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ORIGINAL REPORT

Adjuvant Gemcitabine Alone Versus Gemcitabine-Based Chemoradiotherapy After Curative Resection for Pancreatic Cancer: A Randomized EORTC-40013-22012/FFCD-9203/GERCOR Phase II Study

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical Trials repository link available on JCO.org.

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ABSTRACT

Purpose
The role of adjuvant chemoradiotherapy (CRT) in resectable pancreatic cancer is still debated. This randomized phase II intergroup study explores the feasibility and tolerability of a gemcitabine-based CRT regimen after R0 resection of pancreatic head cancer.

Patients and Methods
Within 8 weeks after surgery, patients were randomly assigned to receive either four cycles of gemcitabine (control arm) or gemcitabine for two cycles followed by weekly gemcitabine with concurrent radiation (50.4 Gy; CRT arm). The primary objective was to exclude a $< 60\%$ treatment completion and a $> 40\%$ rate of grade 4 hematologic or GI toxicity in the CRT arm with type I and II errors of 10%. Secondary end points were late toxicity, disease-free survival (DFS), and overall survival (OS).

Results
Between September 2004 and January 2007, 90 patients were randomly assigned (45:45). Patient characteristics were similar in both arms. Treatment was completed per protocol by 86.7% and 73.3% (80% CI, 63.1% to 81.9%; 95% CI, 58.1% to 85.4%) in the control and CRT arms, respectively, and grade 4 toxicity was 0% and 4.7% (two of 43; 80% CI, 1.2% to 11.9%), respectively. In the CRT arm, three patients experienced grade 3–related late toxicity. Median DFS was 12 months in the CRT arm and 11 months in the control arm. Median OS was 24 months in both arms. First local recurrence was less frequent in the CRT arm (11% *v* 24%).

Conclusion
Adjuvant gemcitabine-based CRT is feasible, well-tolerated, and not deleterious; adding this treatment to full-dose adjuvant gemcitabine after resection of pancreatic cancer should be evaluated in a phase III trial.

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INTRODUCTION

Pancreatic cancer remains a dismal disease and is the fourth leading cause of death from cancer in the United States.[1] At this time, surgery is the only path to cure, but only a small number of patients present with resectable disease at the time of diagnosis. After resection, median survival is limited to around 20 months, strongly indicating that a multimodal approach is needed to decrease the high incidence of both locoregional and distant recurrence.[2-4]

The role of adjuvant therapy in resectable tumors is still debated, particularly the impact of postoperative chemoradiotherapy (CRT). CRT using fluorouracil (FU) is considered standard of care in the United States, based on the small Gastrointestinal Tumor Study Group (GITSG) trial and large case series analysis from Johns Hopkins and the Mayo Clinic.[5-7] By contrast, chemotherapy alone is now widely recommended in Europe in the adjuvant setting, on the basis of the European Study Group for Pancreatic Cancer 1 (ESPAC-1) and Charité Onkologie 001 (CONKO-001) trials, both showing survival benefit using FU or gemcitabine, respectively.[8-10] Data derived from the ESPAC-1 and the previous European Organisation for Research and Treatment of Cancer 40891 (EORTC-40891) study[11] do not support the use of FU-based CRT, but these results cannot be considered definitively conclusive, mainly because of the small

numbers of patients underpowering the EORTC trial,[11] the radiation regimen used (2 × 20 Gy split course) for both studies, the complex design, and the lack of quality control of radiation treatment of the ESPAC-1 trial.[8]

Both FU and gemcitabine given in the adjuvant setting have shown a substantial benefit and were recently reported to have equivalent efficacy after resection of the primary tumor.[12] Gemcitabine has shown less toxicity than FU bolus in the adjuvant setting and a clinical benefit in advanced stages; it is also a good radiosensitizer.[13-15] Preliminary data have shown promising results in locally advanced and neoadjuvant settings using gemcitabine-based CRT by combining gemcitabine at a weekly dose of 300 to 500 mg/m^2 with 30 to 54 Gy of radiation.[16-21]

Optimizing adjuvant strategies should therefore be addressed. This study was initiated to assess a modern gemcitabine-based CRT regimen in the adjuvant setting of pancreatic cancer. This randomized phase II trial primarily aimed to assess the feasibility and toxicity of the CRT treatment compared with standard gemcitabine alone. Secondary end points were late toxicity, disease-free survival (DFS), and overall survival (OS).

