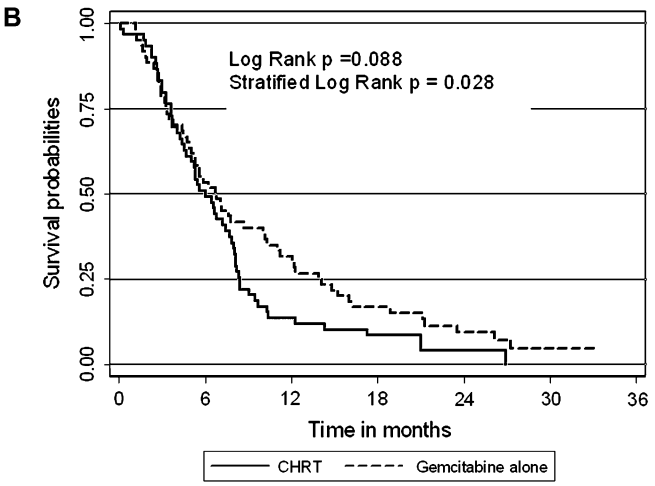
Maintaining a good PS or quality of life is an important objective in the treatment of pancreatic cancer. As disease progression and the response rate are difficult to assess in localized pancreatic cancer, we used WHO PS of three to four free survival as way to assess both the stabilizing effect of the treatment and its tolerance. The duration was clearly longer in the gemcitabine arm and this could partly explain the differences in OS.

The local effect of CHRT could not be determined precisely because the diagnosis of local progression is not always easy after irradiation due to local inflammatory reactions. In our study, disease progression was most often marked only by a deterioration in the PS with anorexia and weight loss; it was difficult to assess local progression precisely by CT scan. In most cases, local progression was suspected with the appearance of peritoneal carcinomatosis and liver or lung metastases, and with regard to this, there were no obvious differences between the two arms.

In conclusion, our results are in accordance with systematic reviews or meta-analyses of the management of LAPC using combined chemotherapy and radiotherapy [24, 25]. In contrast with previous recommendations, there is no evidence that chemoradiation, at least with the regimen used in this study, is superior to chemotherapy alone. However, this study tested aggressive front-line CHRT, but did not assess its efficacy in a selected group of patients. In future trials, the timing of CHRT must be explored as one possibility could be to use CHRT only in subgroups of patients whose tumors had not spread and were well controlled by initial chemotherapy [26–28]. Local control restricted to the pancreatic area could then be a valuable objective in these selected patients. Strict initial staging, including FDG positron tomography and laparoscopy [29], could help to select the best candidates for secondary CHRT. This hypothesis is presently being tested in the LAP07

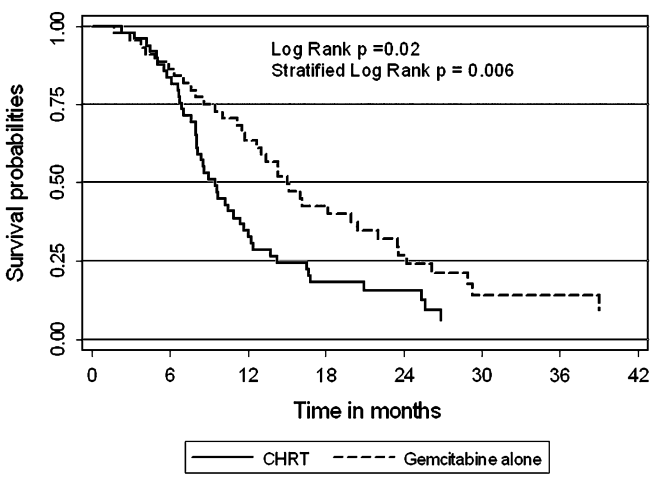



| Patients at Risk: | 0 | 6 | 12 | 18 | 24 | 30 | 36 |
|---|---|---|---|---|---|---|---|
| CHRT Arm | 59 | 47 | 20 | 11 | 8 | 4 | 3 |
| Gemcitabine Alone Arm | 60 | 49 | 33 | 21 | 12 | 6 | 4 |



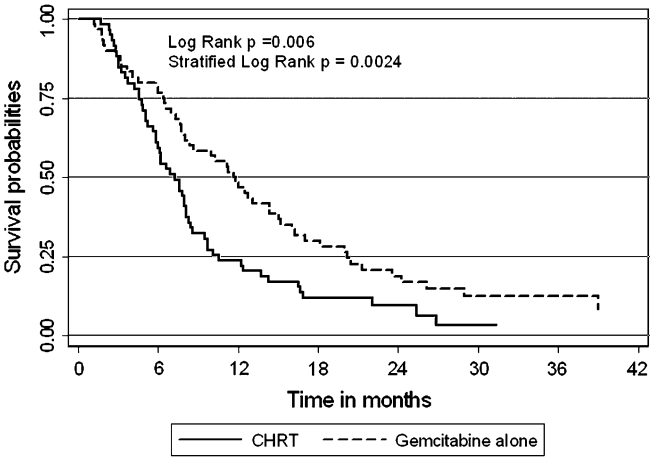

| Patients at Risk: | 0 | 6 | 12 | 18 | 24 | 30 | 36 |
|---|---|---|---|---|---|---|---|
| CHRT Arm | 59 | 30 | 9 | 6 | 3 | 1 | 1 |
| Gemcitabine Alone Arm | 60 | 33 | 20 | 11 | 6 | 3 | 2 |

**Figure 2.** (A) Overall survival (Kaplan–Meier estimate). Intention-to-treat analysis. (B) Progression-free survival (Kaplan–Meier estimate). Intention-to-treat analysis.




| Patients at Risk: | 0 | 6 | 12 | 18 | 24 | 30 | 36 |
|---|---|---|---|---|---|---|---|
| CHRT | 49 | 42 | 18 | 10 | 7 | 3 | 3 |
| GEM | 44 | 39 | 29 | 19 | 11 | 5 | 4 |

**Figure 3.** Overall survival (Kaplan–Meier estimate). Per-protocol analysis in patients who received at least 75% of the planned dose of radiotherapy or 75% of the planned dose of gemcitabine during the induction phase.




| Patients at Risk: | 0 | 6 | 12 | 18 | 24 | 30 | 36 |
|---|---|---|---|---|---|---|---|
| CHRT | 59 | 36 | 15 | 8 | 5 | 2 | 1 |
| GEM | 60 | 47 | 29 | 19 | 11 | 6 | 4 |

**Figure 4.** World Health Organization performance status of three to four free survival (Kaplan–Meier estimate) according to treatment arm, intention-to-treat analysis.

international trial. Until the results are available, gemcitabine alone could be considered the standard treatment in LAPC. In parallel, there is a clear need to develop less toxic and more effective chemoradiotherapy schedules, incorporating or not targeted agents, which should be compared with gemcitabine in future randomized studies.

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