Original Investigation

Effect of Chemoradiotherapy vs Chemotherapy on Survival in Patients With Locally Advanced Pancreatic Cancer Controlled After 4 Months of Gemcitabine With or Without Erlotinib

The LAP07 Randomized Clinical Trial

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IMPORTANCE In locally advanced pancreatic cancer, the role of chemoradiotherapy is controversial and the efficacy of erlotinib is unknown.

OBJECTIVES To assess whether chemoradiotherapy improves overall survival of patients with locally advanced pancreatic cancer controlled after 4 months of gemcitabine-based induction chemotherapy and to assess the effect of erlotinib on survival.

DESIGN, SETTING, AND PARTICIPANTS In LAP07, an international, open-label, phase 3 randomized trial, 449 patients were enrolled between 2008 and 2011. Follow-up ended in February 2013.

INTERVENTIONS In the first randomization, 223 patients received 1000 mg/m^2 weekly of gemcitabine alone and 219 patients received 1000 mg/m^2 of gemcitabine plus 100 mg/d of erlotinib. In the second randomization involving patients with progression-free disease after 4 months, 136 patients received 2 months of the same chemotherapy and 133 underwent chemoradiotherapy (54 Gy plus capecitabine).

MAIN OUTCOMES AND MEASURES The primary outcome was overall survival from the date of the first randomization. Secondary outcomes were the effect of erlotinib and quality assurance of radiotherapy on overall survival, progression-free survival of gemcitabine-erlotinib and erlotinib maintenance with gemcitabine alone at the second randomization, and toxic effects.

RESULTS A total of 442 of the 449 patients (232 men; median age, 63.3 years) enrolled underwent the first randomization. Of these, 269 underwent the second randomization. Interim analysis was performed when 221 patients died (109 in the chemoradiotherapy group and 112 in the chemotherapy group), reaching the early stopping boundaries for futility. With a median follow-up of 36.7 months, the median overall survival from the date of the first randomization was not significantly different between chemotherapy at 16.5 months (95% CI, 14.5-18.5 months) and chemoradiotherapy at 15.2 months (95% CI, 13.9-17.3 months; hazard ratio [HR], 1.03; 95% CI, 0.79-1.34; P = .83). Median overall survival from the date of the first randomization for the 223 patients receiving gemcitabine was 13.6 months (95% CI, 12.3-15.3 months) and was 11.9 months (95% CI, 10.4-13.5 months) for the 219 patients receiving gemcitabine plus erlotinib (HR, 1.19; 95% CI, 0.97-1.45; P = .09; 188 deaths vs 191 deaths). Chemoradiotherapy was associated with decreased local progression (32% vs 46%, P = .03) and no increase in grade 3 to 4 toxicity, except for nausea.

CONCLUSIONS AND RELEVANCE In this open-label, randomized trial involving patients with locally advanced pancreatic cancer with disease controlled after 4 months of induction chemotherapy, there was no significant difference in overall survival with chemoradiotherapy compared with chemotherapy alone and there was no significant difference in overall survival with gemcitabine compared with gemcitabine plus erlotinib used as maintenance therapy.

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Pancreatic cancer is one of the leading causes of cancer-related mortality in the Western world.[1,2] Since 1997, gemcitabine therapy has been the standard treatment for patients with metastatic pancreatic cancer.[3] Thereafter, studies involving gemcitabine in combination with erlotinib found a statistically significant but not clinically meaningful gain of survival.[4] Recently, the fluorouracil-irinotecan-oxaliplatin (FOLFIRINOX) combination and nab-paclitaxel-gemcitabine combination have been shown to be superior to gemcitabine alone in that setting.[5,6]

At the time of diagnosis, 30% of patients have locally advanced pancreatic cancer,[2] which is defined as surgically unresectable, ie, with superior mesenteric artery or celiac axis encasement of more than 180°, unreconstructable superior mesenteric vein or portal vein occlusion, and aortic or nodal involvement beyond the field of resection but no evidence of distant metastases (stage T4).[7] Patients with locally advanced pancreatic cancer have an intermediate prognosis between those with resectable and metastatic tumors with median overall survival of 9 to 11 months.[2]

The role of radiation therapy in the management of locally advanced pancreatic cancer remains controversial. In the early 1980s, fluorouracil-based concomitant chemoradiotherapy was shown to be better than radiotherapy alone.[8] In the late 1990s, gemcitabine was adopted as the preferred treatment strategy, replacing chemoradiotherapy, in patients with locally advanced pancreatic cancer. The results of 5 randomized trials of locally advanced pancreatic cancer patients comparing chemoradiotherapy with chemotherapy were contradictory.[9-13] Some retrospective studies have suggested that induction chemotherapy administered before concurrent chemoradiotherapy could improve survival.[14,15] Such a therapeutic strategy may spare patients with rapidly progressive disease from potentially toxic radiotherapy and help to select those who could potentially benefit from chemoradiotherapy.

The LAP07 international phase 3 trial was designed to assess whether chemoradiotherapy in patients with locally advanced pancreatic cancer controlled after 4 months of gemcitabine-based induction chemotherapy may improve survival compared with chemotherapy alone.

