JAMA Oncology | Original Investigation

Total Neoadjuvant Therapy With FOLFIRINOX Followed by Individualized Chemoradiotherapy for Borderline Resectable Pancreatic Adenocarcinoma
A Phase 2 Clinical Trial

Janet E. Murphy, MD, MPH; Jennifer Y. Wo, MD; David P. Ryan, MD; Wenqing Jiang, MS; Beow Y. Yeap, ScD; Lorraine C. Drapek, NP, PhD; Lawrence S. Blaszkowsky, MD; Eunice L. Kwak, MD, PhD; Jill N. Allen, MD; Jeffrey W. Clark, MD; Jason E. Faris, MD; Andrew X. Zhu, MD, PhD; Lipika Goyal, MD, MPhil; Keith D. Lillemoe, MD; Thomas F. DeLaney, MD; Carlos Fernández-del Castillo, MD; Cristina R. Ferrone, MD; Theodore S. Hong, MD

IMPORTANCE Patients with borderline-resectable pancreatic ductal adenocarcinoma have historically poor outcomes with surgery followed by adjuvant chemotherapy. Evaluation of a total neoadjuvant approach with highly active therapy is warranted.

OBJECTIVE To evaluate the margin-negative (R0) resection rate in borderline-resectable pancreatic ductal adenocarcinoma after neoadjuvant FOLFIRINOX (fluorouracil, irinotecan, and oxaliplatin) therapy and individualized chemoradiotherapy.

DESIGN, SETTING, AND PARTICIPANTS A single-arm, phase 2 clinical trial was conducted at a large academic hospital with expertise in pancreatic surgery from August 3, 2012, through August 31, 2016, among 48 patients with newly diagnosed, previously untreated, localized pancreatic cancer determined to be borderline resectable by multidisciplinary review, who had Eastern Cooperative Oncology Group performance status 0 or 1 and adequate hematologic, renal, and hepatic function. Median follow-up for the analysis was 18.0 months among the 30 patients still alive at study completion.

INTERVENTIONS Patients received FOLFIRINOX for 8 cycles. Upon restaging, patients with resolution of vascular involvement received short-course chemoradiotherapy (5 Gy × 5 with protons) with capecitabine. Patients with persistent vascular involvement received long-course chemoradiotherapy with fluorouracil or capecitabine.

MAIN OUTCOMES AND MEASURES The primary outcome was R0 resection rate; secondary outcomes were median progression-free survival (PFS) and median overall survival (OS).

RESULTS Of the 48 eligible patients, 27 were men and 21 were women, with a median age of 62 years (range, 46-74 years). Of the 43 patients who planned to receive 8 preoperative cycles of chemotherapy, 34 (79%) were able to complete all cycles. Twenty-seven patients (56%) had short-course chemoradiotherapy, while 17 patients (35%) had long-course chemoradiotherapy. R0 resection was achieved in 31 of the 48 eligible patients (65%; 95% CI, 49%-78%). Among the 32 patients who underwent resection, the R0 resection rate was 97% (n = 31). Median PFS among all eligible patients was 14.7 months (95% CI, 10.5 to not reached), with 2-year PFS of 43%; median OS was 37.7 months (95% CI, 19.4 to not reached), with 2-year OS of 56%. Among patients who underwent resection, median PFS was 48.6 months (95% CI, 14.4 to not reached) and median OS has not been reached, with a 2-year PFS of 55% and a 2-year OS of 72%.

CONCLUSIONS AND RELEVANCE Preoperative FOLFIRINOX followed by individualized chemoradiotherapy in borderline resectable pancreatic cancer results in high rates of R0 resection and prolonged median PFS and median OS, supporting ongoing phase 3 trials.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT01591733

JAMA Oncol. 2018;4(7):963-969. doi:10.1001/jamaoncol.2018.0329
Published online May 3, 2018.

Supplemental content

Author Affiliations: Division of Hematology/Oncology, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston (Murphy, Ryan, Jiang, Yeap, Blaszkowsky, Kwak, Allen, Clark, Faris, Zhu, Goyal); Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical School, Boston (Wo, Drapek, DeLaney, Hong); Department of Surgery, Massachusetts General Hospital, Harvard Medical School, Boston (Lillemoe, Fernández-del Castillo, Ferrone).

Corresponding Author: Janet E. Murphy, MD, MPH, Division of Hematology/Oncology, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, 55 Fruit St, Boston, MA 02114 (jemurphy@mgh.harvard.edu).

