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Total Neoadjuvant Therapy With FOLFIRINOX in Combination With Losartan Followed by Chemoradiotherapy for Locally Advanced Pancreatic Cancer
A Phase 2 Clinical Trial

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IMPORTANCE Patients with locally advanced pancreatic cancer have historically poor outcomes. Evaluation of a total neoadjuvant approach is warranted.

OBJECTIVE To evaluate the margin-negative (R0) resection rate of neoadjuvant FOLFIRINOX (fluorouracil, leucovorin, oxaliplatin, and irinotecan) and losartan followed by chemoradiotherapy for locally advanced pancreatic cancer.

DESIGN, SETTING, AND PARTICIPANTS A single-arm phase 2 clinical trial was conducted at a large academic hospital from August 22, 2013, to May 22, 2018, among 49 patients with previously untreated locally advanced unresectable pancreatic cancer as determined by multidisciplinary review. Patients had Eastern Cooperative Oncology Group performance status 0 or 1 and adequate hematologic, renal, and hepatic function. Median follow-up for the analysis was 17.1 months (range, 5.0-53.7) among 27 patients still alive at study completion.

INTERVENTIONS Patients received FOLFIRINOX and losartan for 8 cycles. Patients with radiographically resectable tumor after chemotherapy received short-course chemoradiotherapy (5 GyE × 5 with protons) with capecitabine. Patients with persistent vascular involvement received long-course chemoradiotherapy (50.4 Gy with a vascular boost to 58.8 Gy) with fluorouracil or capecitabine.

MAIN OUTCOMES AND MEASURES R0 resection rate.

RESULTS Of the 49 patients (26 women and 23 men; median age 63 years [range, 42-78 years]), 39 completed 8 cycles of FOLFIRINOX and losartan; 10 patients had fewer than 8 cycles due to progression (5 patients), losartan intolerance (3 patients), and toxicity (2 patients). Seven patients (16%) had short-course chemoradiotherapy while 38 (84%) had long-course chemoradiotherapy. Forty-two (86%) patients underwent attempted surgery, with R0 resection achieved in 34 of 49 patients (69%; 95% CI, 55%-82%). Overall median progression-free survival was 17.5 months (95% CI: 13.9-22.7) and median overall survival was 31.4 months (95% CI, 18.1-38.5). Among patients who underwent resection, median progression-free survival was 21.3 months (95% CI, 16.6-28.2), and median overall survival was 33.0 months (95% CI, 31.4 to not reached).

CONCLUSIONS AND RELEVANCE Total neoadjuvant therapy with FOLFIRINOX, losartan, and chemoradiotherapy provides downstaging of locally advanced pancreatic ductal adenocarcinoma and is associated with an R0 resection rate of 61%.

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Supplemental content

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Pancreatic cancer is a lethal malignant neoplasm, and surgical resection represents the only path to cure. Locally advanced pancreatic ductal adenocarcinoma (LAPC) has been classified as unresectable with conventional surgical techniques and has historically been classified on a continuum of metastatic disease. Combination therapy with gemcitabine and chemoradiotherapy (CRT) has rarely provided tumor downstaging and conversion to resectability. The improved efficacy of the FOLFIRINOX (fluorouracil, leucovorin, oxaliplatin, and irinotecan) regimen raised the question of its potential utility for downstaging LAPC to surgical resection.[1] Several studies have evaluated neoadjuvant FOLFIRINOX in borderline resectable and locally advanced disease, demonstrating increased surgical conversion rates.[2-6]

Preclinical data suggest that manipulating the renin-angiotensin system may have antitumor associations with pancreatic cancer. In addition to governing renal and cardiovascular homeostasis, the renin-angiotensin system mediates cell proliferation, metabolism, and growth.[7,8] Moreover, the renin-angiotensin system has been associated with tumor growth and progression in various cancers (with expression on tumor cells).[7,8] Renin-angiotensin system activation in fibroblasts increases tumor fibrosis and desmoplasia, a key feature of LAPC, via the transforming growth factor β (TGF-β) pathway. The primary effector of the renin-angiotensin system is angiotensin II. Inhibition of the renin-angiotensin system activity is achieved by angiotensin I receptor blockers (ARBs), such as losartan. These drugs have the potential to both reduce the malignant potential of cancer cells and alter the tumor microenvironment, activating immunity and normalizing the extracellular matrix to allow for enhanced delivery of cytotoxic chemotherapy.[8-12] Retrospective observational cohort studies suggest that patients with pancreatic cancer who were already taking angiotensin-converting enzyme inhibitors or ARBs because of preexisting cardiovascular disease had longer survival.[13]

The purpose of this study was to prospectively evaluate losartan with neoadjuvant FOLFIRINOX followed by individualized CRT in patients with LAPC. The primary end point was the margin-negative (R0) resection rate, with secondary end points of safety, progression-free survival (PFS), overall survival (OS), and circulating biomarkers of response.