PATIENTS AND METHODS

Study Design

This is an open, multicenter, randomized, controlled phase II study, promoted by the EORTC Gastrointestinal Group and Radiation Oncology Group (ROG). The study was performed in Europe with the collaboration of the Federation Francophone de Cancérologie Digestive (FFCD) and the Groupe Coopérateur Multidisciplinaire en Oncologie (GERCOR), both in France. Initially, within 8 weeks after curative microscopically complete (R0) resection of pancreatic head adenocarcinoma, patients had to be randomly assigned (1:1) between observation (control arm) and CRT (experimental arm). There was a major amendment to the trial protocol on September 7, 2004, when the control arm was changed to gemcitabine alone instead of observation. After September 7, 2004, patients were randomly assigned (1:1) to gemcitabine alone for four cycles of 4 weeks (control arm) and gemcitabine for two cycles followed by gemcitabine weekly and concurrent radiation therapy (experimental arm). Patients were stratified by institution, WHO performance status (PS), and nodal status. Figure 1 depicts the study flow chart.

Eligibility

Patients with histologically confirmed pancreatic head adenocarcinoma with R0 duodenopancreatectomy (Whipple procedure or pylorus-preserving procedure), documented histologic examination of surgical margins (including retroperitoneal margins), and documented lymph node examination (< 10 *v* ≥ 10; International Union Against Cancer [UICC] TNM classification, 2006) were eligible. Patients had to be recovered completely from surgery within 8 weeks. An abdominal spiral computed tomography (CT) scan had to be performed 8 weeks maximum before random assignment to exclude manifest distant metastases. Other inclusion criteria were age $>$ 18 years; WHO PS 0 to 2; adequate bone marrow, liver, and renal functions; and written informed consent. Exclusion criteria were previous chemotherapy or radiotherapy; previous or coexistent malignant disease (except basal cell carcinoma or carcinoma in situ of the cervix); periampullary, neuroendocrine, intraductal papillary, or mucinous tumors; and incomplete resection. The protocol was approved by appropriate ethics committees at each participating institution.

Treatment

Treatment started within 8 weeks after surgery. In the control arm, treatment consisted of four cycles of gemcitabine 1,000 mg/m^2 by 30-minute infusion during 3 consecutive weeks followed by 1 week of rest. In the experimental arm, treatment consisted of two cycles of gemcitabine 1,000 mg/m^2 by 30-minute infusion during 3 consecutive weeks followed by 1 week of rest. In the experimental arm, cycle 1 treatment was given on days 1, 8, and 15; cycle 2 treatment was given on days 29, 36, and 43.

After the 1-week rest, CRT was started on day 57: gemcitabine 300 mg/m^2 by 30-minute infusion once per week, given 4 hours before radiation (50.4 Gy in 28 fractions, 1.8 Gy per fraction) for 5 to 6 weeks.

Radiotherapy was delivered according to the guidelines of the International Commission on Radiation Units and Measurements Report 50. Patients were treated in the supine position. A CT scan in treatment position was obtained before the start of treatment. The clinical target volume was delineated on this CT scan on the basis of the preoperative radiologic examinations and the pathology report. The clinical target volume included the former pancreatic tumor site and lymph node areas. The retroperitoneal para-aortic lymphatics between the celiac trunk and the upper mesenteric artery to the anterior level of the vertebral bodies had to be included. To reduce toxicity, the inclusion of the pancreatic tail was not mandatory. A safety margin of 5 mm in all directions had to be shaped for subclinical extension of tumor cells.