Pancreatic cancer is a lethal malignant neoplasm, and surgical resection represents the only path to cure. Historically, localized disease has been classified as resectable (no radiographic vascular involvement) or locally advanced (unresectable, with arterial or major venous involvement). More recently, the term *borderline resectable* has been used to describe tumors with potential resectability, but some degree of vascular involvement that may jeopardize a margin-negative (R0) resection.[1] In an attempt to standardize this category of tumor, the National Comprehensive Cancer Network established a definition of borderline resectable disease, characterized by reconstructable venous involvement of the superior mesenteric vein or portal vein, along with abutment but not encasement of arterial structures or removable retroperitoneal structures.[2]

The management of borderline resectable pancreatic cancer has been heterogeneous and based on retrospective series. Historically, chemoradiotherapy had been used to reduce the risk of a positive margin, local recurrence, and metastatic progression. In a retrospective series, of 160 patients who underwent neoadjuvant chemoradiotherapy for borderline resectable pancreatic cancer, 62 patients (39%) achieved an R0 resection.[3] In a review of neoadjuvant therapy for locally advanced and borderline resectable disease at our institution, 29% of patients achieved an R0 resection.[4]

Borderline resectable disease has not historically been treated with intensive neoadjuvant chemotherapy. The FOLFIRINOX regimen (fluorouracil, irinotecan, and oxaliplatin) was introduced in 2011 after a randomized trial comparing it with gemcitabine in patients with stage IV disease. In addition to improving median survival, FOLFIRINOX had a significantly improved objective response rate.[5] Its improved efficacy gave rise to questions of its potential utility in localized disease.

The use of radiotherapy remains controversial, but is recommended in the National Comprehensive Cancer Network guidelines for borderline resectable tumors.[2] Most prior studies used 5 to 6 weeks of radiotherapy in the setting of persistent vessel involvement.[3,4] A phase 2 study using a 1-week course of chemoradiotherapy (25 Gy in 5 fractions with capecitabine) in patients with upfront resectable pancreatic cancer was previously completed at our institution.[6] The current prospective study sought to determine if FOLFIRINOX followed by individualized chemoradiotherapy would produce a higher rate of R0 resection in borderline resectable pancreatic cancer.

Key Points

Question What is the association of total neoadjuvant treatment with chemotherapy and radiotherapy with margin-negative (R0) resection rates in borderline-resectable pancreatic ductal adenocarcinoma?

Findings In this single-arm phase 2 clinical trial of 48 patients, 32 underwent surgery after total neoadjuvant therapy. In this group, 31 patients (97%) achieved R0 resection, a significantly higher rate than historical controls, which translated into a 65% R0 resection rate among all evaluable patients.

Meaning Total neoadjuvant therapy with FOLFIRINOX (fluorouracil, irinotecan, and oxaliplatin) achieves a high rate of R0 resection in patients with borderline-resectable pancreatic ductal adenocarcinoma, a result that correlates with prolonged median progression-free and overall survival.

Methods

Participants

Patients with borderline resectable pancreatic ductal adenocarcinoma were prospectively enrolled in this National Cancer Institute–sponsored clinical trial from August 3, 2012, through August 31, 2016. (The full trial protocol is available in Supplement 1.) Inclusion criteria included biopsy-proven adenocarcinoma of the pancreas, considered by a multidisciplinary team to be radiographically borderline resectable. The study was limited to patients with Eastern Cooperative Oncology Group performance status 0 or 1. Exclusion criteria included ampullary, biliary, or duodenal cancer; presence of metastasis; prior therapy for pancreatic ductal adenocarcinoma; any invasive cancer in the last 5 years requiring radiotherapy or chemotherapy; prior radiotherapy to the upper abdomen; and known deficiency of dihydropyrimidine dehydrogenase. Laboratory evaluation included baseline and serial cancer antigen 19-9 (CA19-9) levels, carcinoembryonic antigen levels, complete blood counts, and liver and renal function tests. Patients were required to have an absolute neutrophil count of 1000 cells/μL or more (to convert to $\times 10^9$ per liter, multiply by 0.001), platelet count of 100×10^3 cells/μL or more (to convert to $\times 10^9$ per liter, multiply by 1.0), aspartate aminotransferase and alanine aminotransferase 2.5 times the upper limit of normal or less, total bilirubin 1.5 times the upper limit of normal or less or 2 consecutive downward trending values if the patient had recent biliary stenting, and serum creatinine within normal range (0.6-1.5 mg/dL [to convert to micromoles per liter, multiply by 88.4]) with a creatinine clearance of 30 mL/min or more. This study was approved by the Dana-Farber Cancer Institute Institutional Review Board. All patients provided written informed consent.