Methods

Patients

Eligible patients were at least 18 years of age; had histologically or cytologically confirmed stage III locally advanced pancreatic cancer according to the International Union Against Cancer staging system[16]; had measurable or evaluable disease as assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.0) criteria, the World Health Organization (WHO) performance status score of 2 or less (0 indicates fully active, 1 indicates ability only to carry out light work, and 2 indicates capacity for self-care but inability to carry out work); had adequate biological hematologic, hepatic, and renal parameters; and had no prior chemotherapy or radiation therapy.

Study Design and Oversight

The LAP07 trial was an international, multicenter, open-label, unblinded, randomized phase 3 study. Patients with locally advanced pancreatic cancer were randomized in a 1:1 ratio using a minimization procedure with stratification according to center and performance status (0-1 vs 2) at the study coordination center at the GERCOR (Groupe Coopérateur Multidiciplinaire en Oncologie) in Paris, France. Randomization consisted of a 2-step randomization process (eFigure A in Supplement 1). In the first step, patients were randomized to induction chemotherapy with gemcitabine or gemcitabine plus erlotinib for 4 cycles. For the second step, patients whose tumor was controlled (ie, stable or with an objective response) and who had a WHO performance status of 2 or less after completion of induction chemotherapy were randomized a second time to receive either chemotherapy or chemoradiotherapy for an additional 2 months. Maintenance therapy with erlotinib was given to patients who were without disease progression, who had a WHO performance status of 2 or less, and who were allocated to receive gemcitabine plus erlotinib or had experienced limiting toxic effects during the first-randomization period.

The primary objective was to assess whether administration of chemoradiotherapy to patients whose tumor was controlled after 4 months of induction chemotherapy increases overall survival from the date of the first randomization compared with continuing the same chemotherapy.

Secondary objectives were progression-free survival from the date of the first randomization, overall survival from the date of the first randomization, progression-free survival from the date of the first randomization of the erlotinib-gemcitabine combination and erlotinib maintenance therapy vs gemcitabine alone, tolerance of erlotinib maintenance after the end of chemotherapy or chemoradiotherapy, and the effect of radiation therapy quality assurance on overall survival from the date of the first randomization.

For preplanned sensitivity analyses, overall survival and progression-free survival from the date of the second randomization of patients achieving the second randomization were calculated.

In addition, an ancillary study about prognostic markers on histology and circulating tumor cells was planned and are reported elsewhere.[17]

The trial initiation, the data collection, and the trial coordination were carried out by the GERCOR group. The study protocol was approved by the independent ethics committee of each participating country and was conducted in accordance with the ethical principles contained in the Declaration of Helsinki (see the study protocol in Supplement 2). All the patients signed an informed consent before entering the study. All the investigators vouched for the adherence to the study protocol.

Treatment

Gemcitabine at a dose of 1000 mg/m^2 was delivered as a 30-minute intravenous infusion weekly for 3 weeks, followed by a 1-week rest (1 cycle), for 4 cycles. Erlotinib was given once-daily orally at a dose of 100 mg. During the maintenance phase, the daily dose of erlotinib was increased to 150 mg.

Three-Dimensional Conformal Radiation Therapy

Patients underwent contrast-enhanced planning computed tomography simulation. Gross tumor volume included the gross primary tumor and any lymph node with short axis diameter of 1 cm or more. The planning target volume encompassed the gross tumor volume with a margin of 3 cm in the superior-inferior direction and 1.5 cm in all other directions to account for the set-up uncertainties and respiratory-induced organ motions.[18] Prophylactic irradiation of uninvolved regional nodes was not performed. The total planned dose to the planning target volume was 54 Gy in 30 daily fractions over 6 weeks. Concurrent capecitabine was given at a dose of 800 mg/m^2 twice daily on days of radiation therapy.

Radiation Therapy Quality Assurance and Quality Control

The mandated radiation therapy quality assurance consisted of detailed radiation therapy guidelines developed by an international board.[18] The radiation therapy quality assurance program included a pretrial test case (benchmark case).[19] All centers were classified in 3 categories according to the radiation therapy quality assurance: per protocol, minor deviation, or major deviation. Those with major deviation were not allowed to include patients until a significant improvement was achieved and the guidelines were rigorously followed. On-trial radiotherapy quality control consisted of a central review and dose-volume histograms for each patient was performed by 2 experts in treatment planning. Centers received a real-time quality control feedback in order to improve the quality of radiotherapy treatment.

Assessments

Tumor outcome was evaluated every 8 weeks by spiral computed tomography scan or magnetic resonance imaging. Serum carbohydrate antigen 19-9 (CA 19-9) was measured at baseline and every 8 weeks thereafter. Safety was monitored for treatment-related adverse events and for serious adverse events before each cycle of chemotherapy. Treatment-related adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf). Patients were followed up for survival until death or study closure.

For primary objectives and analyses of time to event end points, overall survival was defined as the time from the date of the first randomization to the date of death from any cause. Patients who were still alive at the date cutoff were censored. Progression-free survival was defined as the time from the date of the first randomization to the date of tumor progression or death. Patients who were alive without progression at the date cutoff were censored.

For preplanned sensitivity analyses of time to event end points among patients achieving the second randomization: overall survival was defined as the time from the date of the second randomization to the date of death from any cause. Patients who were still alive at the date cutoff were censored.

Tumor control was defined as complete response, partial response, or stable disease.