Participating radiation oncology departments had to fulfill the EORTC ROG Quality Assurance requirements that consisted of a regularly updated facility questionnaire and an external radiation dosimetry audit of their treatment units. Additional details on radiation delivery are provided in the Appendix (online only).

Evaluation and Follow-Up

Before patients were randomly assigned, a complete medical history was taken and a complete physical examination was performed that included routine laboratory studies, carcinoembryonic antigen and carbohydrate antigen 19-9 tumor markers, vital signs, body weight, height, and evaluation of the PS using the WHO scale. Tumor assessment included abdominal CT or magnetic resonance imaging to rule out distant metastases and plan radiation therapy, if any. Before CRT, imaging was repeated only in case of clinical suggestion of early recurrence. All pathologic reports were centrally reviewed to definitively determine the status of the resection (R0, R1, or undetermined).

During the treatment period, all patients were evaluated weekly for clinical and laboratory findings. All adverse events and toxicities were recorded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 2.0).

After treatment completion, all patients included in the study were followed up clinically, biologically, and radiologically every 3 months until death by evaluating blood count, liver tests, tumor markers, PS, weight, late adverse events (Radiation Therapy Oncology Group [RTOG] scale), and disease status by using imaging. Only radiologic findings were considered to determine recurrence.

Statistical Considerations

The coprimary end points of this trial were feasibility and tolerability of the experimental treatment. The primary aim was that the experimental treatment could be completed in 80% (60% being an unacceptable rate) of the enrolled patients and that treatment-related grade 4 hematologic toxicity or GI toxicity occurring up to 30 days after the completion of the treatment be approximately 15% (40% being an unacceptable rate).

Using a one-step Bryant and Day design,[22] 39 patients were required in the experimental arm to reject a $< 60\%$ treatment completion and a $> 40\%$ rate of grade 4 hematologic or GI toxicity with one-sided type I error rate of 10% and type II error rate of 10% under the alternative of an 80% completion rate with $\leq 15\%$ toxicity. The experimental arm was to be considered as feasible if the upper bound of the two-sided 80% CI for grade 4 toxicity excluded 40% and if the lower bound of the two-sided 80% CI for the treatment completion rate excluded 60%. Secondary end points were late toxicity, DFS, and OS.

Statistical Analyses

A total of 97 patients were randomly assigned in this trial, seven patients before the amendment. These seven patients were excluded from the main analysis. The statistical analysis is presented for the 90 eligible patients randomly assigned after amendment (intent-to-treat population; Fig 1).

The rate of full completion administration of the experimental treatment was computed as the percentage of patients who received the full dose