Key Points

Question What is the association of total neoadjuvant treatment with FOLFIRINOX (fluorouracil, leucovorin, oxaliplatin, and irinotecan), losartan, and chemoradiation therapy with margin-negative (R0) resection rates in patients with locally advanced pancreatic adenocarcinoma?

Findings In this single-arm phase 2 trial of 49 patients, the R0 resection rate was 61% among all eligible participants. Thirty-four of 49 patients underwent surgical resection, with 30 of 49 achieving R0 resection in this subset.

Meaning Total neoadjuvant FOLFIRINOX and losartan followed by chemoradiotherapy was associated with an R0 resection rate that exceeded expectations in this historically incurable disease, an outcome associated with prolonged progression-free and overall survival.

Methods

Participants

Patients with previously untreated LAPC were enrolled in this National Cancer Institute–sponsored single-arm phase 2 clinical trial from August 22, 2013, to May 22, 2018. This study was approved by the Dana-Farber Cancer Institute Institutional Review Board. All patients provided written informed consent. Inclusion criteria included biopsy-proved adenocarcinoma of the pancreas considered to be locally advanced by a multidisciplinary team. Locally advanced tumors were included based on the National Comprehensive Cancer Network definition.[14] The study was limited to patients with Eastern Cooperative Oncology Group performance status 0 or 1 and adequate hematologic, renal, and hepatic function. Key exclusion criteria included ampullary, biliary, or duodenal cancer; presence of metastasis; evidence of unresectable nodal metastasis; taking an angiotensin-converting enzyme inhibitor or an ARB at the time of study enrollment; prior therapy for pancreatic ductal adenocarcinoma; invasive cancer in the last 5 years requiring radiotherapy or chemotherapy; prior radiotherapy to the upper abdomen; and known dihydropyrimidine dehydrogenase deficiency. 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.

Interventions

FOLFIRINOX Therapy

FOLFIRINOX was administered for 8 cycles 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 (Supplement 1). Patients were restaged with computed tomographic (CT) scans of the chest, abdomen, and pelvis after 4 and 8 cycles of FOLFIRINOX. Radiographic response to chemotherapy was scored by Response Evaluation Criteria In Solid Tumors (RECIST), version 1.1 criteria.[15]

Losartan

Tolerance of losartan was established during a 1-week trial dose period of 25 mg orally taken daily starting on cycle 1 day 1. If this dose was tolerated during week 1 (based on meeting or exceeding baseline minimum mean arterial pressure criterion),

it was increased to 50 mg orally taken daily at cycle 1, day 8 and continued at this dose daily until the completion of cycle 8, day 14 of FOLFIRINOX treatment. Patients were monitored for drug-related hyperkalemia. Detailed methods and dose modification are listed in Supplement 1.

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 CRT. Standard photon therapy was allowed if protons were not available. If the tumor had persistent vascular involvement, long-course CRT was given.

Target Definition

Gross tumor volume was contoured with the available pancreatic protocol CT scan. Clinical target volume was defined as gross tumor volume with a 1-cm margin, respecting anatomical boundaries, such as the 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 GyE per fraction treatments with protons as previously described[6,16] or 30 Gy in 10 fractions with photons[6,17] 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 by 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.[18] 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 CRT or 4 to 8 weeks after long-course CRT. Intraoperative radiotherapy was allowed at the surgeon's discretion. In the cases in which 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 annual CT for year 3, and visits with laboratory evaluation every 6 months and annual CT for years 4 and 5. Additional evaluations prompted by symptoms, results of laboratory evaluation, or the treating physician's discretion were also used to score events.

Circulating Biomarker Evaluation

A critical mechanism of action of losartan is the inhibition of thrombospondin-1 (TSP1)–mediated activation of latent TGF-β.[9,10] Baseline and serial plasma draws were completed on day 1 and day 8 and at FOLFIRINOX cycles 3, 5, 7, and 8. To capture levels, transformed mink lung epithelial cell TGF-β reporter cells were cultured in medium containing fetal bovine serum for 4 hours, after which the medium was replaced with diluted patient serum samples and incubated for 20 hours.[19] Total TGF-β was prepared by acid activation using 4N HCl, which was neutralized using 4N NaOH,[20] and assessed using a 1:1000 dilution of activated patient serum sample in serum-free medium with 0.1% bovine serum albumin. The TGF-β reporter luciferase assay was performed according to manufacturer's instructions (Promega, luciferase Assay System, E1500).[21] Baseline TGF-β concentrations were calculated using a standard curve established using recombinant TGF-β (Peprotech). The levels of TSP1 in plasma were measured with an enzyme-linked immunosorbent assay (ELISA) (R&D Systems).

