Can we downstage locally advanced pancreatic cancer to resectable? A phase I/II study of induction oxaliplatin and 5-FU chemoradiation

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Background: Half of patients with pancreatic adenocarcinoma (PC) present with regionally advanced disease. This includes borderline resectable and locally advanced unresectable tumors as defined by current NCCN guidelines for resectability. Chemoradiation (CH-RT) is used in this setting in attempt to control local disease, and possibly downstage to resectable disease. We report a phase I/II trial of a combination of 5FU/Oxaliplatin with concurrent radiation in patients presenting with borderline resectable and locally advanced unresectable pancreatic cancer.

Methods: Patients with biopsy-proven borderline resectable or locally advanced unresectable PC were eligible. Chemotherapy included continuous infusion 5FU (200 mg/m^2) daily and oxaliplatin weekly for 5 weeks in dose escalation cohorts, ranging from 30 to 60 mg/m^2. Concurrent radiation therapy consisted of 4,500 cGy in 25 fractions (180 cGy/fx/d) followed by a comedown to the tumor and margins for an additional 540 cGy ×3 (total dose 5,040 cGy in 28 fractions). Following completion of CH-RT, patients deemed resectable underwent surgery; those who remained unresectable for cure but did not progress (SD, stable disease) received mFOLFOX6 ×6 cycles. Survival was calculated using Kaplan-Meier analysis. End-points of the phase II portion were resectability and overall survival.

Results: Overall, 24 subjects (15 men and 9 women, mean age 64.5 years) were enrolled between June 2004 and December 2009 and received CH-RT. Seventeen patients were enrolled in the Phase I component of the study, fifteen of whom completed neoadjuvant therapy. Reasons for not completing treatment included grade 3 toxicities (1 patient) and withdrawal of consent (1 patient). The highest dose of oxaliplatin (60 mg/m^2) was well tolerated and it was used as the recommended phase II dose. An additional 7 patients were treated in the phase II portion, 5 of whom completed CH-RT; the remaining 2 patients did not complete treatment because of grade 3 toxicities. Overall, 4/24 did not complete CH-RT. Grade 4 toxicities related to initial CH-RT were observed during phase I (n=2, pulmonary embolism and lymphopenia) and phase II (n=3, fatigue, leukopenia and thrombocytopenia). Following restaging after completion of CH-RT, 4 patients had progressed (PD); 9 patients had SD and received additional chemotherapy with mFOLFOX6 (one of them had a dramatic response after two cycles and underwent curative resection); the remaining 7 patients (29.2%) were noted to have a response and were explored: 2 had PD, 4 had SD, still unresectable, and 1 patient was resected for cure with negative margins. Overall 2 patients (8.3%) in the study received curative resection following neoadjuvant therapy. Median overall survival for the entire study population was 11.4 months. Overall survival for the two resected patients was 41.7 and 21.6 months.

Conclusions: Combined modality treatment for borderline resectable and locally advanced unresectable

pancreatic cancer with oxaliplatin, 5FU and radiation was reasonably well tolerated. The majority of patients remained unresectable. Survival data with this regimen were comparable to others for locally advanced pancreas cancer, suggesting the need for more novel approaches.

Keywords: Pancreas cancer; radiochemotherapy; neoadjuvant treatment; 5-FU

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Introduction

Pancreatic cancer is the fourth leading cause of cancer death in the United States (1). The 5-year survival rate of patients with newly diagnosed disease remains about 8% (1). The high incidence of metastatic disease at diagnosis and the relative chemo-resistance of this tumor contribute to this poor survival rate. Long term survival is only possible with curative resection. However, only 15% to 20% of patients present with disease confined to the pancreas at the time of diagnosis and as such deemed resectable (2): approximately 40% have distant metastases, and another 30% to 40% have tumors that extend outside the pancreas, in absence of distant metastases. Two terms are currently used by the National Comprehensive Cancer Network (NCCN) guidelines in order to identify this last category of patients: "borderline resectable" and "locally advanced unresectable disease". The difference between these groups relates to the degree of invasion of the regional vasculature (portal vein-superior mesenteric vein confluence, celiac axis and superior mesenteric artery) by tumor, and to the possibility of performing an adequate vascular resection and reconstruction during the operation (3,4). Upfront surgery in this category of patients is either not technically feasible or likely to lead to microscopically positive margins of resection, which does not seem to confer a survival benefit compared with no resection (5). Therefore, neoadjuvant therapy is the appropriate treatment strategy in this setting, with the purpose of controlling local disease and converting to resectable (4,6,7).

Around the end of the last century and the beginning of the new one, some data was published in favor of the use of induction chemotherapy and radiotherapy followed by surgery in the treatment of pancreatic cancer (8-13). Results, however, were not unanimous, with some studies still reporting no survival benefit and a significant higher toxicity for the combined treatment modality (14). Randomized trials, therefore, were being started to assess the new strategy, as the 2000-01 FFCD/SFRO study (15), evaluating the role of radiation together with 5-FU and cisplatin versus gemcitabine alone, or the intergroup study lead by ECOG, comparing radiation therapy plus gemcitabine with gemcitabine alone (16).

In 1997, NYU had undertaken a phase I/II evaluation of a novel combination of Gemcitabine/Cisplatin combined with radiation in patients with locally advanced unresectable disease. The tested regimen was well tolerated and yielded good tumor control, but was limited in its ability to render locally advanced disease resectable (17).