Statistical Analyses

The trial was designed to detect an increase in median overall survival from the date of the first randomization from 9 to 12 months in the chemoradiotherapy group (hazard ratio [HR], 0.75) with a 2-sided type I error of 5% and a statistical power of 80%.[14] With a uniform accrual of 20 patients per month over 24 months, 480 patients were needed with an anticipated 15 months of follow-up after the second randomization to observe the 392 required deaths. The anticipated trial duration was 39 months. With an estimated 30% of patients who had progressive disease and therefore ineligible for the second randomization, we targeted a total sample size of 722 patients (including 5% of patients lost to follow-up).

Interim analysis was planned to assess the futility (H^O is not rejected) and efficacy (H^O is rejected). The nominal significance level for the interim and final overall survival from the date of the first-randomization analyses was determined by means of the α spending function with an O'Brien-Fleming stopping boundary. Interim analysis was performed when 269 patients had reached the second randomization. Median follow-up was 36 months.

Two hundred twenty-one deaths had occurred. Primary analysis had reached the boundaries for futility: an effect size of 0.288 and the *z* score of 0.215 were calculated with upper and lower *z* score boundaries for futility positive 0.548 or less and negative 0.548 or more, according to EAST software version 5 (Cytel). The independent data monitoring committee recommended stopping the inclusion of further patients after concluding that the planned intermediate analysis serve as the final one to answer the primary objective of the study, and hence the final analysis was performed using this database with a final α type one error of 5%. All statistical tests were bilateral and a *P* value ≤.05 was considered as statistically significant.

Efficacy and safety assessments were conducted in the intent-to-treat (ITT) population. Two population data sets were constructed according to patient randomization profile.

The first-randomization ITT population was defined as all patients randomized between gemcitabine and gemcitabine plus erlotinib irrespective of eligibility criteria, treatment received, and the second randomization taking place. This population was used for analysis of the second objective of the study, which compared gemcitabine to gemcitabine plus erlotinib (first randomization).

The second-randomization ITT population, defined as all patients who were free of progression and who had a WHO performance status of 2 or less at 4 months, were randomized to receive either chemoradiotherapy or chemotherapy irrespective of eligibility criteria and treatment received. This population was used for analysis of the primary objective comparing overall survival according to chemoradiotherapy vs chemotherapy (second randomization) and for secondary objectives for the second-randomization patients. Missing data for covariables were not imputed.

Preplanned sensitivity analysis comparing overall survival according to chemoradiotherapy vs chemotherapy (second randomization) in the second ITT population was calculated from the date of the second randomization.

For treatment administration, description of drug exposure, treatment duration, and dose administration was provided

in the ITT and safety populations. Treatment adherence was fixed at 75% of medication dose received regardless of treatment group. Overall survival and progression-free survival from the date of the first randomization were estimated using the Kaplan-Meier method[20] and described by median with 95% CIs. Survival curves were compared using unstratified log-rank test. Bivariable Cox proportional-hazards model was used to estimate HRs with 95% CIs. A shared frailty model with center-specific random effects on the hazard function of the Cox proportional hazards was used to account for the fact that patients were clustered within centers and the reintroduction policy could vary between centers.[21]

Interaction between treatment allocation after the first and second randomization was initially tested before performing survival analyses. Additionally, survival analyses from the date of the first randomization were performed in the subpopulation who received chemoradiotherapy at the second randomization. The reverse Kaplan-Meier method, defined as the time interval between the origin and last follow-up using Kaplan-Meier estimation for patients alive as the event and deaths as censored observations, was used to estimate follow-up.[22]

Analyses of adverse events were conducted and descriptive statistics were provided. In addition, the time to occurrence of grade 3 and 4 toxicities, regardless of their type, was assessed using a Cox proportional-hazards model (after graphical check of proportionality). Analyses were conducted with the use of SAS statistical software, version 9.2 (SAS Institute Inc), and R (version 3.1.2).

Results

Patients

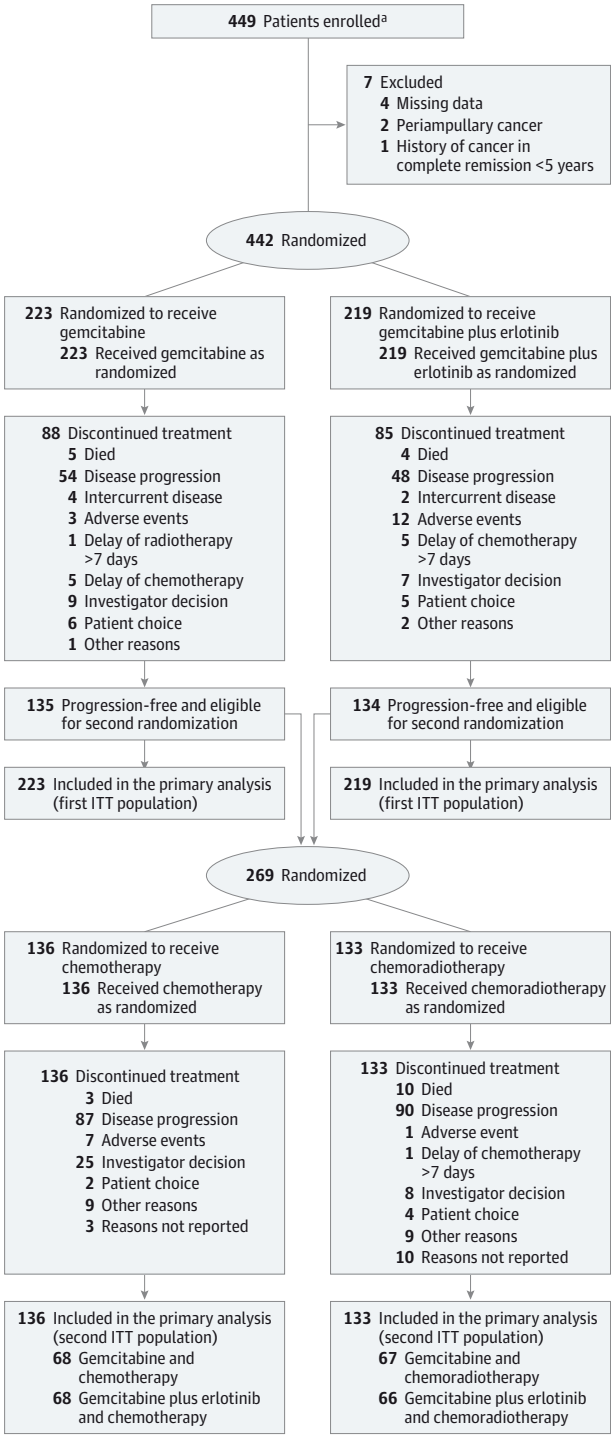
Between February 2008 and December 2011, a total of 449 patients from 80 centers in France, Australia, New Zealand, Belgium, and Sweden were enrolled. Of these, 4 patients had missing data, 2 had a periampullary cancer, and 1 had a history of other previous malignancy that has been in complete remission for less than 5 years, thus leaving 442 eligible patients. A total of 442 patients underwent the first randomization, with gemcitabine administered in 223 (50%) patients and gemcitabine plus erlotinib given in 219 (50%) patients in the first ITT population (**Figure 1**). Demographics and baseline characteristics were well balanced between the 2 groups (**Table 1**).