Interventions

FOLFIRINOX Therapy

FOLFIRINOX was administered on a 14-day cycle. Fluorouracil was administered as a 400-mg/m^2 bolus on day 1, then as a 2400-mg/m^2 continuous infusion for 46 hours. Leucovorin calcium, 400 mg/m^2, oxaliplatin, 85 mg/m^2, and irinotecan hydrochloride, 180 mg/m^2, were administered on day 1. Pegfilgrastim, 6 mg, was administered on day 4. Dose adjustments for toxic effects were defined in the protocol. Patients were restaged with computed tomographic (CT) scans of the chest, abdomen, and pelvis after 4 cycles of FOLFIRINOX. Radiographic response to chemotherapy was scored by Response Evaluation Criteria In Solid Tumors (RECIST), version 1.1, criteria.[7]

Protocol Amendment to Total Neoadjuvant Therapy

The study was initially written for patients to receive 4 cycles of FOLFIRINOX prior to chemoradiotherapy and surgery, with

an additional 4 cycles of chemotherapy planned postoperatively. After 6 patients were enrolled with this approach (1 of whom was subsequently ineligible), the study protocol was amended: patients with no progression detected on a restaging CT scan would receive an additional 4 cycles of FOLFIRINOX (total of 8 cycles), with no postoperative chemotherapy planned.

Chemoradiotherapy

After completion of chemotherapy, results of the restaging CT scan were evaluated by the multidisciplinary team. If the tumor was clearly resectable with no vascular involvement, the patient was recommended to receive short-course proton chemoradiotherapy. Standard photon therapy was allowed if protons were not available. If the tumor had persistent vascular involvement, long-course chemoradiotherapy was given.

Target Definition

Gross tumor volume was contoured with the pancreatic protocol CT scan available. Clinical target volume was defined as gross tumor volume with a 1-cm margin, respecting anatomical boundaries such as stomach and transverse colon, as well as elective nodal coverage including the celiac, porta hepatis, superior mesenteric artery and vein, and para-aortic groups. A planning target volume to encompass set-up variability and internal motion was used.

Short-course radiotherapy was delivered to the planning target volume either as a dose of 25 GyE in 5 treatments with protons as previously described[6] or 30 Gy in 10 fractions with photons as described by Katz et al[3] based on resource availability and scheduling. Proton treatments were delivered using 240-MeV protons generated from a cyclotron. Proton beam therapy was delivered using 3-dimensional, passively scattered protons. Most commonly, 3 fields were used, with 2 fields being treated per day. Photon treatments were delivered using intensity modulated radiotherapy using 6-MV photons. Capecitabine, 825 mg/m^2 twice daily, was given Monday through Friday for 2 weeks.

Long-course radiotherapy was delivered to a dose of 50.4 Gy in 28 fractions using intensity modulated radiotherapy. The vascular margin abutting the tumor received a total dose of 58.8 Gy in 28 fractions as previously described.[8] Capecitabine, 825 mg/m^2 twice daily, or fluorouracil continuous infusion, 225 mg/m^2/d, was given Monday through Friday during radiotherapy.

Surgery

Surgery was performed 1 to 3 weeks after short-course radiotherapy or 4 to 8 weeks after long-course radiotherapy. Intraoperative radiotherapy was allowed at the surgeon's discretion. In the cases where intraoperative radiotherapy was used, 10 Gy was given if the tumor was resected, and 15 Gy if the tumor was not resected.

Follow-up

Patients had follow-up visits with laboratory evaluation every 3 months and CT scans every 6 months for the first 2 years, visits with laboratory evaluation every 3 months and an annual CT scan for year 3, and visits with laboratory evaluation every 6 months and an annual CT scan for years 4 and 5. Additional evaluations prompted by symptoms, results of laboratory tests, or the treating physician's discretion were also used to score events.

Pathologic Evaluation

Pathologic findings were scored per standard institutional practices, including margin status (pancreatic transection, biliary, uncinate, and retroperitoneal) and nodal status (total assessed and total positive). The American Joint Committee on Cancer definition of R0 resection, any microscopically positive surgical margin on final pathologic review, was used.[9]

Statistical Analysis

The protocol was designed with 90% power to demonstrate an improvement in the rate of R0 resection to 40% from a historical baseline of 20% if R0 resection was achieved in at least 16 of 50 patients. The decision rule is associated with 3% probability of a type 1 error. We calculated 95% CIs for the rate of R0 resection based on the exact binomial distribution. Progression-free survival and OS were measured starting from the first day of chemotherapy. Overall survival time was censored at the date of last follow-up for patients still alive. Progression-free survival was defined as detection of locoregional recurrence, distant metastases, or death without documented progression, whichever date was earliest, or censored at the date of last follow-up. Rates of OS and PFS were estimated by the Kaplan-Meier method, with 95% CIs obtained by the log-log transformation. Statistical analyses were performed using SAS, version 9.4 (SAS Institute). $P < .05$ (2-sided) was considered significant.

Results

Patient Characteristics

Of the 50 patients enrolled in the study, 48 were eligible. Two patients were ineligible: 1 owing to lung metastases and the other with negative biopsy results on institutional rereview. One patient was excluded before the amendment, and one after. The 5 eligible patients prior to the amendment received 4 cycles of preoperative FOLFIRINOX rather than 8 cycles, and are excluded from the postamendment analysis of efficacy. Patient characteristics, including vascular involvement, can be found in **Table 1**.