At that time, oxaliplatin had been identified as a promising new agent, with greater activity compared to cisplatin and a demonstrated *in vitro* cytotoxic effect against pancreatic cancer cell lines (18,19). Furthermore, a synergistic effect of oxaliplatin in combination with 5FU had already been demonstrated, preclinically (20), in metastatic colorectal cancer patients (21), and even in patients with metastatic pancreatic cancer (22). Such a combination, moreover, had been tested in association with radiotherapy in patients with recurrent or locally advanced rectal cancer, and the regimen was well tolerated (23).

Based on promising pre-clinical data and the need for more effective therapy in combination with radiation for loco-regionally advanced pancreatic cancer, we designed a phase I/II study to test the safety and efficacy of combined weekly infusional 5-FU and oxaliplatin with concurrent radiotherapy.

Methods

Eligibility and evaluation

Patients with locoregionally advanced pancreatic carcinoma were enrolled at New York University Medical Center and Bellevue Hospital Center. The protocol (NYU 03-64) was

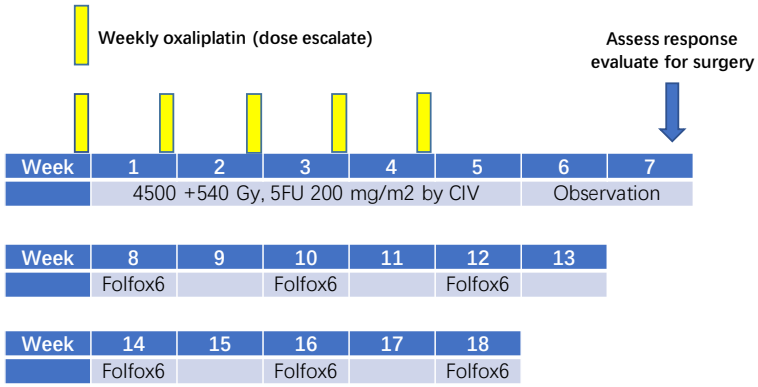


Figure 1 Protocol schema.

approved by the NYU School of Medicine Institutional Review Board (FWA 00004952), which oversees both participating institutions, and written informed consent was obtained for all patients before performing study-related procedures.

Eligibility criteria included pathologic diagnosis of pancreatic adenocarcinoma (PC), locoregionally advanced, non-metastatic disease on computed tomography (CT) imaging, Eastern Cooperative Oncology Group (ECOG) performance status ≤1, and adequate bone marrow, liver and renal function. When the study was initiated, the current NCCN guidelines to define resectability status had not been established yet. Borderline resectable and unresectable diseases were retrospectively defined according to the M.D. Anderson criteria for resectability, which were subsequently incorporated into the guidelines of National Comprehensive Cancer Network (NCCN) (4).

Exclusion criteria included histology other than adenocarcinoma, metastatic disease, prior chemotherapy and/or radiotherapy, active uncontrolled infection, inadequate respiratory, renal, cardiac, hepatic or hematologic organ function, and pregnancy.

Pre-study evaluation and staging included a complete history and physical examination, chest radiograph, blood analysis (complete blood cell count, basic metabolic profile, coagulation profile, and liver function tests), carcinoembryonic antigen and cancer antigen 19-9 levels, and abdomen/pelvis CT or magnetic resonance imaging. Staging laparoscopy was performed in selected cases.

Throughout and after various phases of treatment, patients were followed regularly, through regular reevaluations of ECOG performance status, physical examinations including body weight, and laboratory values. Serial CT or magnetic resonance imaging was used to reevaluate disease stage after administration of chemoradiation (CH-RT) treatment. When feasible, post-treatment follow-up was pursued every 3 months until patient death.

Study regimen and design

Radiation consisted of 4,500 cGy in 25 fractions (180 cGy/fx daily) over 5 weeks, followed by a comedown to the tumor and margins for an additional 540 cGy in 3 fractions, for a total dose of 5,040 cGy in 28 fractions over 5 and a half weeks.

Radiation was combined with 5FU 200 mg/m^2 daily by continuous infusion for 5 weeks and weekly oxaliplatin for 5 weeks in dose escalation cohorts as following: level I =30 mg/m^2; level II =40 mg/m^2; level III =50 mg/m^2; level IV =60 mg/m^2. Following the phase I portion of the trial, a phase II trial at the recommended dose continued.

Two weeks following completion of CRT, patients were re-staged with CT scan. Those considered resectable underwent surgery; those who remained unresectable for cure (stable disease, SD) but did not progress (PD) received a modified FOLFOX6 (Oxaliplatin 85 mg/m^2 administered at day 1 as a 2-hour IV infusion concurrently with Leucovorin 350 mg administered as a 2-hour IV infusion, followed by 5-FU 400 mg/m^2 as an IV bolus, followed by 5-FU 2,400 mg/m^2 as a 46-hour infusion) every 2 weeks for 6 cycles (*Figure 1*).

Throughout treatment, patients were evaluated at least weekly by history, physical examination, and laboratory values to monitor for toxicity.

Toxicity was graded according to the NCI Common Toxicity Criteria (NCI CTC), Version 2.0 (24). Neurosensory toxicity was graded according to the Neurologic Toxicity Scale for Oxaliplatin (25).