Among the 442 eligible patients who participated in the first randomization, 269 (61%) underwent the second randomization after 4 months, including 136 randomized to receive chemotherapy and 133 randomized to receive chemoradiotherapy (second ITT population). One hundred seventy-three patients (39%) were not randomized, mostly due to tumor progression (102 patients [23.1%]; Figure 1). Median overall follow-up time was 36.7 months (95% CI, 27.6-44.2 months).

Efficacy

Complete survival data were collected until the databases lock on February 22, 2013. The median follow-up was 34.3 months (95% CI, 27.6-43.8 months) for the first ITT population. Three hundred seventy-nine patients died by the end of the follow-up.

Figure 1. Flow of Patients in the LAP07 Study



ITT indicates intent-to-treat.

Overall, median overall survival was 12.8 months (95% CI, 11.8-14.1 months). The ITT analysis according to the first-randomization status showed no significant difference in overall survival between patients receiving gemcitabine alone (n = 223) or gemcitabine plus erlotinib (n = 219), with median overall survival of 13.6 months (95% CI, 12.3-15.3 months) and

Table 1. Characteristics of the Patients With Locally Advanced Pancreatic Cancer According to Treatment Group at the First and Second Randomizations

	First Randomization, No. (%)		Second Randomization, No. (%)	
	Gemcitabine (n = 223)	Gemcitabine- Erlotinib (n = 219)	Chemotherapy (n = 136)	Chemoradiotherapy (n = 133)
Age, median (IQR), y	64.0 (57.0-70.0)	63.0 (58.0-71.0)	63.0 (57.0-70.0)	62.0 (55.0-70.0)
Sex				
Men	117 (52.5)	111 (50.7)	76 (55.9)	58 (43.6)
Women	106 (47.5)	108 (49.3)	60 (44.1)	75 (56.4)
WHO Performance Status score[a]				
0	109 (48.9)	88 (40.2)	76 (55.9)	64 (48.1)
1	91 (40.8)	112 (51.1)	48 (25.3)	60 (45.1)
2	15 (6.7)	16 (7.3)	8 (5.9)	7 (5.3)
Unknown	8 (3.6)	3 (1.4)	4 (2.9)	2 (1.5)
Tumor location in the pancreas				
Head	146 (65.5)	156 (71.2)	93 (68.4)	88 (66.2)
Body or tail	76 (34.1)	62 (28.3)	43 (31.6)	44 (33.1)
Unknown	1 (0.4)	1 (0.5)	0	1 (0.7)
Grade[b]				
Well differentiated	56 (25.1)	51 (23.3)	33 (24.3)	31 (23.3)
Moderately differentiated	37 (16.6)	38 (17.4)	23 (16.9)	22 (16.5)
Poorly differentiated	18 (18.1)	23 (10.5)	10 (7.3)	9 (6.8)
Unknown	112 (50.2)	107 (48.8)	70 (51.5)	71 (53.4)
Nodal status				
N0	134 (60.1)	124 (56.6)	79 (58.1)	77 (56.6)
N1	85 (38.1)	94 (42.9)	57 (41.9)	54 (39.7)
Unknown	4 (1.8)	1 (0.5)	0	2 (0.1)

Abbreviation: IQR, interquartile range.

[a] A score of 0 indicates normal activity; 1, symptoms but nearly fully ambulatory; and 2 some bed times but the need to be in bed less than 50% during the day.

[b] Well differentiated indicates that more than 95% of the tumor is composed of glands; moderately differentiated, 50% to 95% of the tumor is composed of glands; and poorly differentiated, less than 50% of the tumor is composed of glands.