Pathologic Evaluation

Pathologic findings were scored per standard institutional practices, including margin status (pancreatic transection, biliary, uncinate, and retroperitoneal) and nodal status (total assessed, total positive). The American Joint Committee on Cancer definition of R0 resection, any microscopically positive surgical margin on final pathologic review, was used.[22]

Statistical Analysis

The protocol was designed to demonstrate an improvement in the rate of R0 resection to 25% from a historical baseline of 10% or lower. We calculated 95% CIs for the rate of R0 resection based on the exact binomial distribution. The change in plasma levels of TSP1 and TGF-β from pretreatment levels was expressed as fold-change from the nadir during chemotherapy and analyzed using the signed rank for a 2-sided hypothesis. Total TGF-β assays below the minimum detection limit were analyzed as the lowest detectable level. The PFS and OS were measured starting from the first day of chemotherapy. The OS 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 the 95% CIs obtained by log-log transformation. Two-sided *P* values were reported only for the biomarker analysis. As the biomarker analysis was exploratory and not designed to test an a priori hypothesis, no prespecified level of statistical significance was set. Statistical analyses were performed using SAS, version 9.4 (SAS Institute) and R, version 3.3.1 (R Foundation).

Table 1. Patient and Tumor Characteristics at Baseline in 49 Eligible Patients

Characteristic	No. (%)
Sex	
Male	23 (47)
Female	26 (53)
Age, median (range), y	63 (42-78)
ECOG PS	
0	36 (73)
1	13 (27)
CA19-9, U/mL	
Median (range)	167 (1-8478)
<35 Normal	9 (18)
≥35 Elevated	40 (82)
CEA level, ng/mL[a]	
Median (range)	2.7 (0.5-57.9)
<3.4 Normal	30 (62)
≥3.4 Elevated	18 (38)
Tumor site	
Head	31 (63)
Body	14 (29)
Tail	4 (8)
Tumor size, median (range), mm	41 (18-68)
Vascular involvement (n = 47)	
Arterial alone	15 (31)
Venous alone	11 (22)
Arterial + venous	21 (43)

Abbreviations: CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; ECOG PS, Eastern Cooperative Oncology Group performance status.

[a] Patient 37 not evaluated.

Table 2. Preoperative Toxicity of Grade 3 or Worse Related to FOLFIRINOX-Losartan and Chemoradiotherapy-Losartan in 49 Eligible Patients

	No. (%)	
CTCAE Term	Grade 3	Grade 4
Neutropenia	5 (10)	2 (4)
Febrile neutropenia	2 (4)	0
Thrombocytopenia	6 (12)	1 (2)
Leukopenia	0	2 (4)
Anemia	3 (6)	0
Elevated AST/ALT	2 (4)	1 (2)
Elevated alkaline phosphatase	1 (2)	0
Diarrhea	7 (14)	0
Nausea/vomiting	4 (8)	0
Abdominal pain	2 (4)	0
Colitis	1 (2)	0
Mucositis, oral	1 (2)	0
Dehydration	2 (4)	0
Hypokalemia	2 (4)	0
Hyponatremia	1 (2)	0
Fatigue	2 (4)	0
Weakness	1 (2)	0
Weight loss	1 (2)	0
Myocardial infarction	1 (2)	0
Ataxia	1 (2)	0
Worst overall	20 (41)	5 (10)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events.

Results

Patient Characteristics

Of the 50 patients enrolled in the study from August 2013 through May 2018, all were eligible, but 1 patient withdrew consent before treatment for a total of 49 patients (26 women and 23 men; median age 63 years [range, 42-78 years]). Patient and tumor characteristics, including location, size, and vascular involvement, can be found in **Table 1**.

Common Terminology Criteria for Adverse Events, version 3.0 toxicity criteria, were used for grading.[23] Grade 3 or greater toxicity occurred in 25 of 49 eligible patients (51%) (**Table 2**). The most common severe toxic effects were neutropenia (7 patients), thrombocytopenia (7 patients), diarrhea (7 patients), and nausea/vomiting (4 patients). Grades 1 and 2 peripheral neuropathy were prevalent (36 and 5 patients, respectively), but no grade 3 or higher peripheral neuropathy was reported. No single grade 3 or greater toxic effect occurred in more than 14% of patients. All grades 3 and 4 toxic effects were reported during FOLFIRINOX induction, with only grades 1 and 2 toxic effects reported during CRT. There were no deaths associated with toxic effects.

