Original Article

Dose-escalated proton therapy with elective nodal irradiation and concomitant chemotherapy for unresectable, borderline resectable, or medically inoperable pancreatic cancer: a phase II trial

Cooper T. Rapp, Michael S. Rutenberg^, Christopher G. Morris, Romaine C. Nichols^

Department of Radiation Oncology, University of Florida College of Medicine, Jacksonville, FL, USA

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Correspondence to: Romaine C. Nichols, MD. Department of Radiation Oncology, University of Florida College of Medicine, 2015 North Jefferson Street, Jacksonville, FL, 32206, USA. Email: rnichols@floridaproton.org.

Background: To report outcomes of a phase II single-institution trial of dose-escalated proton radiotherapy with elective nodal irradiation (ENI) and concomitant chemotherapy for patients with unresectable, borderline resectable, or medically inoperable pancreatic adenocarcinoma.

Methods: Patients received 40.5 GyRBE in 18 fractions to the gross disease and elective nodal volumes followed by 22.5 GyRBE as a 10-fraction boost to the gross disease for a cumulative dose of 63 GyRBE over 28 fractions. Oral capecitabine (1,000 mg taken orally twice daily) was given on radiation treatment days. The primary objective of this study was to improve the proportion surviving to at least 1 year from the historical rate of 50% to 75%. Secondary objectives included assessing gastrointestinal (GI) toxicity and weight loss during treatment, and evaluating the safety of subsequent surgical resection. This single-institution study was closed to accrual early after the opening of the multicenter PAN009-18 trial by the Proton Collaborative Group (PCG), which follows a similar protocol.

Results: At enrollment, 10 (67%) patients had unresectable disease, 3 (20%) had borderline-resectable disease, and 2 (13%) refused surgery. All 15 patients successfully completed radiation therapy as prescribed. With regard to toxicity, a single patient experienced grade 3 nausea requiring cessation of capecitabine, which ultimately resolved by treatment completion. The median percentage weight loss during treatment was −3.0% (range, −9.6% to +12.0%). Two (13%) initially borderline patients ultimately underwent R0 resection: their total operating room times were 267 and 410 minutes, and blood loss was 700 and 400 mL, respectively. Neither patient experienced intraoperative or postoperative complications. Both were discharged on postoperative day 6. The median follow-up was 0.93 years (range, 0.21 to 2.14 years). The 1-year overall survival (OS) rate was 47%. Three enrolled patients are currently alive: 2 with no evidence of disease and 1 with stable disease.

Conclusions: The primary objective of 1-year OS of 75% was not reached. Proton therapy was well-tolerated. Patients undergoing surgery did not experience operative or perioperative complications, suggesting that patients with borderline resectable or even resectable disease may benefit from neoadjuvant proton therapy. The PCG will test this premise as patients accrue to the multicenter PAN009-18 trial.

Trial Registration: NCT02598349.

Keywords: Pancreatic cancer; radiation therapy; particle therapy; oncology outcomes

^ ORCID: Michael S. Rutenberg, 0000-0001-6945-7883; Romaine C. Nichols, 0000-0003-2171-7791.

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Introduction

The prognosis for patients with localized pancreatic adenocarcinoma who are not surgical candidates is poor; median survival among those with unresectable disease and enrolled on the LAP-07 trial were in the 15.2 to 16.4 months range (1). Patients with borderline resectable pancreatic cancer fare somewhat better; however, many patients are not converted to resectable disease even with aggressive neoadjuvant therapy (2). Achieving extirpative surgery following conversion to resectable disease is a meaningful prognostic indicator, with previous data demonstrating a median survival of 23 months in borderline resectable patients achieving an R0/R1 resection and only 10 months if surgery cannot be performed (3). In addition to the issues surrounding unresectable and borderline resectable disease, the inherent morbidity of surgical resection also creates a substantial pool of patients with inherently resectable disease who are otherwise medically unfit to undergo surgery or refuse surgery entirely.