11.9 months (95% CI, 10.4-13.5 months), respectively. The HR representing the ratio of instantaneous hazard death probabilities of gemcitabine plus erlotinib vs gemcitabine alone was 1.19 (95% CI, 0.97-1.45; $P = .09$; **Figure 2**A). Similarly, progression-free survival from the date of the first randomization was not different between the 2 groups (HR, 1.12; 95% CI, 0.92-1.36; $P = .26$; Figure 2B). There was no significant interaction between the administered treatments for overall survival from the date of the first randomization by combining the first and second-randomization status (first randomization as the starting point) ($P = .24$ for log-rank global test) (eFigure, A in Supplement 1). For the 173 patients who did not reach the second randomization, the median overall survival from the date of the first randomization was 7.7 months (95% CI, 6.6-8.7 months).

The ITT analysis according to the second-randomization status showed no difference in survival with median overall survival from the date of the first randomization of 15.2 months (95% CI, 13.9-17.3 months) in the chemoradiotherapy group vs 16.5 months (95% CI, 14.5-18.5 months) in the chemotherapy group (HR, 1.03; 95% CI, 0.79-1.34; $P = .83$; **Figure 3**A). Similar results were obtained with post hoc analysis using a frailty approach to take into account the center potential effect in the Cox model ($P = .89$). There was no statistically significant difference in progression-free survival from the date of the first randomization between chemotherapy group (median, 8.4 months; 95% CI, 7.8-9.4 months) and the chemoradiotherapy group (median, 9.9 months; 95% CI, 8.8-10.4 months; HR, 0.78; 95% CI, 0.61-1.01; $P = .06$; Figure 3B)

In the group of patients who received gemcitabine plus erlotinib and achieved the second randomization, patients with erlotinib maintenance therapy had a lower overall survival from the date of the first randomization compared with those receiving gemcitabine; 14.5 months (95% CI, 13.2-16.1) vs 17.1 (95% CI, 15.3-19.0; HR, 1.32; 95% CI, 1.01-1.72; $P = .04$). Median overall survival from the date of the second randomization was 10.8 months (95% CI, 9.33-12.65 months) with erlotinib and 13.44 months (95% CI, 11.60-15.18 months) with erlotinib plus gemcitabine.

Delivery of Treatment

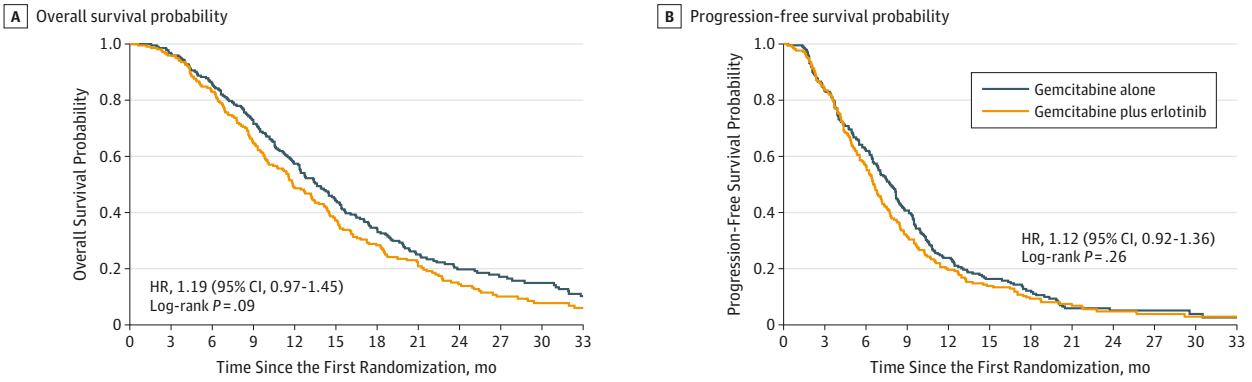
Cumulative Dose of Chemotherapy

Treatment details were available for all but 1 patient in the gemcitabine group and 5 in the gemcitabine-erlotinib group. Of 431 patients, 162 of 220 (74%) treated with gemcitabine and 149 of 211 (71%) treated with gemcitabine-erlotinib completed more than 75% of the planned dose of gemcitabine. Overall adherence rates were 99% (211 of 214) for the erlotinib induction phase and 92% (47 of 51) for the erlotinib maintenance phase.

Radiotherapy Quality Assessment

Of the 133 patients treated with chemoradiotherapy, 4 patients (3%) were not assessable for radiotherapy quality and

Figure 2. Kaplan-Meier Curves of Overall Survival and Progression-Free Survival, According to the First Randomization