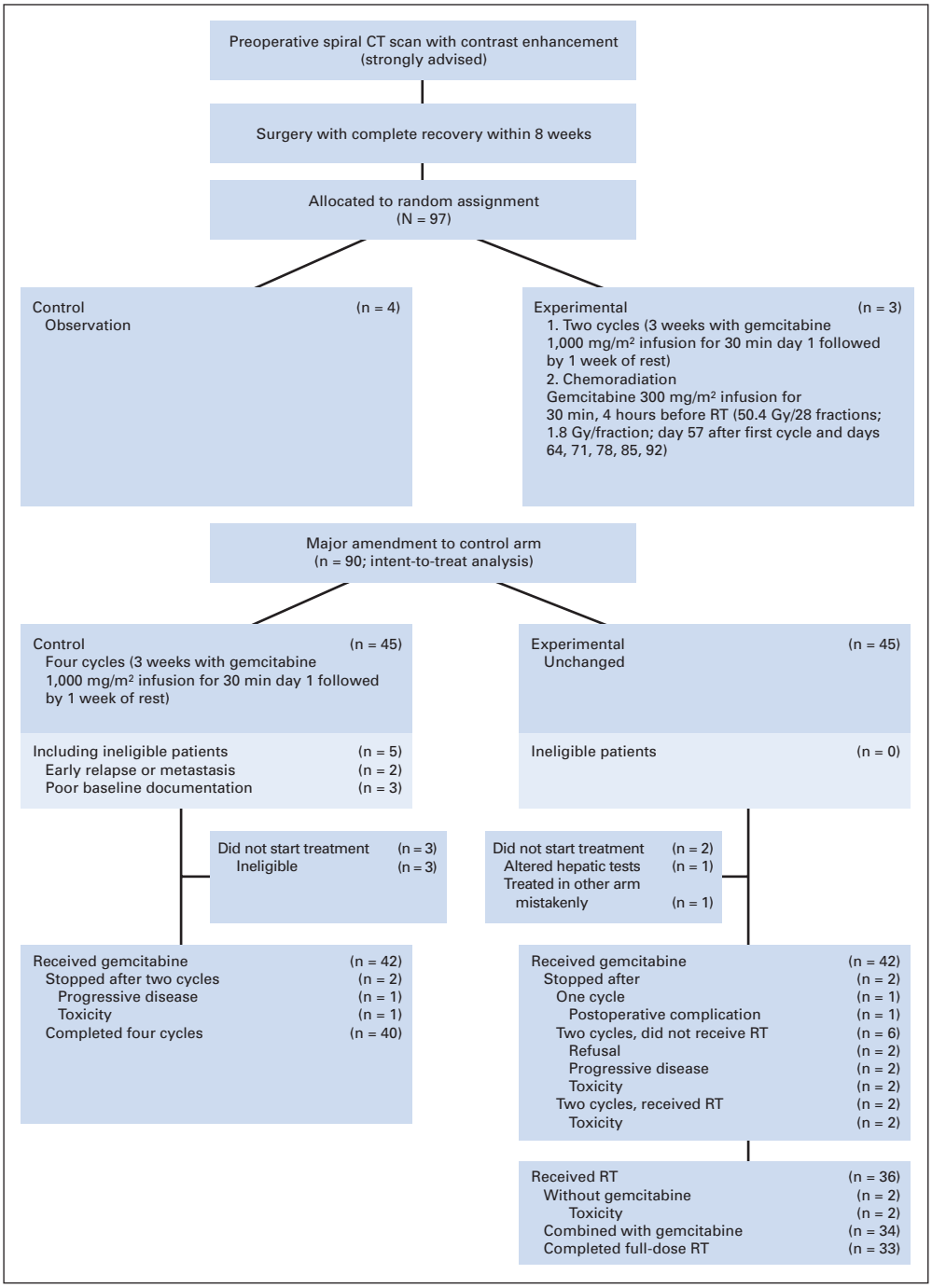

Fig 1. Study flowchart. CT, computed tomography; RT radiation therapy.

of radiation and chemotherapy prescribed according to the protocol in the intent-to-treat population. Dose delays were not considered as treatment failures.

DFS was defined as the time from random assignment to disease recurrence or death, whichever came first. OS was defined as the time from random assignment to death. The analyses of DFS and OS were done in the intent-to-treat population, and a sensitivity analysis excluded the patients who did not start the allocated treatment or had no radiation therapy in the experimental arm (treated population was 42 in the control arm and 36 in the experimental arm). Kaplan-Meier curves were used to estimate DFS and OS in both arms. Patients without events were censored at the date of last contact. CIs are presented at the two-sided 80% (primary end points) and 95% level. Toxicity data are presented per treatment allocated at random assignment in patients randomly assigned after the amendment who had started their allocated treatment. Statistical analysis was conducted at the EORTC Headquarters by two statisticians (L.C. and M.M.).

RESULTS

Patient Characteristics

Between September 2004 and January 2007, 90 patients were enrolled by 29 centers, 45 in each arm. Five patients, all in the control

arm, were considered to be ineligible (two because of early discovery of recurrence or metastases and three because they lacked data from one center).