Common Terminology Criteria for Adverse Events, version 4.0, toxicity criteria were used for grading.[10] Grade 3 or greater toxicity occurred in 9 of 48 eligible patients (19%) (**Table 2**). The most common severe toxic effects were diarrhea (5 patients), neutropenia (2 patients), and peripheral neuropathy (2 patients). All grade 3 and 4 toxicities were reported during FOLFIRINOX induction, with only grade 1 and 2 toxicities reported during chemoradiotherapy. There were no deaths associated with toxic effects.

Therapy Completion Rates

Of the 48 eligible patients, 39 (81%) received all planned cycles of FOLFIRINOX (with dose modifications per protocol), in-

Table 1. Patient and Tumor Characteristics at Baseline

Characteristic	Patients, No. (%) (N = 48)
Sex	
Male	27 (56)
Female	21 (44)
Age, median (range), y	62 (46-74)
CA19-9 level, U/mL	
Median (range)	97.5 (0-7730)
<35 (normal)	12 (25)
≥35 (elevated)	36 (75)
CEA level, ng/mL	
Median (range)	3.6 (0.6-90.7)
<3.4 (normal)	23 (48)
≥3.4 (elevated)	25 (52)
Tumor site	
Head	35 (73)
Body	11 (23)
Tail	2 (4)[a]
Tumor size, median (range), cm[a]	3.75 (2.1-5.6)
Vessel involvement	
Venous	28 (58)
Arterial	7 (15)
Both	12 (25)
None[b]	1 (2)

Abbreviations: CA19-9, cancer antigen 19-9; CEA, carcinoembryonic antigen.

SI conversion factor: To convert CEA to micrograms per liter, multiply by 1.0; to convert CA19-9 to kilounits per liter, multiply by 1.0.

[a] Including 1 patient with smaller tumor at head of pancreas; analysis based on larger tumor.

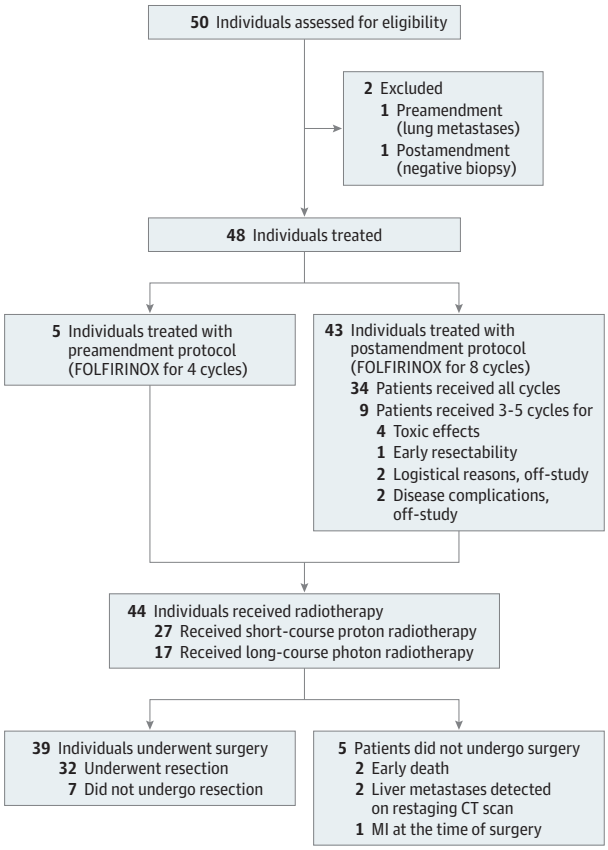
[b] Macroscopic invasion into the right kidney.

Table 2. Preoperative Toxicity of Grade 3 or Worse Related to FOLFIRINOX and Chemoradiotherapy

	Patients, No. (%) (N = 48)	
CTCAE Term	Grade 3	Grade 4
Diarrhea	5 (10)	0
Neutropenia	1 (2)	1 (2)
Febrile neutropenia	1 (2)	0
Lymphopenia	0	1 (2)
Thrombocytopenia	1 (2)	0
Anemia	1 (2)	0
Elevated alkaline phosphatase level	0	1 (2)
Elevated bilirubin level	1 (2)	0
Elevated AST or ALT level	1 (2)	0
Peripheral neuropathy	2 (4)	0
Abdominal pain	1 (2)	0
Constipation	1 (2)	0

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; FOLFIRINOX, fluorouracil, irinotecan, and oxaliplatin.