Treatment Completion Rates

Of the 49 eligible patients, 39 (80%) received all 8 cycles of FOLFIRINOX and losartan. Ten patients had between 1 and 7 cycles. Of these, 3 patients experienced hypotension after losartan treatment; all continued on the study. Two patients experienced toxicity, 1 of whom discontinued enrollment before CRT. Five patients had progression during chemotherapy, 3 of whom discontinued treatment: 1 with peritoneal spread and 2 with local progression. Two patients with local progression proceeded to CRT. Of the 49 eligible patients, 45 (92%) proceeded to CRT, including 6 patients who received fewer than 8 cycles. Seven (16%) patients received short-course CRT, and 38 (84%) received long-course CRT (**Figure 1**).

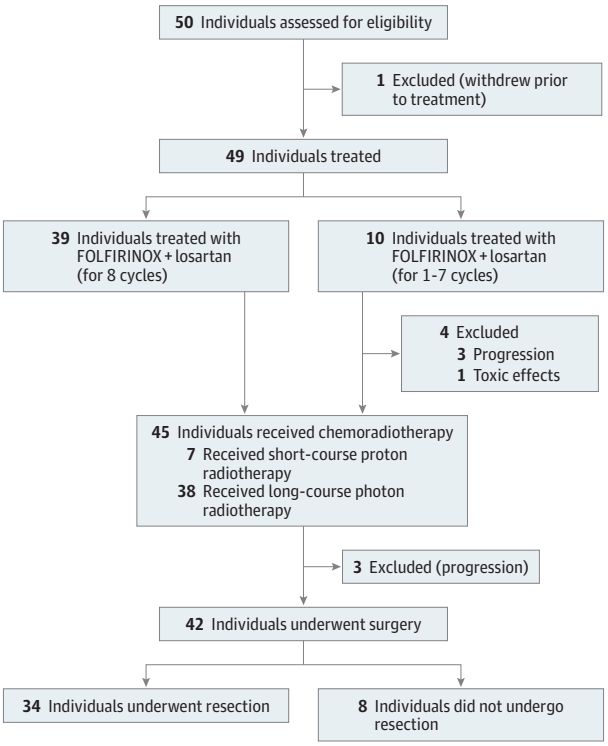
Radiographic Response Evaluation

Radiographic response was measured with RECIST 1.1 after completion of FOLFIRINOX and losartan, with 47 patients evaluated; follow-up scans were missing for 2 patients who discontinued chemotherapy early because of losartan intolerance. One patient (2%) had a radiographic complete response. Twenty-three patients (49%) had a partial response, while 21 (45%) had stable disease. Two patients (4%) had progressive disease by RECIST criteria. **Figure 2** shows the degree of radiographic response.

Efficacy

Among 49 evaluable patients, 34 (69%; 95% CI, 55%-82%) underwent resection, while 15 patients remained unresectable, including 4 who did not proceed to CRT but went off-study after

Figure 1. CONSORT Diagram



Flowchart of enrolled patients; those who completed chemotherapy with FOLFIRINOX (fluorouracil, leucovorin, oxaliplatin, and irinotecan); those who proceeded to photon or proton radiation; and those who proceeded to attempted surgical resection.

fewer than 8 cycles of neoadjuvant FOLFIRINOX and losartan. In 3 patients who received chemotherapy and CRT, resection was not attempted due to early progression by imaging. In total, 42 patients were taken to surgery. Eight patients were surgically explored but did not undergo resection because of persistent vascular invasion (5 patients), metastatic disease (2 patients), or extensive vessel collateralization (1 patient). R0 resection was achieved in 30 of 49 patients (61%; 95% CI, 46%-75%) of evaluable patients. Among patients who underwent surgical resection, 30 of 34 (88%; 95% CI, 73%-97%) patients had an R0 resection. Only 5 patients required vessel resection with reconstruction: 4 of the portal or superior mesenteric vein and 1 of the hepatic artery.

Pathologic Findings

In the 34 patients who underwent resection, median pathologic tumor size was 1.8 cm (range, 0.0-6.2 cm). Nine patients (26%) had positive lymph nodes, and 4 patients (12%) had positive margins (eTable 1 in Supplement 2). There were pathologic complete responses in 3 patients, corresponding to 6% of evaluable patients (95% CI, 1%-17%) and 9% of patients who underwent resection (95% CI, 2%-24%).