Patients' baseline characteristics were similar in both treatment arms (Table 1). Most of the tumors were pT3N1 with perineural invasion. R0 resection was performed in 43 patients (96%) in the experimental arm and in 44 patients (98%) in the control arm. Follow-up was also similar in both arms, with a median follow-up of 30.7 months in the experimental arm and 33.3 months in the control arm ($P = .44$).

Table 1. Patient Demographic and Clinical Characteristics

Characteristic	Gemcitabine + Radiotherapy (n = 45) No.	%	Gemcitabine Alone (n = 45) No.	%	Total (N = 90) No.	%
Age, years						
Median	61		58		59	
Range	44-75		32-77		32-77	
Sex						
Male	24	53	27	60	51	57
Female	21	47	18	40	39	43
WHO PS						
0	22	49	22	49	44	49
1	22	49	20	44	42	47
2	1	2	3	7	4	4
Type of surgery						
Whipple	28	62	23	51	51	57
PPPD	15	34	20	45	35	39
Unknown	2	4	2	4	4	4
Mesentericoportal resection						
No	34	75	31	69	65	72
Yes	8	18	13	29	21	23
Unknown	3	7	1	2	4	5
CA 19-9 (baseline)						
Normal	29	64	23	51	52	58
Above normal	14	31	19	42	33	37
Unknown	2	5	3	7	5	5
Number of lymph nodes examined						
Median	12		12		12	
Range	5-36		3-28		3-36	
pT status						
1	3	7	2	4	5	6
2	9	20	8	18	17	19
3	32	71	30	67	62	69
4	0		4	9	4	4
Unknown	1	2	1	2	2	2
pN status						
pN0	13	29	14	30	27	30
pN1a	12	27	9	20	21	23
pN1b	19	42	22	50	41	46
pNx	1	2	0	0	1	1
pM status						
pM0	44	98	44	98	88	98
pM1	0		1	2	1	1
Unknown	1	2	0		1	1
Vascular invasion +	15	33	18	40	33	37
Lymphatic invasion +	15	33	17	38	32	36
Perineural invasion +	33	73	34	76	67	74
Grade						
1	10	22	12	27	22	24
2	20	44	26	58	46	51
3	10	22	6	13	16	18
Unknown	5	12	1	2	6	7
Margin of resection						
R0	43	96	44	98	87	97
Rx	2	4	1	2	3	3
Baseline CA 19-9 levels						
Normal	29	64,4	23	51	52	58
Above normal	14	31	19	42	33	37
Unknown	2	4§	3	7	5	5

Abbreviations: PS, performance status; PPPD pylorus-preserving pancreaticoduodenectomy; CA 19-9, carbohydrate antigen 19-9; +, presence of.

Treatment Delivery

In the control arm, two patients did not start treatment, and data are missing for a third patient. In the experimental arm, one patient did not start treatment, and one was allocated to the wrong treatment arm by mistake. For patients who started the allocated treatment (42:43), the gemcitabine median relative dose intensity was 88.6% in the control arm and 87.3% in the experimental arm. The median dose intensity was 664.6 mg/m^2 × week × cycle for the control arm and 480.6 mg/m^2 × week × cycle for the experimental arm. Thirty-two (76%) and 34 (79%) patients in the control and experimental arms, respectively, received > 70% of the planned dose.

Radiation therapy was started in 36 (80%) of 45 patients, nine of them being not irradiated for several reasons, mainly the patient's refusal (two), rapid progression (two), early postoperative death (one), gemcitabine-alone toxicity (two), and altered liver tests (one; Fig 1 and Table 2).

Toxicity

Globally, the experimental treatment was well tolerated and no deaths due to toxicity were reported. Main acute toxicities were hematologic, fatigue, nausea/vomiting, diarrhea, and gastritis and were slightly more frequent in the experimental arm (Table 3).