Figure 1. CONSORT Diagram



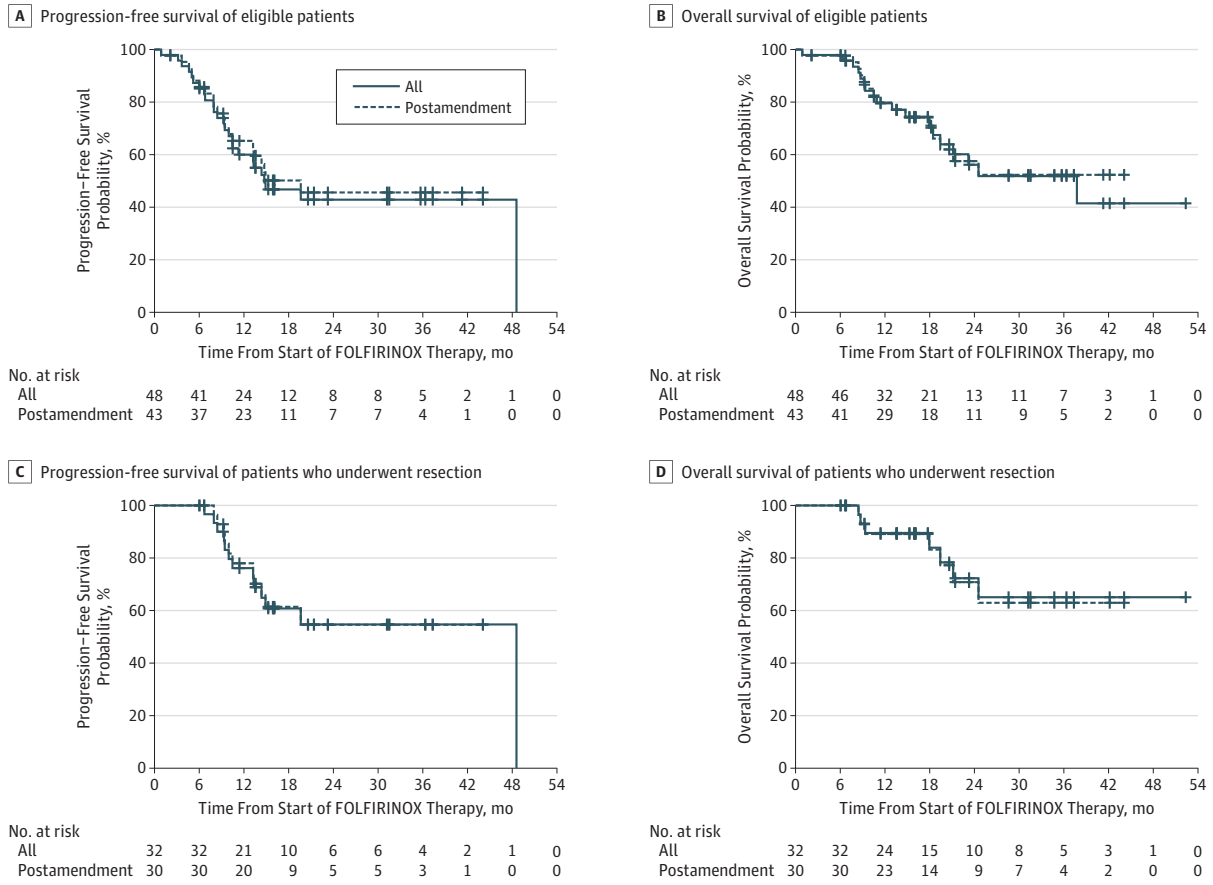
CT indicates computed tomography; FOLFIRINOX, fluorouracil, irinotecan, and oxaliplatin; and MI, myocardial infarction.

cluding the 5 initial patients who completed 4 preoperative cycles and 34 of 43 postamendment patients (79%) who received 8 preoperative cycles. Reasons for not completing chemotherapy were patient withdrawal for logistical reasons (2 patients), physician decision due to development of a large pancreatic cyst (1 patient), small bowel obstruction and sepsis (1 patient), and resectable tumor after resolution of vascular involvement after cycle 4 (1 patient). This last patient was included in the pathologic analysis of the 32 patients who underwent resection. Four patients discontinued chemotherapy owing to toxic effects. A total of 44 of 48 patients (92%) proceeded to chemoradiotherapy: 27 patients (56%) received short-course chemoradiotherapy (15 protons and 12 photons) and 17 patients (35%) received long-course chemoradiotherapy. Therapy completion rates are in **Figure 1**.

Postamendment Radiographic Response Evaluation

Radiographic response to induction chemotherapy was evaluated. Of 43 postamendment patients who were mandated to receive 8 cycles of neoadjuvant FOLFIRINOX, 19 (44%) had a partial response by RECIST criteria, 13 (30%) had a stable disease, and 2 (5%) had progression (liver metastasis). A total of 22 postamendment patients (51%) proceeded to receive short-course radiotherapy based on resolution of vascular involvement, along with the 5 patients who were enrolled before the amendment. As the interval from initiation of short-course radiotherapy to surgical intervention was minimal, restaging before surgery was performed only in patients receiving long-course chemoradiotherapy, with CT scans occurring 4 to 6

Figure 2. Progression-Free Survival and Overall Survival of Eligible Patients and Patients Who Underwent Resection



A, Progression-free survival of eligible patients. B, Overall survival of eligible patients. C, Progression-free survival of patients who underwent resection. D, Overall survival of patients who underwent resection. Dashed lines represent the postamendment subset. FOLFIRINOX indicates fluorouracil, irinotecan, and oxaliplatin.

weeks after completion of therapy. Three of 17 patients had partial response by RECIST criteria, 1 of 17 had progressive local disease in the setting of new liver metastases, and 13 of 17 had stable disease.