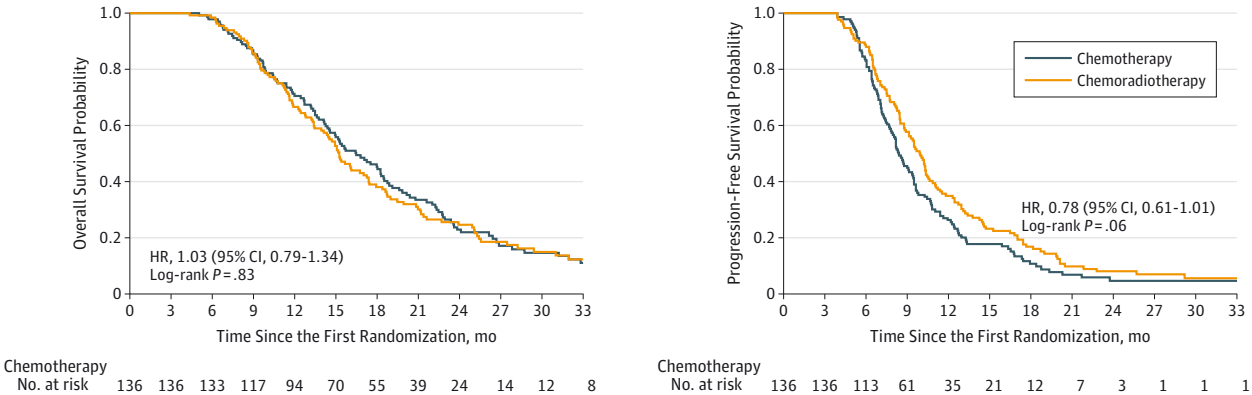


Gemcitabine alone												
No. at risk	223	215	191	157	123	91	66	45	33	25	20	12
No. of events	0	9	33	64	95	123	143	160	168	172	176	182
Gemcitabine plus erlotinib												
No. at risk	219	209	180	140	104	76	56	38	24	14	10	7
No. of events	0	10	38	77	111	136	153	167	179	185	188	190

Gemcitabine alone												
No. at risk	223	186	138	90	51	34	23	9	7	6	3	2
No. of events	0	38	86	134	170	186	194	204	205	205	207	208
Gemcitabine plus erlotinib												
No. at risk	219	182	122	67	42	28	18	11	6	4	3	3
No. of events	0	38	96	150	174	187	195	200	202	204	204	204

A, The 223 patients who experienced 188 events randomized to receive gemcitabine alone survived a median of 13.6 months (95% CI, 12.3-15.3 months) and were followed up a median of 35.9 months (interquartile range [IQR], 23.5-53.0 months). The 219 patients who experienced 191 events randomized to receive gemcitabine plus erlotinib survived a median of 11.9 months (95% CI, 10.4-13.5 months) and were followed up a median of 34.3 months (IQR, 25.5-46.2 months). B, The 223 patients who experienced 208 events randomized to receive gemcitabine alone experienced progression-free survival a median of 7.8 months (95% CI, 6.8-8.4 months) and were followed up a median of 27.3 months (IQR, 21.0-53.0 months). The 219 patients who experienced 204 events randomized to receive gemcitabine plus erlotinib experienced progression-free survival a median of 6.5 months (95% CI, 6.0-7.2 months) and were followed up a median of 25.5 months (IQR, 18.3-51.2 months).

Figure 3. Kaplan-Meier Curves of Overall Survival and Progression-Free Survival, According to the Second Randomization



Chemotherapy												
No. at risk	136	136	133	117	94	70	55	39	24	14	12	8
No. of events	0	0	4	20	40	60	73	87	99	104	106	109
Chemoradiotherapy												
No. at risk	133	133	131	113	87	66	45	34	26	18	12	9
No. of events	0	0	3	20	45	63	80	89	96	101	105	106

Chemotherapy												
No. at risk	136	136	113	61	35	21	12	7	3	1	1	1
No. of events	0	0	24	76	101	112	119	124	125	125	125	125
Chemoradiotherapy												
No. at risk	133	133	117	76	45	30	21	11	8	7	4	4
No. of events	0	0	18	57	87	102	110	118	120	120	121	121

A, The 136 patients who experienced 112 events randomized to receive chemotherapy survived a median of 16.5 months (95% CI, 14.5-18.5 months) and were followed up a median of 35.9 months (interquartile range [IQR], 24.2-44.1 months). The 133 patients who experienced 109 events randomized to receive chemoradiotherapy survived a median of 15.2 months (95% CI, 13.9-17.3 months) and were followed up a median of 36.7 months (IQR, 25.0-51.3 months). B, The 136 patients who experienced 125 events randomized to receive chemotherapy experienced progression-free survival for a median of 8.4 months (95% CI, 7.8-9.4 months) and were followed a median of 24.0 months (IQR, 22.0-25.6 months). The 133 patients who experienced 122 events randomized to receive chemoradiotherapy experienced progression-free survival for a median of 9.9 months (95% CI, 8.8-10.4 months) and were followed up a median of 46.2 months (IQR, 22.9-51.3 months).

12 (9%) did not receive chemoradiotherapy. One hundred seventeen patients (88%) were assessable for radiation therapy quality analysis. Among these patients, 37 (32%) had radiation per protocol, with minor deviation in 59 (50%) or major deviation in 21 (18%). Protocol violations were mainly due to the dose distribution heterogeneities. Deviations from the planned schedule did not significantly influence overall survival from the date of the first and the second randomization.

Median survival from the date of the first randomization was 17.0 months (95% CI, 15.1-18.8 months) with per protocol and minor deviations vs 13.4 months (95% CI, 9.3-16.0 months) with major deviations (HR, 1.43; 95% CI, 0.86-2.36; *P* = .17), and median survival from the date of the second randomization was 12.7 months (95% CI, 11.3-15.0 months) with per protocol and minor deviations vs 10.1 months (95% CI, 5.8-12.3 months) with major deviations (*P* = .19).

Adverse Events

Tables 2 summarizes grade 3 or 4 toxicities observed during the first and second phase of treatment.

During the induction chemotherapy (first randomization), patients treated with gemcitabine plus erlotinib had more grade 3 or 4 anemia (*P* = .05), febrile neutropenia (*P* = .03), diarrhea (*P* = .006), and acneiform rash (*P* = .007) than those treated with gemcitabine alone.