Survival and Patterns of Relapse

Median follow-up for the analysis was 17.1 months (range, 5.0-53.7) among the 27 patients still alive. For all 49 eligible patients, the median PFS was 17.5 months (95% CI, 13.9-22.7), while median OS was 31.4 months (95% CI, 18.1-38.5) (**Figure 3**A and B). For the 34 patients who underwent resection, median PFS was 21.3 months (95% CI, 16.6-28.2), and median OS was 33.0 months (95% CI, 31.4 to not reached) (Figure 3C-D). eTable 2 in Supplement 2 shows PFS and OS estimates for all eligible patients and patients who underwent resection. Among patients who underwent resection (N = 34), 17 (50%) remain alive with no relapse. Two died but without relapse. Five patients (15%) had local relapse only, while 10 (29%) had distant progression in liver, lungs, metastatic lymph nodes, and peritoneal cavity.

Circulating Biomarker Analyses

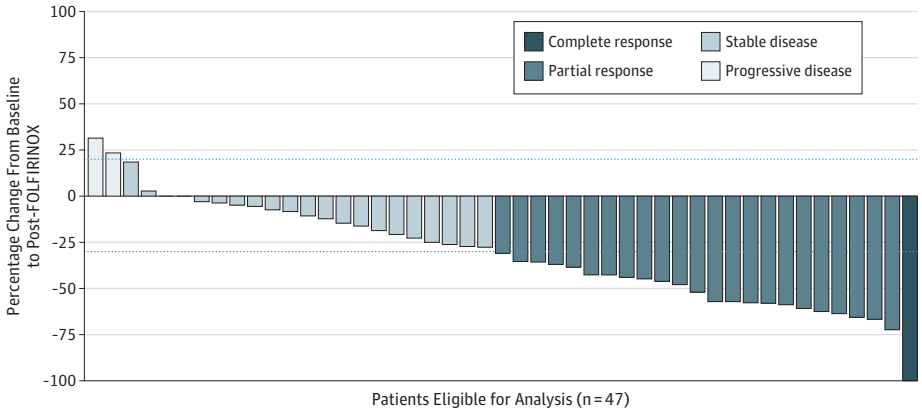
TGF-β and TSP1 pretreatment levels were measured respectively in 41 and 45 patients, with serial measurements obtained on 40 and 44 patients. At baseline, median level of total TGF-β was 285 pg/mL (range, 4.5-2073 pg/mL) and the median TSP1 was 1528 ng/mL (range, 94.6-5000 ng/mL). Compared with pretreatment levels, FOLFIRINOX and losartan were associated with a significant decrease in plasma levels of TGF-β (with a median fold-change of 0.34 [range, 0.01-9.31; $P < .001$] at the nadir during chemotherapy) and TSP1 (with a median fold-change of 0.34 [range, 0.01-3.17; $P < .001$] at the nadir). The TGF-β and TSP1 levels were higher than pretreatment levels in only 2 and 4 patients, respectively.

Discussion

Locally advanced pancreatic ductal adenocarcinoma is generally considered an incurable presentation of pancreatic cancer. In the LAP07 study, in which patients with LAPC were randomized to gemcitabine with or without erlotinib with or without CRT, median OS was 13.6 months (gemcitabine alone) and 11.9 months (gemcitabine/erlotinib), with only 4% of patients downstaged to pancreatectomy.[24] After the introduction of FOLFIRINOX for metastatic disease, a multidisciplinary team composed of surgeons, radiation oncologists, and medical oncologists launched 2 concurrent phase 2 studies in borderline resectable pancreatic cancer and LAPC.[6] Both studies used the same platform of neoadjuvant FOLFIRINOX for 8 cycles followed by CRT and then surgical attempt. Losartan was included in the LAPC study based on preclinical data showing that inhibition of the renin-angiotensin system signaling may enhance the delivery of chemotherapy to the tumor and the efficacy of CRT by diminishing peritumoral stroma and increasing perfusion.