Treatment toxicity including gastrointestinal symptoms, fever, fatigue, neutropenia, thrombocytopenia, anemia,

Table 1 Patient characteristics at baseline (n=24)

Characteristics	Value
Sex, n (%)	
Male	15 (62.5)
Female	9 (37.5)
Age (years)	
Mean	64.5
Median	63
Range	46–76
Race, n (%)	
Caucasian	16 (66.7)
Hispanic	4 (16.7)
Asian	2 (8.3)
Black	2 (8.3)
Primary tumor site, n (%)	
Head/neck	16 (66.7)
Body/tail	7 (29.2)
N/A	1 (4.2)
Tumor size at presentation (cm)	
Mean	4.03
Median	3.75
Range	1.50–7.90

and high liver function tests was monitored. Appropriate chemotherapy and/or radiation dose modification was performed accordingly; the dose was held for absolute neutrophil count <500 cells/μL, platelet count <25,000/μL, grade 3–4 non-hematologic toxicity (except neurologic toxicity and grade 3 diarrhea). Treatment was resumed when absolute neutrophil count >1,000/μL, platelets >50,000/μL, resolution of non-hematologic toxicity to grade 2 or less. If toxicity required a dosing delay of more than three weeks from the last planned Oxaliplatin dose, study treatment was discontinued.

Dose-limiting toxicity was defined as: prolonged grade 4 neutropenia or complicated grade 3–4 neutropenia (fever >38.5 ℃ or sepsis); grade 4 thrombocytopenia or symptomatic grade 3–4 thrombocytopenia (hemorrhage); any other grade 4 toxicity of clinical relevance that is not reduced to grade 1 within 2 days of appropriate therapy.

Primary endpoint for the phase I portion of the study was to determine the safety and the MTD of the combined CIV5FU, oxaliplatin and radiation. Secondary endpoints were rates of R0 resectability and overall survival (OS), calculated from time since first treatment. Primary endpoint for the phase II portion was resectability rate, with secondary outcomes including overall survival and toxicity.

Resectability rate included the proportion of patients who successfully underwent complete surgical resection with microscopically negative margins as a function of all patients treated with CH-RT therapy. Survival was measured from the date of start of treatment to the time of death from any cause.

Statistical analyses

A standard 3+3 cohort dose-escalation design was utilized for the phase I portion of the trial. The recommended phase II dose was defined as the highest dose tested in which none or one patient experienced dose-limiting toxicity attributable to the study drug. At least six patients were treated at the recommended phase II dose.

Overall survival time was illustrated using Kaplan-Meier curves. Descriptive statistics were provided according to the nature of variables. All analyses were performed with SPSS statistical software, version 13.0 (SPSS, Chicago, IL, USA).

Results

Patient characteristics

Between June 2004 and December 2009, 15 men and 9 women were enrolled in the study. Demographics and tumor characteristics are reported in *Table 1*. The mean age was 64.5 (range, 46–76) years. A total of 16 cancers arose in the head/neck of the pancreas. The median tumor size at presentation as measured radiographically by computed tomography was 3.75 (range, 1.50–7.90) cm. Thirteen tumors were classified retrospectively as "borderline resectable" and eleven as "unresectable".

Maximum tolerated dose and toxicity

CH-RT

Seventeen patients were enrolled in the phase I portion of the study. They received radiation therapy combined with daily 5-FU and weekly oxaliplatin in 4 dose cohorts. Six patients were included in cohort 1 (oxaliplatin 30 mg/m^2), three patients in cohort 2 (oxaliplatin 40 mg/m^2), three

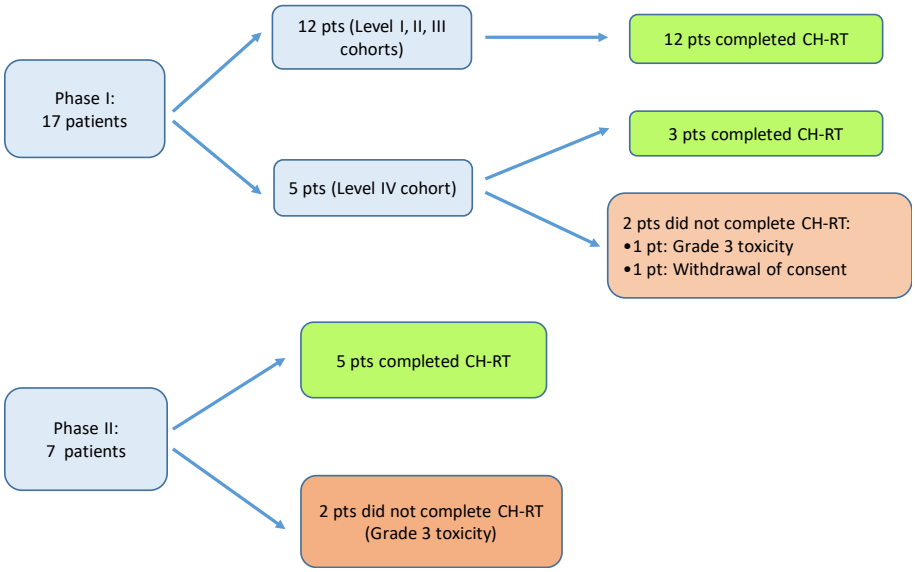


Figure 2 Enrollment and completion of chemo-radiation treatment (CH-RT). Pts, patients.

Table 2 Doses of chemotherapy received per cohort and number of toxicities during chemo-radiation treatment

Dose level	Oxaliplatin (mg/m^2)	n	No. of toxicities			
			Grade I	Grade II	Grade III	Grade IV
I	30	6	47	28	14	1
II	40	3	13	10	4	1
III	50	3	29	8	7	0
IV	60	12	73	40	27	3

patients in cohort 3 (oxaliplatin 50 mg/m^2) and five patients in cohort 4 (oxaliplatin 60 mg/m^2).

All of the 12 patients in the first three cohorts completed 5 weeks of treatment without need for dose reduction. Among the 5 patients in level 4 cohort, three patients completed the treatment, one patient developed grade 3 toxicity (gastritis and dehydration) that mandated interruption of treatment, and one patient withdrew consent for research. The highest dose (60 mg/m^2) of oxaliplatin, thus, was well tolerated and it was therefore carried forward in the phase II portion of the study.