The potential to convert borderline resectable to resectable disease, and the concern for patients with technically resectable disease who do not undergo resection, has led to a considerable push among oncologists for more effective neoadjuvant or definitive non-surgical treatment. Considerable progress has been made in the field of systemic therapy, particularly with the use of mFOLFIRINOX—a regimen of fluorouracil, leucovorin, irinotecan, and oxaliplatin—over gemcitabine in both the neoadjuvant and adjuvant setting (4,5).

In the field of radiation oncology, there has been considerable interest in increasing the intensity of radiation therapy in the hopes of increasing local control and frequency of R0 resections. Typical photon radiation is constrained to doses of approximately 50–56 Gy due to the presence of multiple radiosensitive organs near the pancreas. In response to this limitation, considerable efforts have been made to study the utility of stereotactic body radiotherapy (SBRT), taking advantage of its favorable dose falloff properties. Indeed, a meta-analysis of 19 trials and approximately 1,000 pancreas SBRT patients demonstrated a grade 3 or higher toxicity rate below 10% with modern treatment techniques (6). Another meta-analysis by Tchelebi demonstrated that SBRT lowered acute G3-4 toxicity compared to conventionally fractionated radiation therapy from 38% to 6% while late toxicity rates were unchanged (7).

Proton therapy has offered an alternative means of intensifying radiation therapy through the use of dose escalation. Compared to traditional photon radiation, proton therapy allows for dosimetric advantages with regards to organ-at-risk dose to critical structures such as the stomach, liver, small bowel, and kidneys (8). Improving integral dose delivery to these critical structures may improve acute and late toxicity over conventional and dose-escalated photon therapy regimens. The use of protons also allows for the treatment of large primaries, locally advanced node-positive disease, and elective nodal irradiation (ENI), all of which are limitations for SBRT.

The role of ENI for pancreatic cancer is controversial; however, it is clear that most pancreatic cancer patients are node-positive at presentation. A pathology review by investigators at Johns Hopkins of 905 patients undergoing pancreaticoduodenectomy between 1995 and 2005 demonstrated a 79.3% rate of lymph node positivity (9). Data from a similar review by investigators at Memorial Sloane-Kettering Cancer Center of 625 pancreaticoduodenectomy patients treated between 2000 and 2009 demonstrated a 70% rate of lymph node positivity (10). With improvements in neoadjuvant therapy and borderline resectable conversion to resectable disease, ENI may play a valuable role in local-regional control. Additionally, a previous phase II study performed at our institution demonstrated that dose escalation to 59.4 GyRBE, including ENI, with concomitant low-dose oral capecitabine resulted in an encouraging 18.4-month median survival and 69% 2-year freedom from local progression. Five of the 15 initially unresectable patients were ultimately able to undergo resection, and there were no grade 2 or greater gastrointestinal (GI) side effects or increase in surgical complications (11).

The primary purpose of this dose-escalation phase II study was to improve 12-month overall survival (OS) from 50% to 75%. Our secondary goal included improving local and regional disease control, increasing the share of borderline resectable and unresectable patients who are converted to having resectable disease, and evaluating the

GI toxicity resulting from dose escalation compared to historical benchmarks. We present the following article in accordance with the TREND reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-21-593/rc).

Methods

We conducted this prospective single-institution study at the University of Florida Health Proton Therapy Institute with institutional review board approval (IRB201702633). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and the informed consent was taken from all individual participants. The study was open to patients with unresectable or borderline resectable disease and patients who were otherwise medically inoperable or refused surgery. A histologic diagnosis of pancreatic adenocarcinoma or adenosquamous carcinoma was required. Patients with evidence of metastatic disease, including ascites or peritoneal seeding, were excluded from participation. Any biliary obstruction was required to have drainage before beginning treatment. Prior chemotherapy was allowed but not required. All patients were offered proton therapy if they met the study's inclusion criteria and no patients were rejected because of insurance.