Except for the 6 patients (5.9%) in the chemoradiotherapy group who had grade 3 or 4 nausea vs none in the chemotherapy group (*P* = .008), the adverse toxic effects during the second randomization were not different between the 2 groups.

Progression

Of all the study patients, 385 (87%) had tumor progression. For 130 patients (34%), it was locoregional; 207 (54%), metastatic; 48 (12%) unknown type.

Among the 269 patients who underwent the second randomization, 236 patients (88%) had tumor progression, which was locoregional in 93 patients (39%), metastatic in 122 patients (52%), and of unknown type in 21 patients (9%). Locoregional progression was less frequent in the chemoradiotherapy group (35 [32%]) than in the chemotherapy group (58 [46%]), whereas metastatic progression was more common in the chemoradiotherapy group (67 [60%]) than in the chemotherapy group (55 [44%]; *P* = .04).

Time Without Chemotherapy or Radiotherapy After Protocol Completion

Chemotherapy, radiotherapy, or both were reintroduced in 190 patients (42.9%) after protocol completion. The median delay to treatment reintroduction was 6.1 months (95% CI, 4.8-7.0 months) for the chemoradiotherapy group, significantly longer than the 3.7 months (95% CI, 3.0-4.6) for the chemotherapy group (*P* = .02). Second lines of chemotherapies were used, mainly flurouracil/platinum salt-based, but the rate was well-balanced across the 2 groups.

Surgery

Eighteen patients (4%) underwent a curative-intent resection, 6 before the second randomization (these were excluded from the study) and 12 after the completion of protocol (8 [6%] after chemotherapy and 4 [3%] after chemoradiotherapy, *P* = .25 for Fisher exact test). Eleven patients (2.5%) had an R0 resection, 2 (0.5%) had an R1 resection, and 5 (1.1%) had unknown margins status. Median overall survival from the date of the first randomization for these 18 patients was 30.9 months (95% CI, 12.3-NA).

Discussion

This open-label, randomized clinical trial showed no survival benefit of chemoradiotherapy compared with chemotherapy in patients with locally advanced pancreatic cancer controlled after 4 months of induction chemotherapy, with median overall survival from the date of the first randomization of 15.2 months and 16.5 months, respectively.

The lack of superiority of chemoradiotherapy cannot be explained by insufficient power of the study. The trial was stopped after the independent data monitoring committee concluded that the planned intermediate analysis could be the final one to answer the primary objective of the study. Quality of radiation therapy could be questioned because deviations from the protocol can impact negatively on the outcome of patients receiving chemoradiotherapy.[23]

However, this study included both a radiation therapy quality assurance program and quality control to ensure that the protocol was well understood and that the modalities of radiation therapy were followed. Although deviations from the planned protocol occurred after the second randomization (minor 50%, major 18%), these did not affect significantly the overall survival duration of patients who received chemoradiotherapy. Moreover, the tolerance of chemoradiotherapy in this study was similar to that of chemotherapy except for nausea; therefore, the lack of superiority of chemoradiotherapy cannot be explained by excessive treatment toxicity in the chemoradiotherapy group as it was suggested in a previous study.[12]

In patients attending the second randomization, the final overall survival rates from the date of the first randomization were higher (15.2 and 16.5 months) than those we hypothesized (9 and 12 months). In 2 other prospective studies, overall survivals were 13 and 11.1 months.[12,13] It is likely that induction chemotherapy was selected for patients with a more favorable prognosis. Indeed, patients who were excluded before the second randomization had a median survival of 7.7 months.

The SCALOP phase 2 randomized trial,[24] a study with a similar design to ours, showed overall survival of 15.2 months for capecitabine plus radiotherapy and 13.4 months for gemcitabine plus radiotherapy. Increased use of subsequent chemotherapy lines and improvement of supportive care likely contributed to the survival improvement. Although in the LAP07 trial chemoradiotherapy did not increase overall survival compared with chemotherapy, increase in progression-free survival resulted in a longer period without treatment (6.1 vs 3.7 months, *P* = .02) and less frequent locoregional tumor progressions (32% vs 46%, *P* = .04), the latter confirming the efficacy of chemoradiation for local control. Whether this could translate to a major benefit in terms of quality of life remains uncertain. A loss of tumor control that could have occurred during the period without treatment could be questioned. However, patients of both groups were evaluated equally every 2 months, and a treatment was initiated in all patients as soon as a progressive disease was observed.

The LAP07 trial was designed to assess the effect of the gemcitabine-erlotinib combination based on the results from an earlier report by Moore et al.[4] Unlike this report, in our study,

Table 2. Patients With Grade 3 or 4 Adverse Events Occurring After the First and Second Randomization