For the predefined coprimary toxicity end point (grade 4 WBC, platelet, hemoglobin, vomiting, or diarrhea toxicities), the rate of occurrences was zero (0%) of 42 in the control arm and two (4.7%) of 43 in the experimental arm (80% CI, 1.2% to 11.9%; 95% CI, 0.5% to 15.8%). The upper bound of the 80% CI is below the protocol-specified threshold of 15% for the experimental arm.

In the experimental arm, three patients who received CRT, experienced grade 3–related late toxicities consisting of anorexia and gastritis (one), epigastric pain (one), and insulin requirement (one). There were no related late toxicities in the control arm.

Table 2. Radiation Therapy

Total Dose (Gy)	Gemcitabine + Radiotherapy (n = 45) No. of Patients	%
25.2 in 14 fractions (postoperative occlusion)	1	2.2
48.7 in 27 fractions (scaphogia)	1	2.2
50.4 in 28 fractions	28	62.2
54 in 30 fractions (protocol mistake)	5	11.1
Unknown (radiation therapy received)	1	2.2
Did not receive radiation therapy	9	20.0
Refusal	2	
Rapid progression	2	
Postoperative death	1	
Gemcitabine toxicity	2	
Wrong arm	1	
Altered liver tests	1	

NOTE. Temporary treatment interruption (≤ 4 days) was observed in 24 patients (68.6%).

Table 3. No. of Patients With Relevant Acute Toxicities (CTC version 2.0)

Toxicity	Grade	Treatment: Gemcitabine + Radiotherapy (n = 43) No.	%	Gemcitabine Alone (n = 42) No.	%	Total (N = 85) No.	%
WBC	All	39		38		77	
	3	7	16	6	14	13	15
	4	0		0		0	
Neutrophils	All	32		33		65	
	3	12	28	15	36	27	32
	4	2	5	3	7	5	6
Platelets	All	20		18		38	
	3	1	2	0		1	1
	4	0		0		0	
Hemoglobin	All	42		40		83	
	3	2	5	0		2	2
	4	1	2	0		1	1
SGPT	All	30		29		59	
	3	5	12	5	12	10	12
	4	0		0		0	
Fatigue	All	31		28		59	
	3	3	7	2	5	5	6
	4	0		0		0	
Fever	All	15		12		27	
	3	3	7	0	0	3	4
	4	0		0		0	
Weight loss	All	10		6		16	
	3	1	2	0	0	1	1
	4	0		0		0	
Anorexia	All	21		8		29	
	3	1	2	0		1	1
	4	1	2	0	0	1	1
Nausea	All	27		24		51	
	3	1	2	0		1	1
	4	0		0		0	
Vomiting	All	20		8		28	
	3	0		0		0	
	4	1	2	0		1	1
Gastritis	All	2		0		2	
	3	1	2	0		1	1
	4	1	2	0		1	1
Diarrhea	All	26		18		44	
	3	0		0		0	
	4	1	2	0		1	1
Hemorrhage	All	1		2		3	
	3	0	0	1	2	1	1
	4	1	2	0	0	1	1
Other GI toxicity	All	17		14		31	
	3	0		0		0	
	4	1	2	0	0	1	1
Other toxicity	All	30		22		52	
	3	7	16	2	5	9	11
	4	1	2	1	2	2	2

Abbreviations: CTC, Common Toxicity Criteria; SGPT, serum glutamic-pyruvic transaminase.

Completion of the Treatment According to Protocol (coprimary end point)

Of the 90 randomly assigned patients, 33 (73.3%) of 45 completed treatment according to protocol in the experimental arm (80% CI, 63.1% to 81.9%; 95% CI, 58.1% to 85.4%) and 39 (86.7%) of 45 completed treatment according to protocol in the control arm (95% CI, 73.2% to 95.0%). The lower bound of the 80% CI excludes the protocol-specified threshold of 60%.