Statistical analysis

This study was designed to test the primary hypothesis that dose-escalation proton therapy would improve the proportion of pancreatic cancer patients surviving to at least one year to 75% relative to the historical control rate of 50%. Power analysis was conducted with an exact test for binomial proportion via PROC POWER in SAS version 9.4 (SAS Institute, Cary, NC, USA). With a minimum of 45 patients, there would 96% power to determine that the true proportion surviving to 1 year was at least 75% if that was in fact true. There would be 95% confidence in a conclusion that the dose-escalation proton therapy surviving proportion was no different than the historical rate of 50% if that was in fact true. We planned to accrue an additional 15 patients to account for loss to follow-up and/or patient withdrawal; thus, a total sample size of 60 patients was planned.

Secondary endpoints included local control and regional disease control, increasing the share of borderline and unresectable patients able to convert to resectable, and comparing the GI toxicity of protocol therapy with historic benchmarks. We hypothesized that local and local-regional control would improve with dose escalation compared to historic standards, with the dosimetric benefits of proton therapy preventing worsening GI toxicity.

Patients received a total dose of 40.5 GyRBE over 18 fractions to the internal gross tumor volume (iGTV) and the elective nodal volume followed by a sequential boost of 22.5 GyRBE to the iGTV alone. Assuming an α/β of 10 Gy, the biologically effective dose for this fractionation is 77.18 Gy. Patients received 5 fractions per week, once daily, and took 1,000-mg oral capecitabine twice-daily on radiation treatment days.

The elective nodal volume was defined as a 2-cm expansion on the combined celiac artery (most proximal 1 cm from its origin at the aorta) and superior mesenteric artery (most proximal 2.5 cm from its origin at the aorta). This elective nodal volume was determined per findings by Dholakia et al, who reported that 90% of local-regional recurrences occurred within this volume (12).

Typical beam arrangement consisted of a right posterior oblique and a right lateral or anterior oblique field. Weekly cone-beam computed tomography (CT) was performed for image-guided radiotherapy. Active breathing control and 4-dimensional CT scans were allowed but not required.

Weekly Zubrod performance status, CTCAE toxicities, FACT-HEP quality-of-life questionnaires, and nutrition evaluations were performed. Specific CTCAE toxicities included anorexia, fatigue, weight loss, generalized muscle weakness, dehydration, nausea, mucositis, vomiting, and abdominal pain. Toxicities were graded per CTCAE version 4.03. Outcomes and toxicities were analyzed using descriptive statistics.

The follow-up visit and follow-up scan schedule were not determined by the protocol. Patients were typically seen 4 to 6 weeks after treatment and subsequently every 3 months with chest-abdomen-pelvis CT and/or magnetic resonance imaging of the abdomen. Per the protocol, CA19-9 was evaluated prior to treatment and then once at the end of treatment.

We enrolled patients from 2016 to 2019, but the study was closed early due to the opening of the PAN0098-18 trial, which is a multi-institutional trial of the Proton Collaborative Group (PCG) following a similar treatment regimen.

Results

A total of 15 patients consented to participation and were enrolled on the study and treated prior to its closure;

Table 1 Patient, tumor, and prior treatment characteristics

Demographics	No. [%] of patients or other value
Median age (range)	73.7 (49.3–88) years
Sex	
Male	10 [67]
Female	5 [33]
Histology	
Adenocarcinoma	14 [93]
Adenosquamous	1 [7]
Resectability	
Unresectable	10 [67]
Borderline resectable	3 [20]
Medically inoperable	0
Patient refusal	2 [13]
Prior chemotherapy	
Yes	13 [87]
No	2 [13]