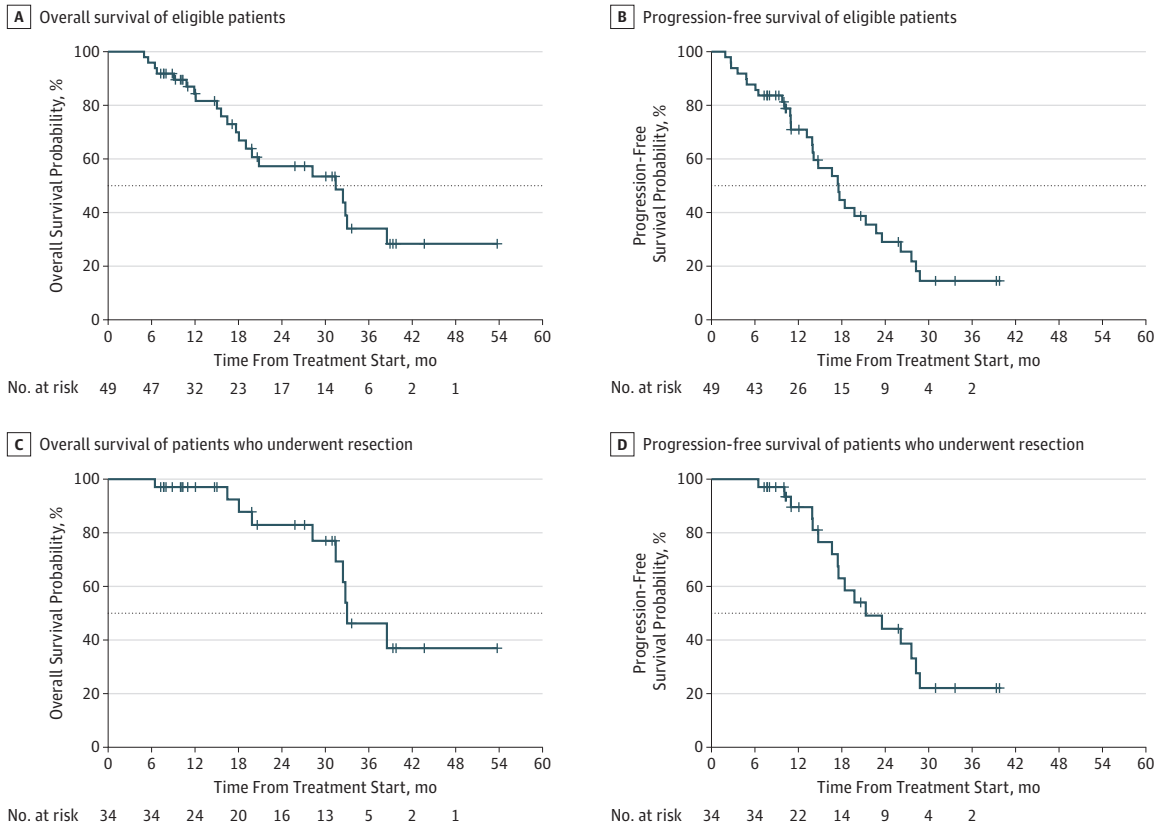
Because surgical resection is central to cure, we chose the R0 resection rate as our primary outcome in the current study. To our knowledge, this is the first study of LAPC with a surgical primary end point. Retrospective experience with induction FOLFIRINOX followed by CRT in LAPC has been reported by other centers. A review of 415 patients with LAPC included 189 patients treated with induction FOLFIRINOX; of these, 53 underwent attempted surgical resection, while 136 were managed medically.[5] In a meta-analysis of 13 studies of FOLFIRINOX in LAPC (with variable administration of CRT), the pooled propor-

Figure 2. Waterfall Plot of Percentage Change in Tumor Dimension



The dashed line above the x-axis represents 20% increase in sum of target lesions from baseline (disease progression), and dashed line below the x-axis represents 30% decrease in sum of target lesions from baseline (partial response). Twenty-three patients (47%) had a partial response, while 21 (43%) had stable disease for an overall disease control rate of 96%. Two patients (4%) had progressive disease.

Figure 3. Survival Curves



A, Overall survival among evaluable patients (n = 49). B, Progression-free survival among evaluable patients (n = 49). C, Overall survival among patients who underwent resection (n = 34). D, Progression-free survival among patients who underwent resection (n = 34).

tion of patients undergoing resection attempt was 25.9%, of whom 74% achieved R0 resection.[4] In the last decade, there has been increased awareness that patients with borderline resectable disease and LAPC represent a continuum, and a more assertive surgical approach, often involving periadventitial dissections and vascular resections with reconstruction, is used in some centers of excellence. In the current study, the R0 resection rate was 61% among 49 evaluable patients and 88% of patients who underwent resection, achieved despite a low frequency of major vessel resection and reconstruction (15%). While limited by relatively small numbers, this outcome represents a new benchmark in this disease. Surgical resection is associated with PFS and OS rates that exceed historical data. There are multiple potential drivers of this outcome, such as highly active chemotherapy, the addition of losartan, and individualized CRT strategy.