Seven patients were enrolled in the phase II portion of the study and they all received Oxaliplatin at a dose of 60 mg/m^2. One patient developed grade 3 toxicities (mucositis, lymphopenia, fatigue) which did not allow for completion of the 5 weeks. Another patient had to interrupt the treatment because of grade 3 lymphopenia. Overall, 5 patients out of 7 in the phase II portion completed CH-RT.

A schematic of patients' enrollment and number of patients who completed CH-RT treatment is shown in *Figure 2*.

Overall number of toxicities within each cohort and specific grade 3/4 toxicities are summarized in *Table 2* and *Table 3*. Overall, grade 4 toxicities related to initial CH-RT were observed during phase I (n=2, pulmonary embolism and lymphopenia) and phase II (n=3, fatigue, leukopenia and thrombocytopenia).

Folfox6

Fourteen patients started additional chemotherapy with Folfox6: eleven from phase I (of the initial 17) and three from phase II (of the initial 7). As will be described in detail next section, these were patients who had stable, still unresectable disease after CH-RT, either at imaging or at exploratory laparotomy, plus one patient who had regression of disease and received Folfox6 after radical resection.

The eleven phase I patients included four out of

Table 3 Grade 3 and grade 4 toxicities during chemo-radiation treatment

Symptom/sign	Grade 3, n (%)	Grade 4, n (%)
Hematologic		
Lymphopenia	15 (62.5)	1 (4.2)
Neutropenia	3 (12.5)	0
Anemia	2 (8.3)	0
Leukopenia	0	1 (4.2)
Thrombocytopenia	0	1 (4.2)
Non-hematologic		
Dehydration	5 (20.8)	0
Anorexia	4 (16.7)	0
Fatigue	4 (16.7)	1 (4.2)
Hypokalemia	3 (12.5)	0
Nausea	2 (8.3)	0
Elevated serum alkaline phosphatase	2 (8.3)	0
Elevated serum AST	2 (8.3)	0
Cholecystitis	1 (4.2)	0
Diarrhea	1 (4.2)	0
Neuropathy	1 (4.2)	0
Vomiting	1 (4.2)	0
Gastritis	1 (4.2)	0
Hyponatremia	1 (4.2)	0
Hyperglycemia	1 (4.2)	0
Hypernatremia	1 (4.2)	0
Mucositis	1 (4.2)	0
Renal failure	1 (4.2)	0
Pulmonary embolism	0	1 (4.2)

six patients from cohort 1, two of three patients from cohort 2, all three patients from cohort 3 and two of five patients from cohort 4. Nine of these 11 patients were able to complete all 6 cycles. Treatment was stopped in 2 patients, one for clinical progression of disease and one for development of toxicity.

Of the three phase II patients that started Folfox6, none completed the treatment. One patient withdrew consent after 3 cycles. One patient experienced toxicity that precluded continuation of treatment after the second cycle.

Table 4 Grade 3/4 toxicities during treatment with Folfox6

Symptom/sign	Grade 3, n (%)	Grade 4, n (%)
Hematologic		
Neutropenia	4 (28.6)	1 (7.1)
Leukopenia	0	2 (14.3)
Lymphopenia	1 (7.1)	0
Thrombocytopenia	1 (7.1)	0
Non-hematologic		
Hyperglycemia	2 (14.3)	0
Ascites	1 (7.1)	0
Dizziness	1 (7.1)	0
Hiccoughs	1 (7.1)	0
Hypotension	1 (7.1)	0
Hypothermia	1 (7.1)	0
Vertigo	1 (7.1)	0
Hypernatremia	1 (7.1)	0
Hyponatremia	1 (7.1)	0
Elevated serum alkaline phosphatase	1 (7.1)	0
Hypokalemia	1 (7.1)	0
Sepsis	0	1 (7.1)

Finally, the last patient experienced a significant regression during Folfox6 after the second cycle, appeared to have become resectable, and was brought to the operating room for a pancreaticoduodenectomy.

Grade 3/4 toxicities during treatment with Folfox6 are reported in *Table 4*.

Overall, grade 4 toxicities related to additional treatment with Folfox6 were observed twice during phase I (one each leukopenia and sepsis) and twice in phase II (one each leukopenia and neutropenia).

Overall patient response

The overall response of patients to treatment as they progressed through the protocol is outlined in *Figure 3*.

Twenty-four patients began CH-RT treatment. Of those, 20 patients (15 from phase I and 5 from phase II) completed it. Reasons for stopping CH-RT were grade 3 toxicity (n=3) and withdrawal of consent (n=1).