Secondary End Points

Median OS was 24.4 months (95% CI, 21.5 to ∞ months) in the control arm and 24.3 months (20.5 to ∞ months) in the experimental arm (Fig 2A); the 2-year survival rate was 50.2% (95% CI, 34.8% to 63.8%) and 50.6% (95% CI, 34.3% to 64.8%), respectively. When restricted to the treated population, results were similar, with 2-year survival rates of 53.8% (95% CI, 37.6% to 67.6%) in the control arm and 53.8% (95% CI, 35.4% to 69.1%) in the experimental arm.

Median DFS was 10.9 months (95% CI, 8.3 to 16.0 months) in the control arm and 11.8 months (95% CI, 10.1 to 19.3 months) in the experimental arm (Fig 2B). In the treated population, the medians were 10.9 months (95% CI, 8.3 to 16.7 months) and 12.4 months (95% CI, 10.1 to 19.3 months), respectively.

The rate of local recurrence alone as first progression was notably lower in the experimental arm (11% *v* 24%). The rate of simultaneous local and distant progression as first progression was 13% in the control arm versus 20% in the experimental arm, and the rate of distant progression only was quite similar in both arms (40% in the control arm and 42% in the experimental arm).

DISCUSSION

Postoperative adjuvant therapy remains a challenge in pancreatic cancer for several reasons. Long-term survival data after surgical resection

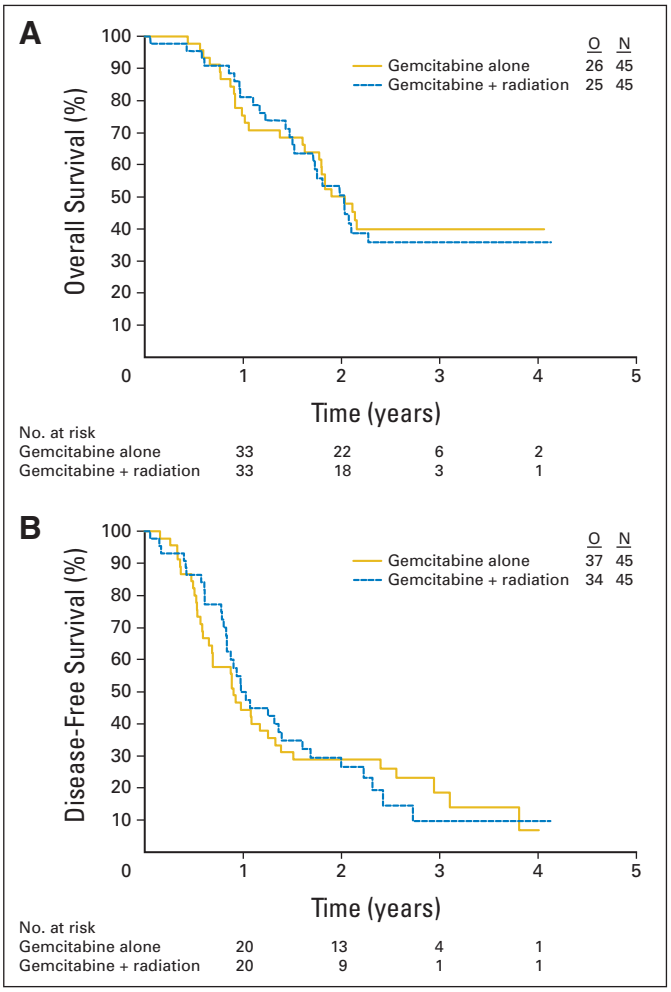

Fig 2. Kaplan-Meier curves for overall survival (A) and disease-free survival (B). O, No. of observed events; N, No. of patients.

are disappointing and only slightly improved by adjuvant therapy.[8-12] Both local and distant recurrences are frequent and difficult to control.[3] Combining chemotherapy and radiation therapy in adjuvant therapy has shown conflicting results over the last two decades, and the true impact of postoperative CRT remains questionable. Chemotherapy based on FU (plus folinic acid) or gemcitabine is now advocated as standard adjuvant therapy in Europe.[8-10] In the United States, FU-based CRT is still widely proposed on the basis of the nonrandomized experience of high-volume expertise centers[6,7] and the small randomized GITSG trial.[5] Subsequent trials from European organizations[8,11] could not confirm the GITSG results. These trials can be criticized for lack of quality control of radiotherapy and suboptimal FU-based CRT schedules according to current standards.