Efficacy

R0 resection was achieved in 31 of 48 evaluable patients (65%; 95% CI, 49%-78%) and 29 of 43 postamendment patients (67%; 95% CI, 51%-81%). Among the 32 patients who underwent surgical resection, 31 had an R0 resection. In 5 cases, patients completed chemotherapy and chemoradiotherapy, but pancreatectomy was not possible owing to early death from disease progression (2 patients), liver metastasis detected on restaging CT scan (2 patients), and aborted procedure due to myocardial infarction (1 patient). An additional 7 patients underwent surgical exploration and were found to have unresectable tumor. Among these patients, 3 underwent short-course chemoradiotherapy and were unable to undergo resection owing to vascular encasement. Four patients underwent long-course chemoradiotherapy and were unable to undergo resection owing to intraoperative detection of liver metastases (3 patients) and vascular encasement (1 patient).

Pathologic Findings

In the 32 patients who underwent resection, median pathologic tumor size was 4.9 cm (range, 0.4-14.0 cm). Twelve patients (38%) had positive lymph nodes and 1 patient (3%) had positive margins (eTable in Supplement 2). There were no pathologic complete responses observed in this study, irrespective of the modality of radiotherapy.

Survival and Patterns of Relapse

For all 48 eligible patients, the median PFS was 14.7 months (95% CI, 10.5 to not reached), with 2-year PFS of 43%. For the 43 postamendment patients, median PFS was 19.6 months. Median OS for all 48 eligible patients was 37.7 months (95% CI, 19.4 to not reached), with 2-year OS of 56%; median OS has not been reached for the 43 postamendment patients (**Figure 2**A and B). Median follow-up for the analysis was 18.0 months among the 30 patients still alive. For the 32 eligible patients who underwent resection, median PFS was 48.6 months (95% CI, 14.4 to not reached) and median OS has not been reached, with a 2-year PFS of 55% and a 2-year OS of 72% (Figure 2C and D). The eTable in Supplement 2 shows PFS and OS estimates for all eligible patients and postamendment patients.

Three of 48 eligible patients (6%) experienced isolated locoregional recurrence as the initial site of failure. Eighteen patients (38%) developed distant metastases only, most commonly in the liver (n = 12) and lung (n = 7). Change in CA19-9 levels after neoadjuvant therapy was measured. All patients with normal CA19-9 levels at baseline (<35 U/mL) remained at normal levels after chemotherapy or radiotherapy. Of the 36 patients with elevated CA19-9 levels at baseline, 33 proceeded to chemoradiotherapy; CA19-9 levels in 19 of these patients declined to the normal range after chemotherapy or radiotherapy. However, change in CA19-9 levels was not associated with PFS or OS.

Discussion

In this phase 2 study, a neoadjuvant approach of systemic chemotherapy followed by chemoradiotherapy was used in the treatment of borderline pancreatic cancer, with 2 primary objectives. The first was to enhance the odds of a chance of cure for patients with localized disease by improving rates of R0 resection compared with historical controls. In resectable pancreatic cancer, patients who undergo upfront surgery have a 40% to 70% chance of an R1 resection and a 60% to 80% chance of a node-positive resection, either of which is associated with a cure rate of less than 10%.[1] There is no other gastrointestinal malignancy for which such a high rate of margin-positive resections is tolerated without preoperative therapy.

The second goal was to prolong survival by limiting disease progression locally and distantly with arguably the most active chemotherapy regimen for pancreatic cancer, FOLFIRINOX.[5] By using this more active regimen in this study, the 2-year median PFS and median OS appear substantially better than in historical controls where only adjuvant chemotherapy was used.[11] The profile of toxicity effects of neoadjuvant FOLFIRINOX followed by chemoradiotherapy was favorable, with no single grade 3 toxicity exceeding 10%, and no deaths associated with toxic effects.