Of the twenty patients who completed the oxaliplatin-

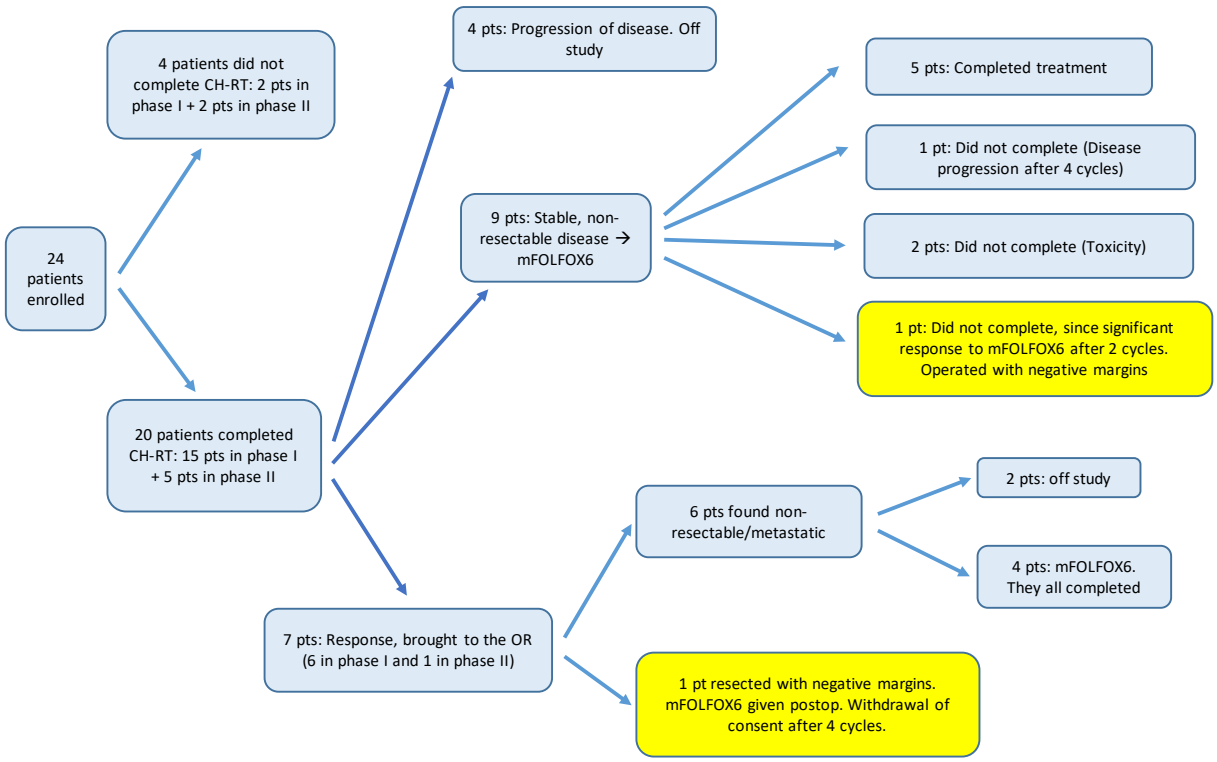


Figure 3 Patient response. CH-RT, chemo-radiation treatment; pts, patients; OR, operating room; mFOLFOX6, modified FOLFOX6.

based CH-RT, at re-staging after CH-RT, 4 patients had progressive disease.

Seven patients (29.2%) were noted to have a response following CH-RT, and were offered exploratory laparotomy and potential resection. Of these seven patients, 5 initially had borderline resectable disease, and 2 had locally advanced unresectable disease. Of these patients, however, 6 were found with non-resectable disease at the time of surgery: 2 with carcinomatosis and 4 with stable, but non-resectable disease. Only 1 patient was found to be resectable at the time of surgery, and received radical resection. This patient had originally presented with a cT2N0M0, 3.8-cm mass of the uncinate process, and was deemed borderline resectable on retrospective analysis, based on current NCCN guidelines (4). Postoperative pathology revealed a 2 cm mass, T1N1M0, resected with negative microscopic margins.

Nine patients had stable, non-resectable disease following CH-RT and received additional chemotherapy with Folfox6. Five completed all 6 cycles of Folfox6; one patient had disease progression after 4 cycles, and two patients stopped their treatment due to toxicity after 2 and 4 cycles, respectively; finally, one patient demonstrated a dramatic tumor response after the second Folfox6 treatment cycle and underwent curative intent resection at another institution. She had originally presented with a cT4N0M0 mass of the head of pancreas, retrospectively deemed borderline resectable. Outside postoperative pathology revealed a T3N0M0 adenocarcinoma, resected with negative microscopic margins.

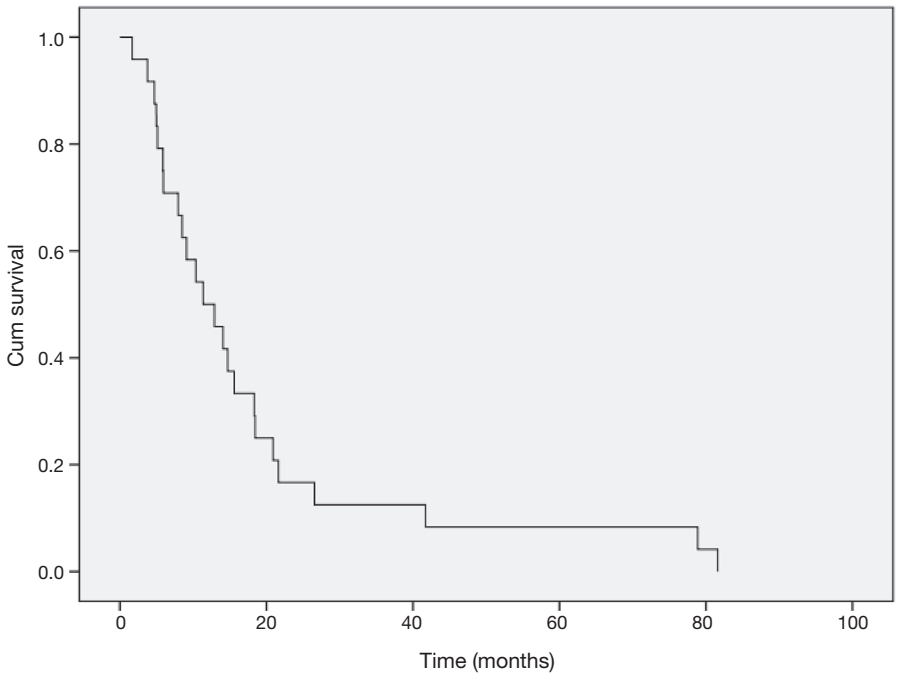
Overall, thus, two patients (8.3%) received curative resection.