Our multicenter study aimed to evaluate a modern regimen of radiation therapy, applied in the framework of expert multicenters, combined with the currently most active drug in advanced pancreatic cancer—gemcitabine. Gemcitabine is also known to be a good radiosensitizer and was reported to be easily combined with radiation in pancreatic cancer, both in neoadjuvant and locally advanced disease[16-19]; we also generated phase II data showing a good feasibility and toxicity profile for combining radiation with weekly gemcitabine.[20,21]

This multicenter phase II trial was designed to investigate feasibility and toxicity of this new regimen in the postoperative adjuvant setting before continuing with a large phase III trial. Before knowing the results from the CONKO-001 trial, we chose to treat our patients with 4 months of gemcitabine to provide similar periods of postoperative therapy in both arms. The results show that the combination of gemcitabine and CRT is feasible and only slightly more toxic than gemcitabine alone. By contrast to the ESPAC-1–derived results, well-conducted CRT was not shown to be deleterious here; poor results from the ESPAC-1 trial could be explained by the low total dose regimen that was used and the poor quality control for radiation delivery in many centers, possibly leading to treatment deviation.[8] Moreover, the good tolerability we observed is probably due to the sequence of starting initially with gemcitabine alone and then proceeding with CRT when the patient had shown good postoperative recovery and absence of early disease progression. This sequential concept has been suggested as clinically appropriate in the locally advanced setting.[23] In view of this experience, the sequence with CRT in the end portion of the adjuvant treatment will be evaluated in the joint RTOG-0848/EORTC-40084-22084 phase III study.

Our randomized phase II study did not reveal DFS and survival benefits. Obviously, the current phase II design is not appropriate to detect such differences, but the DFS seems disappointing even if most of the tumors were pT3N1. Of note, we did find a lower rate of local recurrence as first progression in the CRT arm, and the survival data we observed in the experimental arm, although not methodologically comparable to that in the control arm, may suggest that CRT, without any deleterious effects, could lead to a similar effect, as reported with only adjuvant chemotherapy in other studies.[8-10,12] The potential effect of CRT on local recurrence of pancreatic cancer could possibly be underestimated in our study because we included only patients with an R0 resection. Yet R1 resections are quite common and often underestimated, and they pose an important prognostic factor in pancreatic cancer.[24-26] It is likely that achieving local control is relatively more important in patients with an R1 resection and that the impact of CRT should thus be evaluated after R1 resection. Therefore, in the abovementioned joint RTOG-EORTC phase III study, patients with R0 or R1 disease are both eligible. Again, we can hypothesize that adding CRT to full-dose adjuvant gemcitabine therapy could offer a more beneficial multimodal approach after resection by optimizing local control.

Finally, selection of patients who will benefit from gemcitabine-based adjuvant therapy may be improved by the use of specific biomarkers, as recently shown.[27,28] These markers need to be prospectively incorporated in future adjuvant trials. Similarly, patterns of therapy failure for treatment of pancreatic cancer can be represented and therefore predicted by distinct genetic subtypes, notably *DPC4* status, that can be used to stratify patients for local control versus systemic therapy.[29]

In conclusion, our randomized phase II trial shows that adjuvant gemcitabine, followed by gemcitabine-based modern CRT is feasible and only slightly more toxic than gemcitabine alone. In view of the remaining uncertainty about the role of CRT as a complement to systemic therapy, in particular after R1 resection, such multimodal approach should be further investigated in a phase III trial.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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