To our knowledge, this study represents the largest experience of preoperative FOLFIRINOX in a prospectively identified group of patients with borderline resectable pancreatic cancer. One of the earliest retrospective observational analyses of patients with borderline and locally advanced disease showed a median PFS of 11.7 months and an R0 resection in 5 of 22 patients (23%).[12] The largest evaluation of FOLFIRINOX in localized pancreatic cancer is a meta-analysis of retrospective studies evaluating this regimen in 315 patients with locally advanced disease, which showed a rate of R0 resection of 25.2% and a median OS of 24.2 months.[13] This study did not report on the use of chemoradiotherapy, nor did it evaluate patients with borderline resectable cancer. To our knowledge, the only published prospective evaluation of FOLFIRINOX specifically in patients with borderline resectable cancer is a small feasibility study by Katz et al.[14] This study was somewhat different in design: patients received 4 cycles of FOLFIRINOX, followed by surgery and 2 cycles of adjuvant gemcitabine. In this study, an R0 resection was achieved in 14 of 22 patients (64%), and a median OS of 21 months was reported. In our study, median OS demonstrates modest improvement compared with the study by Katz et al.[14] Although there can be many explanations for the discrepancy in median OS, one major design difference is that in the study by Katz et al,[14] fewer induction cycles of FOLFIRINOX were administered, and only 10 of 22 patients received adjuvant gemcitabine. Given the micrometastatic proclivity of pancreatic cancer, maximizing upfront chemotherapy with FOLFIRINOX during the window of preoperative tolerability may affect survival. In addition, the postoperative rate of positive lymph nodes of 37% among patients who underwent resection is far below the reported rate for patients eligible for upfront resection who undergo immediate surgery (range, 60%-80%[1]). It is widely reported that the strongest prognostic factor is lymph node status. In aggregate, results of our prospective study, in combination with other existing data, suggest a favorable rate of R0 resection in patients with borderline resectable disease compared with prior non–FOLFIRINOX-based studies that have suggested rates of R0 resection of approximately 40%.[3]

The primary confounding factor in interpretability of the rate of R0 resection in this study is the use of individualized radiotherapy. The use of radiotherapy is clearly associated with better local control, but whether this translates into improved OS is the subject of an ongoing intergroup phase 3 trial.[15] In this study, the locoregional recurrence rate of 6% (3 of 48 patients) compares favorably with that in historical controls. In rectal cancer, short- and long-course radiotherapy affords similar rates of local control. Prospective evaluations of short-course regimens (5 Gy × 5 or 3 Gy × 10) in pancreatic and rectal cancers suggest similar rates of R0 resection, are more convenient, and are well tolerated.[6,16] However, because prior prospective experience with short-course radiotherapy was limited to resectable disease, as well as the relatively modest dose in 2-Gy equivalents of 32 Gy for the short-course regimens, it was unclear if short-course radiotherapy would be adequate in the setting of persistent vascular involvement. For this reason, long-course radiotherapy was used because of the higher 2-Gy equivalent (59 Gy) in this higher-risk group to give patients a theoretically better chance of an R0 resection. Since the design of this study, more recent prospective data evaluating stereotactic body radiotherapy (6.6 Gy × 5) have emerged indicating that it is a safe and effective therapy in locally advanced pancreatic cancer with comparable quality of life and reduction of abdominal pain.[17] Although data specific to borderline pancreatic cancer still do not exist, this schedule has been selected in the Alliance A021501 study,[15] in which patients are randomized to undergo 8 cycles of FOLFIRINOX vs 7 cycles of FOLFIRINOX followed by stereotactic body radiotherapy; all patients undergo pancreatectomy and 4 cycles of adjuvant FOLFOX (fluorouracil and oxaliplatin).

Limitations

There are several limitations to this study in addition to the individualized radiotherapy regimens discussed above. First, varying definitions of *R0 resection* in the United States and Europe make it a challenge to benchmark the success of this approach to historical controls; reported rates vary from 14% to 85% based on the surgical series and the definition of R0 vs

R1 (especially whether microscopic tumor is found within 1 mm of the resection margin). Second, pathologic samples were evaluated by several gastrointestinal pathologists, which introduces variability; rereview by a single-blinded pathologist is under way. A counterpoint to the limitations of pathologic evaluation is the objective end point of node positivity: the low rate of positive lymph nodes, known to correlate with survival, supports these findings. Third, the use of intraoperative radiotherapy is a potential confounder that may improve outcomes; as this technology is not widely available, it may limit generalizability. Finally, the median follow-up of 18 months is relatively short, limiting the interpretability of OS relative to PFS; longer-term outcomes will be presented as the data mature.

Conclusions

This prospective evaluation of FOLFIRINOX followed by individualized chemoradiotherapy shows a high rate of R0 resection and prolonged survival. This study supports the design of the phase 3 Alliance trial for borderline pancreatic cancer.

ARTICLE INFORMATION

Accepted for Publication: January 22, 2018.

Published Online: May 3, 2018. doi:10.1001/jamaoncol.2018.0329

Author Contributions: Drs Murphy and Hong had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Murphy, Ryan, Yeap, Clark, Faris, Lillemoe, Fernández-Del Castillo, Hong.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Murphy, Ryan, Yeap, Clark, Hong.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Jiang, Yeap, Hong.
Obtained funding: Ryan, Delaney, Hong.
Administrative, technical, or material support: Murphy, Wo, Ryan, Blaszkowsky, Clark, Zhu.
Study supervision: Ryan, Yeap, Clark, Lillemoe, Fernández-Del Castillo, Ferrone, Hong.