Follow-up and survival

There is complete follow up on all patients and all 24 patients have died of disease.

The median survival for the entire study group was 11.4 (range, 1.7–81.6) months (*Figure 4*).

Among the 20 patients who completed CH-RT, median overall survival was 12.9 months. Fourteen of these twenty had stable disease after CH-RT: their median survival was 14.1 months. Six of the 20 who completed CH-RT showed immediate progression or were explored and found to have progression on the basis of carcinomatosis and their median survival was only 9.1 months. The two survival curves are shown in *Figure 5*.



Time (months)	0	5	10	15	20	25	30	35	40	50	60	70	80	90
No. at risk	24	20	14	9	6	4	3	3	3	2	2	2	1	0

Figure 4 Overall survival.

Overall survival for patients initially diagnosed with borderline resectable disease was 11.4 months, while it was 14.1 months for patients originally deemed to have locally advanced unresectable disease. The difference was not significant (*Figure 6*).

The two resected patients had a survival of 41.7 and 21.6 months, respectively. Overall survival in non-resected patients was 10.4 months (*Figure 7*).

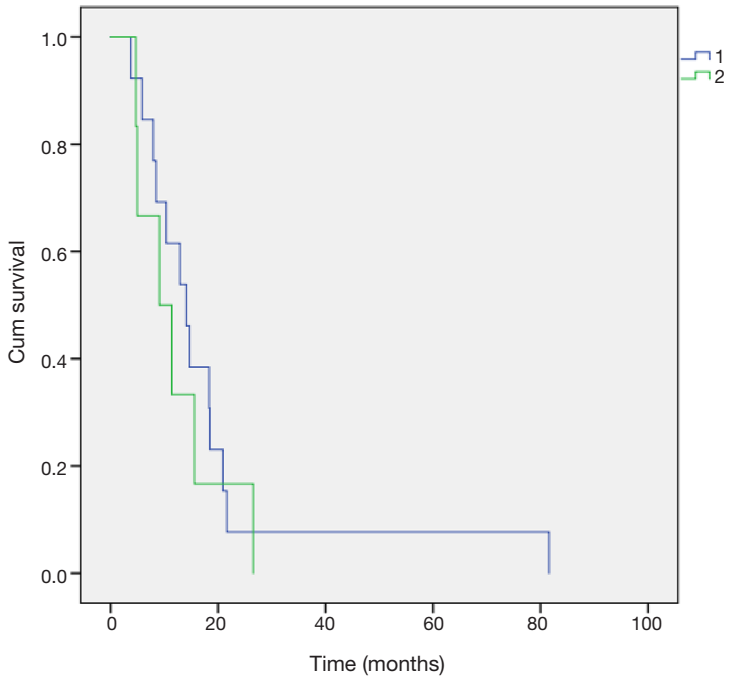
Discussion

The present report demonstrates that combined modality treatment for NCCN-designated borderline resectable and locally advanced unresectable pancreatic cancer with Oxaliplatin, 5-FU and radiation was reasonably well tolerated in our phase I/II study. The majority of patients in the study (91.7%), however, remained unresectable. Of note, two patients who were resected had negative margins on postoperative pathology. Survival data with the tested regimen were comparable to other studies for locally advanced pancreas cancer, with a better outcome, as expected, for those patients who had stable disease or were resected versus those who progressed on study.

At present, surgical resection is the main curative modality for the adenocarcinoma of the pancreas. However, in the setting of NCCN-defined borderline resectable or locally advanced unresectable disease, resection for cure (defined as both gross and microscopically negative margins) is generally not possible. In addition, an R1 surgical resection does not confer a survival benefit compared with no resection (5). The use of neoadjuvant therapy, therefore, is reasonable in for this patient population in order to control local disease, prevent development of metastases and to possibly downstage to a resectable status, thus maximizing the potential for an R0 resection (4).

At the time when our study was initiated, several protocols had already demonstrated the potential benefit for induction chemotherapy and radiation therapy followed by surgery in the treatment of pancreatic cancer (8-12,26,27).

In 1997, NYU undertook a phase I/II evaluation of a novel combination of gemcitabine/cisplatin before and combined with radiation in patients with locally advanced



1= stable disease
2= progression of disease

Time (months)	0	5	10	15	20	25	30	35	40	50	60	70	80	90
No. at risk (stable disease)	14	13	10	6	4	2	2	2	2	1	1	1	1	0
No. at risk (progression of disease)	6	4	3	2	1	2	0	0	0	0	0	0	0	0

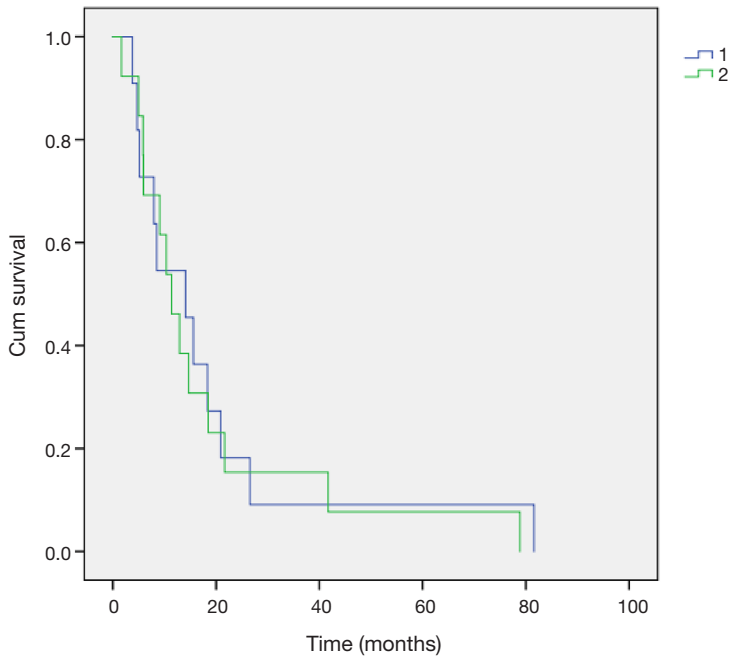
Figure 5 Overall survival (stable disease versus progression of disease).