In a parallel study using FOLFIRINOX with CRT (without losartan) in 48 patients with borderline resectable disease, R0 resection was achieved in 31 of 48 eligible patients (65%).[6] However, because the rate of surgical resection is higher by definition in borderline resectable disease compared with LAPC, the analogous R0 rate in patients with LAPC in the current study suggests a possible additional benefit from losartan. This supposition is further supported by the median PFS (14.7 months) and median OS (37.7 months) in patients with borderline resectable disease after neoadjuvant FOLFIRINOX and CRT, similar to LAPC. Moreover, there were 3 pathologic complete responses in the LAPC study and none in the borderline analysis. While FOLFIRINOX may account for these findings, the degree of benefit seen in patients with inherently more advanced disease suggests that inhibition of the renin-angiotensin system signaling with losartan may be associated with an antitumor effect.

This conclusion is supported by our biomarker analysis. Treatment with FOLFIRINOX and losartan was associated with significant decreases in plasma TSP1 and TGF-β levels, which is highly suggestive of biologic activity; isolating the impact of losartan from chemotherapy will be the focus of a correlative biomarker analysis in an upcoming randomized clinical trial. Analysis of in situ levels from operative samples was not possible because the tissue integrity is significantly compromised by preoperative radiotherapy. Measuring intratumoral biomarkers (with a second postchemotherapy and preradiotherapy biopsy) will potentially provide more insight into the changes in signaling and expression of key markers of excessive matrix deposition (desmoplasia) as well as activation of adaptive and innate immunity.

Individualized CRT may have also contributed to these results. The role of neoadjuvant or adjuvant radiation in LAPC remains unclear. Interim analysis from the Preoperative Chemoradiotherapy Versus Immediate Surgery for Resectable and Borderline Resectable Pancreatic Cancer (PREOPANC-1)[25] study shows a significant improvement in R0 resection rate, local recurrence rate, and median disease-free survival with neoadjuvant CRT compared with surgery alone in resectable and borderline resectable disease. However, because prior prospective experience with short-course radiotherapy was limited to resectable disease,[16,17] it was unclear if short-course treatment would be adequate in the setting of vascular involvement. We therefore administered long-course radiotherapy in the setting of persistent vascular involvement after 4 months of FOLFIRINOX to potentially enhance the odds of an R0 resection. Local control was achieved in most patients who underwent resection, with 5 patients (15%) relapsing only locally after R0 resection in all but 1 patient. In contrast, our borderline resectable disease study demonstrated a local recurrence rate of 6%.

Limitations

Lack of randomization in a single-arm phase 2 clinical trial limits our ability to assess the specific role of losartan in the degree of benefit seen in LAPC patients. The comparison with a parallel study in borderline resectable disease offers some insights. Similar pathology (except for disease extent), chemotherapy (save losartan administration), CRT, and surgical treatments suggest that losartan may be associated with LAPC downstaging and favorable survival outcomes.

Conclusions

This prospective evaluation of FOLFIRINOX and losartan therapy followed by individualized CRT showed a high rate of R0 resection and prolonged survival rates in LAPC. This study supports the design of a multicenter randomized phase 2 study using these agents alone or with immunotherapy, which is now under way (NCT03563248).

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REFERENCES

1. 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. doi:10.1056/NEJMoa1011923

2. 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 A021101. *JAMA Surg*. 2016;151(8):e161137. doi:10.1001/jamasurg.2016.1137

3. Petrelli F, Coinu A, Borgonovo K, et al; Gruppo Italiano per lo Studio dei Carcinomi dell'Apparato Digerente (GISCAD). FOLFIRINOX-based neoadjuvant therapy in borderline resectable or unresectable pancreatic cancer: a meta-analytical review of published studies. *Pancreas*. 2015;44(4):515-521. doi:10.1097/MPA.0000000000000314

4. 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. doi:10.1016/S1470-2045(16)00172-8

5. Gemenetzis G, Groot VP, Blair AB, et al. Survival in locally advanced pancreatic cancer after neoadjuvant therapy and surgical resection [published online June 18, 2018]. *Ann Surg*. 2018. doi:10.1097/SLA.0000000000002753

6. Murphy JE, Wo JY, Ryan DP, et al. Total neoadjuvant therapy with FOLFIRINOX followed by individualized chemoradiotherapy for borderline resectable pancreatic adenocarcinoma: a phase 2 clinical trial. *JAMA Oncol*. 2018;4(7):963-969. doi:10.1001/jamaoncol.2018.0329