Conflict of Interest Disclosures: Dr Ryan reported serving as a consultant for MPM Capital. Dr Kwak reported active employment for Novartis. Dr Faris reported active employment for Novartis, serving as a consultand for N-of-One and Merrimack Pharmaceuticals, and receiving clinical trial funding from Exelixis, Takeda, and Roche. No other disclosures were reported.

Funding/Support: This study was funded by National Institutes of Health Proton Beam National Cancer Institute/Federal Share Program grant CO6-CA05926 and in part by the Cancer Clinical Investigator Team Leadership Award awarded by the National Cancer Institute through a supplement to grant P30CA006516 (Dr Hong).

Role of the Funder/Sponsor: The funding sources are aware of, and approve, the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, and approval of the manuscript; and decision to submit the manuscript for publication.

REFERENCES

1. Ryan DP, Hong TS, Bardeesy N. Pancreatic adenocarcinoma. *N Engl J Med*. 2014;371(11):1039-1049.

2. National Comprehensive Cancer Network. NCCN guidelines. https://www.nccn.org/professionals/physician_gls/default.aspx. Accessed March 15, 2018.

3. Katz MH, Pisters PW, Evans DB, et al. Borderline resectable pancreatic cancer: the importance of this emerging stage of disease. *J Am Coll Surg*. 2008;206(5):833-846.

4. Arvold ND, Ryan DP, Niemierko A, et al. Long-term outcomes of neoadjuvant chemotherapy before chemoradiation for locally advanced pancreatic cancer. *Cancer*. 2012;118(12):3026-3035.

5. Conroy T, Desseigne F, Ychou M, et al; Groupe Tumeurs Digestives of Unicancer; PRODIGE Intergroup. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med*. 2011;364(19):1817-1825.

6. Hong TS, Ryan DP, Borger DR, et al. A phase 1/2 and biomarker study of preoperative short course chemoradiation with proton beam therapy and capecitabine followed by early surgery for resectable pancreatic ductal adenocarcinoma. *Int J Radiat Oncol Biol Phys*. 2014;89(4):830-838.

7. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247. doi:10.1016/j.ejca.2008.10.026

8. Wo JY, Niemierko A, Ryan DP, et al. Tolerability and long-term outcomes of dose-painted neoadjuvant chemoradiation to regions of vessel involvement in borderline or locally advanced pancreatic cancer [published online January 27, 2017]. *Am J Clin Oncol*. 2017. doi:10.1097/COC.0000000000000349

9. American Joint Committee on Cancer. AJCC cancer staging manual. 7th ed. https://cancerstaging.org/references-tools/deskreferences/Documents/AJCC%207th%20Ed%20Cancer%20Staging%20Manual.pdf. Accessed March 15, 2018.

10. National Cancer Institute. Common terminology criteria for adverse events (CTCAE) v4.0. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_40. Accessed March 15, 2018.

11. Hammel P, Huguet F, van Laethem JL, et al; LAP07 Trial Group. Effect of chemoradiotherapy vs chemotherapy on survival in patients with locally advanced pancreatic cancer controlled after 4 months of gemcitabine with or without erlotinib. *JAMA*. 2016;315(17):1844-1853.

12. Faris JE, Blaszkowsky LS, McDermott S, et al. FOLFIRINOX in locally advanced pancreatic cancer: the Massachusetts General Hospital Cancer Center experience. *Oncologist*. 2013;18(5):543-548.

13. Suker M, Beumer BR, Sadot E, et al. FOLFIRINOX for locally advanced pancreatic cancer: a systematic review and patient-level meta-analysis. *Lancet Oncol*. 2016;17(6):801-810.

14. Katz MH, Shi Q, Ahmad SA, et al. Preoperative modified FOLFIRINOX treatment followed by capecitabine-based chemoradiation for borderline resectable pancreatic cancer: Alliance for Clinical Trials in Oncology Trial AO21101. *JAMA Surg*. 2016;151(8):e161137.

15. Clinicaltrials.gov. Combination chemotherapy with or without hypofractionated radiation therapy before surgery in treating patients with pancreatic cancer. https://clinicaltrials.gov/ct2/show/NCT02839343. Accessed March 15, 2018.

16. Marijnen CAM, Nagtegaal ID, Kapiteijn E, et al; Cooperative investigators of the Dutch Colorectal Cancer Group. Radiotherapy does not compensate for positive resection margins in rectal cancer patients: report of a multicenter randomized trial. *Int J Radiat Oncol Biol Phys*. 2003;55(5):1311-1320.

17. Herman JM, Chang DT, Goodman KA, et al. Phase 2 multi-institutional trial evaluating gemcitabine and stereotactic body radiotherapy for patients with locally advanced unresectable pancreatic adenocarcinoma. *Cancer*. 2015;121(7):1128-1137.