unresectable pancreatic cancer. The regimen was well tolerated and allowed for good tumor control, although was limited in converting locally advanced disease to resectable (17).

The present trial was conceived with a similar design, but with different agents. Oxaliplatin was chosen for its superior pre-clinical efficacy in pancreatic cancer, its radiosensitizing properties, and its synergistic effect with 5-FU (18-23,28).

In terms of our primary endpoint of toxicity for this regimen, oxaliplatin fared quite well. One of the issues regarding the use of oxaliplatin is its potential neurotoxicity, which is considered its dose-limiting factor. The most common acute side effect is a transient peripheral neurotoxicity characterized by paresthesia and dysesthesia in hands, feet and the perioral area, triggered and/or enhanced by contact with cold. These symptoms, though, are dose-dependent, becoming observable usually at doses of 90 mg/m^2, and, interestingly, disappear within 12 weeks after stopping treatment in 50% of patients and in the majority after 30 weeks (29). The maximum dose used in our study, however, was 60 mg/m^2: only one patient developed grade 3 neuropathy (4.2%).

At doses higher than 45 mg/m^2, oxaliplatin induces nausea and vomiting with rapid onset in the great majority of patients, but this is usually controlled by the standard anti-emetic measures used for all platinum derivatives. We only had two cases of grade 3 nausea (8.3%), and one single case of grade 3 vomiting (4.2%) during induction CH-RT. Furthermore, as expected, no significant renal toxicity was associated with the use of oxaliplatin. The regimen was overall well tolerated, and the most frequent single hematologic toxicity was lymphopenia, with 15 grade 3 episodes (62.5%) and 1 grade 4 episode (4.2%) (overall



1= locally advanced unresectable disease
2= borderline resectable disease

Time (months)	0	5	10	15	20	25	30	35	40	50	60	70	80	90
No. at risk (locally advanced unresectable disease)	11	9	6	5	3	2	1	1	1	1	1	1	1	0
No. at risk (borderline resectable disease)	13	11	8	4	3	2	2	2	2	1	1	1	0	0

Figure 6 Overall survival (borderline resectable versus locally advanced unresectable disease).

grade 3–4: 66.7%). Among non-hematologic toxicities, dehydration, with 5 grade 3 episodes (20.8%), was most common. Other grade 3–4 toxicities are summarized in *Table 3*.

Overall, 20 patients out of 24 completed CH-RT treatment (83.3%).

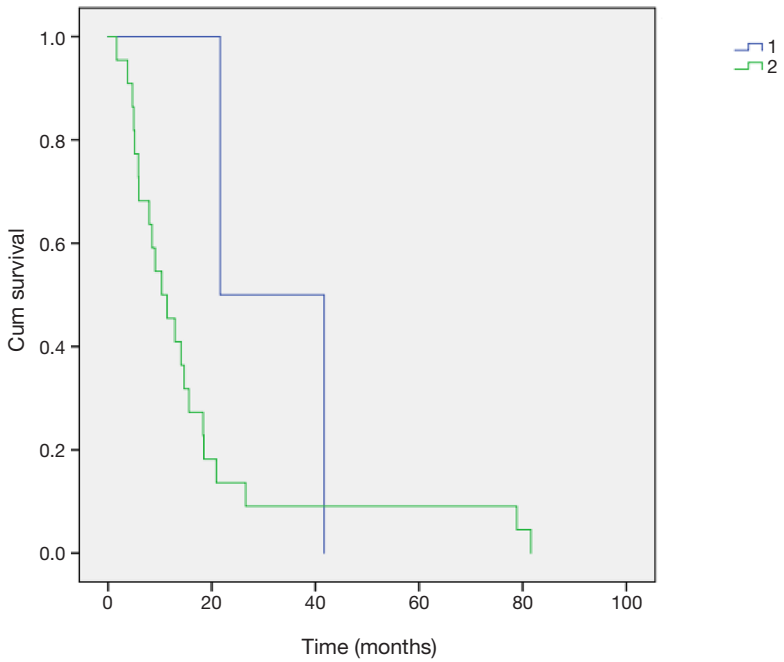
Other studies assessing combination regimens in advanced pancreas cancer with oxaliplatin have reported similar or higher rates of toxicity.

The phase III GERCOR/GISCAD Intergroup trial randomized 326 patients with locally advanced or metastatic unresectable pancreatic cancer to either gemcitabine alone or gemcitabine (1 g/m^2 every 2 weeks) + oxaliplatin (100 mg/m^2 every 2 weeks). It reported an overall good tolerance of the combination therapy, although with a higher incidence of grade 3 and 4 thrombocytopenia, vomiting, neurosensory symptoms, nausea and neutropenia in the Gem/Ox arm (30).