7. George AJ, Thomas WG, Hannan RD. The renin-angiotensin system and cancer: old dog, new tricks. *Nat Rev Cancer*. 2010;10(11):745-759. doi:10.1038/nrc2945

8. Pinter M, Jain RK. Targeting the renin-angiotensin system to improve cancer treatment: implications for immunotherapy. *Sci Transl Med*. 2017;9(410):eaan5616. doi:10.1126/scitranslmed.aan5616

9. Chauhan VP, Martin JD, Liu H, et al. Angiotensin inhibition enhances drug delivery and potentiates chemotherapy by decompressing tumour blood vessels. *Nat Commun*. 2013;4:2516. doi:10.1038/ncomms3516

10. Diop-Frimpong B, Chauhan VP, Krane S, Boucher Y, Jain RK. Losartan inhibits collagen I synthesis and improves the distribution and efficacy of nanotherapeutics in tumors. *Proc Natl Acad Sci U S A*. 2011;108(7):2909-2914. doi:10.1073/pnas.1018892108

11. Liu J, Liao S, Diop-Frimpong B, et al. TGF-β blockade improves the distribution and efficacy of therapeutics in breast carcinoma by normalizing the tumor stroma. *Proc Natl Acad Sci U S A*. 2012;109(41):16618-16623. doi:10.1073/pnas.1117610109

12. Kumar V, Boucher Y, Liu H, et al. Noninvasive assessment of losartan-induced increase in functional microvasculature and drug delivery in pancreatic ductal adenocarcinoma. *Transl Oncol*. 2016;9(5):431-437. doi:10.1016/j.tranon.2016.07.004

13. Liu H, Naxerova K, Pinter M, et al. Use of angiotensin system inhibitors is associated with immune activation and longer survival in nonmetastatic pancreatic ductal adenocarcinoma. *Clin Cancer Res*. 2017;23(19):5959-5969. doi:10.1158/1078-0432.CCR-17-0256

14. National Comprehensive Cancer Network practice guidelines in oncology for pancreatic adenocarcinoma-v. 1. November 2008. http://www.nccn.org. Accessed March 15, 2018.

15. 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

16. Hong TS, Ryan DP, Borger DR, et al. A phase 1/2 and biomarker study of preoperative short course chemoradiotherapy with proton beam therapy and capecitabine followed by early surgery for resectable pancreatic ductal adenocarcinoma. *Int J Radiat Oncol Biol Phys*. 2014;89:803-808. doi:10.1016/j.ijrobp.2014.03.034

17. Wo JY, Mamon HJ, Ferrone CR, et al. Phase I study of neoadjuvant accelerated short course radiation therapy with photons and capecitabine for resectable pancreatic cancer. *Radiother Oncol*. 2014;110(1):160-164. doi:10.1016/j.radonc.2013.10.027

18. 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 and locally advanced pancreatic cancer. *Am J Clin Oncol*. 2018;41(7):656-661. doi:10.1097/COC.0000000000000349

19. Annes JP, Chen Y, Munger JS, Rifkin DB. Integrin αVβ6-mediated activation of latent TGF-β requires the latent TGF-β binding protein-1. *J Cell Biol*. 2004;165(5):723-734. doi:10.1083/jcb.200312172

20. Khan SA, Joyce J, Tsuda T. Quantification of active and total transforming growth factor-β levels in serum and solid organ tissues by bioassay. *BMC Res Notes*. 2012;5:636. doi:10.1186/1756-0500-5-636

21. Ritsma L, Dey-Guha I, Talele N, et al. Integrin β1 activation induces an anti-melanoma host response. *PLoS One*. 2017;12(4):e0175300. doi:10.1371/journal.pone.0175300

22. American Joint Committee on Cancer. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2010. https://cancerstaging.org/references-tools/deskreferences/Documents/AJCC%207th%20Ed%20Cancer%20Staging%20Manual.pdf. Accessed March 15, 2018.

23. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) v3.0. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcaev3.pdf. Published August 9, 2009. Accessed April 20, 2019.

24. 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: the LAP07 randomized clinical trial. *JAMA*. 2016;315(17):1844-1853. doi:10.1001/jama.2016.4324

25. Van Tienhoven G, Versteijne E, Suker M, et al. Preoperative Chemoradiotherapy Versus Immediate Surgery in Resectable and Borderline Resectable Pancreatic Cancer (PREOPANC-1): a randomized, controlled, multicenter phase III trial [published online June 7, 2018]. *J Clin Oncol*. doi:10.1200/JCO.2018.36.18_suppl.LBA4002