	No. of Patients With Missing Data	Patients With Adverse Events, No. (%)		*P* Value
		Gemcitabine (n = 223)	Gemcitabine-Erlotinib (n = 219)	
First Randomization				
Hematologic toxicity	14	74 (34.1)	85 (40.3)	.19
Neutrophils, <900/mm^3	17	70 (32.4)	78 (37.3)	.29
Platelets, <49.9 × 10^9/mm^3	15	3 (1.4)	7 (3.3)	.21
Hemoglobin, <7.9 × 10^9/mm^3	15	5 (2.3)	13 (6.2)	.05
Febrile neutropenia	16	0	5 (2.4)	.03
Nonhematologic toxicity	12	88 (40.4)	87 (41.0)	.89
Nausea	14	6 (2.8)	7 (3.3)	.74
Vomiting	14	3 (1.4)	6 (2.8)	.33
Diarrhea	13	3 (1.4)	14 (6.6)	.006
Mucositis	13	0	2 (0.9)	.15
Acne	13	0	7 (3.3)	.007
Rash	13	1 (0.5)	5 (2.4)	.12
Dry skin	13	0	1 (0.5)	.31
Dyspnea	13	3 (1.4)	2 (0.9)	>.99
Allergic reaction	13	1 (0.5)	0	>.99
Fever	13	2 (0.9)	1 (0.5)	>.99
Aspartate transaminase, >5.1 × ULN	25	20 (9.5)	22(10.7)	.68
Alanine transaminase, >5.1 × ULN	26	35 (16.7)	30 (14.6)	.55
Alkaline phosphatase, >5.1 × ULN	29	22 (10.5)	16 (7.8)	.35
Bilirubin, >1.5 × ULN	25	11 (5.2)	11 (4.9)	.88
γ-Glutamyl transpeptidase	75	64 (34)	46 (25.7)	.08
Creatinine, >3.1 × ULN	22	2 (0.9)	0	.50
		Chemotherapy (n = 136)	Chemoradiotherapy (n = 133)	
Second Randomization				
Hematologic toxicity	52	12 (10.4)	4 (3.9)	.07
Neutrophils, <900 × mm^3	56	8 (7.0)	3 (3.1)	.20
Platelets, <49.9 × 10^9/mm^3	55	3 (2.6)	0	.25
Hemoglobin, <7.9 × 10^9/mm^3	55	1 (0.9)	1 (1.0)	>.99
Febrile neutropenia	54	0	0	NA
Nonhematologic toxicity	49	23 (19.8)	24 (23.1)	.56
Nausea	51	0	6 (5.9)	.008
Vomiting	51	0	3 (2.9)	.10
Diarrhea	51	1 (0.9)	5 (4.9)	.10
Fever	52	0	1 (1.0)	.47
Aspartate transaminase, >5.1 × ULN	76	5 (4.6)	0	.07
Alanine transaminase, >5.1 × ULN	76	6 (5.6)	2 (2.4)	.47
Alkaline phosphatase, >5.1 × ULN	80	4 (3.9)	0	.13
Bilirubin, >1.5 × ULN	73	5 (4.5)	2 (2.4)	.70
γ-Glutamyl transpeptidase	95	14 (14.9)	12 (15.0)	.98

Abbreviation: ULN, upper limit of normal.

the addition of erlotinib to gemcitabine, despite excellent adherence (92%), failed to improve survival and yet was associated with increased grade 3 hematologic, digestive, and skin toxicities. Whether the results of this study could have implications for trials addressing erlotinib or chemoradiotherapy in the adjuvant setting, ie, RTOG 0848, cannot be addressed by our trial, which focused only on the locally advanced pancreatic cancer question.

This suggests that in patients with locally advanced pancreatic cancer, more efficient systemic treatments are needed to treat any early micrometastatic spread and to downstage tumors. FOLFIRINOX or nab-paclitaxel-gemcitabine regimens may address better these issues and allow consideration of other locoregional treatments, eg, secondary surgical resection or more optimized chemoradiation.[5,6,25,26]

The LAP07 study has several limitations. First, nonoptimal drugs were used for chemotherapy because the study was designed in 2005, before the advent of FOLFIRINOX and nab-paclitaxel. In addition, despite the protocol suggested FOLFOX administration as a second-line treatment, subsequent lines of chemotherapy were not systematized. Quality-of-life and cost-efficacy analyses were not planned as secondary objectives, assessment of pain was not optimal, and the evaluation of tumor response and progress-free survival was not centralized.

Although LAP07 confirmed the safety of radiation therapy with concurrent capecitabine, a further intensification of the chemoradiotherapy regimen seems to be needed. Intensity-modulated radiation therapy (IMRT) and stereotactic body radiation therapy are highly conformal modes of radiation delivery that allow for improved sparing of nearby normal structures while increasing the dose to the target volume. A phase 1 and 2 study has shown the feasibility of dose escalation from 50 to 60 Gy with IMRT and concurrent gemcitabine with promising results.[27]

The low secondary surgical resection rate of 4% in the LAP07 study confirms that gemcitabine alone or in combination with erlotinib does not provide a significant downstaging of locally advanced pancreatic cancer. A higher rate of resection (33.2%) has been reported in a meta-analysis by Gillen et al,[28] but most series analyzed in this report were small-sized and heterogeneous regarding the distinction between borderline and locally advanced tumors and the treatments applied. Our study suggests that tumors were properly diagnosed as locally advanced pancreatic cancer and that secondary resection is rarely possible.

An ancillary study of LAP07 showed that evaluation of micrometastatic disease using circulating tumor cells detection was a promising prognostic tool in patients with locally advanced pancreatic cancer.[17]

Conclusions

In this open label, randomized trial among patients with locally advanced pancreatic cancer with disease controlled after 4 months of induction chemotherapy, there was no significant difference in overall survival with chemoradiotherapy compared with chemotherapy alone, and there was no significant difference in overall survival with gemcitabine compared with gemcitabine plus erlotinib used as maintenance therapy.

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