A prospective, phase II clinical trial by Sahora *et al.* evaluated gemcitabine (900 mg/m^2) and oxaliplatin (60 mg/m^2) weekly for patients with locally advanced, non-metastatic pancreatic cancer: the most common toxicities observed were neutropenia/leukopenia (25%) and peripheral neuropathy (18%); diarrhea was described in 4% of patients and vomiting in 14% (31).

Other combination regimens have been reported in advanced diseases that were not oxaliplatin based. Grade 3/4 toxicities were again similar or higher (32,33).

Finally, the use of gemcitabine plus nab-paclitaxel is in the current NCCN guidelines as a first-line therapy option for locally advanced pancreatic cancer (4), although no data have been published to date in this group of patients: all available



1= resected
2= non-resected

Time (months)	0	5	10	15	20	25	30	35	40	50	60	70	80	90
No. at risk resected)	2	2	2	2	2	1	1	1	1	0	0	0	0	0
No. at risk non-resected)	22	11	12	7	4	3	2	2	2	2	2	2	1	0

Figure 7 Overall survival (resected versus non-resected patients).

evidence is derived from patients with metastatic disease. The phase III multinational randomized trial in metastatic disease reported grade 3 or 4 toxicity in the gemcitabine/nab-paclitaxel arm of neutropenia (38%), thrombocytopenia (13%), febrile neutropenia (3%), fatigue (17%), diarrhea (6%), and neuropathy (17%) (34). These data show an overall higher rate of adverse events than our regimen, although data regarding survival are not comparable because of the different type of studied population. A modified regimen of gemcitabine + nab-paclitaxel has recently been proposed for metastatic cancer, and a preliminary report presented at 2015 ASCO Gastrointestinal Cancer Symposium showed similar survival rates with a better grade 3–4 toxicity profile: neutropenia 10%, fatigue 6%, neuropathy 2%, thrombocytopenia 4%, diarrhea 0% (35). However, even with a better toxicity profile, the use of gemcitabine/nab-paclitaxel is costly, currently the highest among the most common regimens (36).

Our survival results are comparable with those of other regimens for treatment of locally advanced pancreatic cancer.

Among those studies which evaluated the use of Gemcitabine in mixed populations of patients with both locally advanced and metastatic disease (30,32,37), the GERCOR/GISCAD trial showed combined therapy to be superior to monotherapy only in terms of response rate (26.8% *vs.* 17.3%), progression-free survival (5.8 *vs.* 3.7 months), but not for median overall survival, which was 9.0 and 7.1 months, respectively (30).

A phase II study by Ishii *et al.*, instead, focusing exclusively on locally advanced pancreatic carcinoma, reported a median overall survival of 15.0 months for 50 patients treated with gemcitabine alone (38).

Thirteen patients (39%) had a curative resection after neoadjuvant therapy with gemcitabine and oxaliplatin in the study by Sahora *et al.*: median overall survival of patients undergoing resection was 22 months, as opposed to 12 months for those without resection (31).

In the last few years, combination chemotherapy with

FOLFIRINOX has become a standard regimen in metastatic disease based on randomized data (39), for patients with a good performance status, a favorable comorbidity profile, and a support system to permit aggressive medical therapy. Although it appears that objective response rates in the primary tumor are at least as good as they are in metastatic disease, few data and no randomized studies are today available for locally advanced unresectable disease (40-46).

However, a systematic review and meta-analysis of studies for locally advanced pancreatic cancer patients treated with FOLFIRINOX has recently been published in which 490 patients across ten studies were included: the median overall survival was of 24.2 (range, 10.0–32.7) months; the proportion of patients who underwent surgical resection ranged from 0% to 43%, with a pooled proportion of 25.9%. The pooled proportion of patients who had R0 resection of those who underwent resection was 78.4% (47).

With respect to borderline resectable disease, no randomized data exist. The use of neoadjuvant therapy in patients with borderline resectable disease has been evaluated only in small single institution series and small phase II trials. The largest single institution series included 160 patients; of these, 125 (78%) completed preoperative therapy and restaging, and 66 (41%) underwent pancreatectomy. Sixty-two patients (94%) had a margin-negative postoperative pathology; at a median follow-up of 27 months, the median survival durations for the unresectable and resectable cohorts were 13 and 40 months, respectively (48). Interestingly, a 2011 meta-analysis of phase II trials testing a variety of neoadjuvant strategies concluded that approximately one third of tumors initially considered marginal for resection were able to be ultimately resected after neoadjuvant treatment and that the median survival in this group was 22.3 (range, 18–26) months (49). In general, current recommendations from NCCN in the setting of borderline resectable disease are for an initial attempt at neoadjuvant therapy, followed by restaging and surgical exploration in the absence of metastatic disease, rather than upfront surgery (4). This is particularly appropriate, when considering that borderline resectable tumors are usually more likely to have a curative resection as opposed to a truly defined locally advanced unresectable disease (17). In fact, both patients who underwent curative resection in our study were originally classified as borderline resectable.

Overall, despite its limited size, our phase I/II trial has demonstrated that the addition of 5-FU and oxaliplatin to radiation therapy in the neoadjuvant setting for patients with locally advanced unresectable and borderline resectable pancreatic tumor is feasible and well tolerated. However, the greater majority of patients remained unresectable after treatment, and survival rates were comparable to those shown by other reports about different therapy combinations. Thus, more novel approaches will have to be tested in order to truly improve outcomes in patients with locally advanced unresectable and borderline resectable disease.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The protocol (NYU 03-64) was approved by the NYU School of Medicine Institutional Review Board (FWA 00004952), which oversees both participating institutions, and written informed consent was obtained for all patients before performing study-related procedures.

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