Table 2 Toxicity, follow-up, and outcome details

Parameter	No. [%] of patients or other value
Treatment toxicity	
Grade 3	1 [7]
Grade 4	0
Grade 5	0
Median weight change (range)	–3.0% (–9.6% to +12.0%)
Median follow-up (range)	0.93 (0.21 to 2.14) years
1-year overall survival	47%
Outcome	
Resection performed	
Yes	2 [13]
No	13 [87]
Recurrence	
Yes	10 [67]
No	4 [33]
Unknown	1 [7]
Recurrence pattern	
Local	2 [13]
Regional	1 [7]
Metastatic	7 [47]

statistical power to detect an improvement to 75% survival was reduced from 96% to 46%. Most participants were male, and the median age was 73.7 years. *Table 1* provides additional patient and disease characteristics. Two-thirds of patients were unresectable at presentation, while 3 patients were borderline resectable and 2 were technically resectable but refused surgery. Thirteen of the patients had previously received chemotherapy. Of the two who had not received prior chemotherapy, one was resectable at presentation but refused both chemotherapy and surgery, while the other was unresectable at presentation. Six patients had received gemcitabine or gemcitabine/paclitaxel, 4 had received FOLFIRINOX, 2 had received both, and one patient had received 5FU alone.

All patients were treated to the full treatment dose of 63 GyRBE over 28 2.25-GyRBE fractions using 4-dimensional computed tomography with either seed fiducials or using the patient's radio-opaque stent as a surrogate fiducial. Patients received 40.5 GyRBE over 18 fractions to gross disease and elective nodal volumes, with an additional 22.5 GyRBE delivered over a 10-fraction boost to gross disease alone. There were no unexpected treatment breaks for any of the patients. All patients completed twice-daily capecitabine as well, with the exception of 1 who experienced significant nausea. Capecitabine was discontinued in this patient; however, the patient completed their radiation as planned. This was the only grade 3 toxicity in this patient population, and this patient's nausea resolved by the end of treatment.

Table 2 describes the details regarding treatment toxicity, follow-up and outcomes. There were no grade 4 or 5 toxicities among the cohort. The median weight loss was 3.0%, and no patient lost >10% of their baseline weight during treatment. Two of the 3 initially borderline resectable patients were ultimately able to undergo surgical resection. Total operating room time was 267 and 410 minutes, and total blood loss was 700 and 400 mL, respectively. Both patients achieved an R0 resection. Neither patient experienced operative, perioperative, or postoperative complications. Both patients were discharged from the hospital on postoperative day 6.

The 1-year OS rate was 47%. Ten patients subsequently recurred, with one patient's recurrence status unknown. Of the 10 recurrences, 7 were metastatic, 2 were local, and 1

was regional. Of the 7 metastatic recurrences, 1 was both regional and metastatic, and 1 was both local and metastatic. Three patients were alive at the time of writing this report. Two patients, 1 with a subsequent R0 resection and 1 with unresectable disease treated with neoadjuvant therapy alone, were alive with no evidence of disease. The third patient was alive with stable disease.

With regards to CA19-9 lab values, the median pretreatment value was 41 U/mL (1–2,299 U/mL) and the post-treatment median value was 69 U/mL (1–6,372 U/mL). Of note, 3 patients did not have post-treatment values available. Of the 3 patients alive at the time of writing this report, both patients with no evidence of disease had relatively low pretreatment values, 16 and 11 U/mL, and decreased slightly after treatment to 9 and 10 U/mL, respectively. The patient with stable disease had a pretreatment CA19-9 of 2,299 U/mL, which decreased to 101 U/mL following treatment.

Discussion

The role of radiation therapy for pancreatic cancer has evolved in recent years. Adjuvant chemoradiation and radiation-alone trials have had mixed results, with some demonstrating a benefit (13) and others showing no benefit or a detriment compared to chemotherapy or observation alone (14,15). The traditional rationale for the inclusion of adjuvant radiation therapy has been that recurrence rates of >50% are still seen even after R0 resection. The transition towards neoadjuvant radiation therapy has been fueled in part by the observation that several major trials have demonstrated that around 50% of up-front resections anticipated to be R0 actually result in R1 resections (5,16).

In addition to improving the rate of R0 resections in patients with resectable pancreatic cancer, the use of neoadjuvant therapies may allow for the conversion of unresectable to resectable disease. Current evidence indicates that neoadjuvant therapy may allow for a rate of conversion approaching 40% for initially borderline resectable patients (17,18). Moreover, these trials have demonstrated similar survival rates for patients with initially resectable disease and those who were initially unresectable but converted to resectable disease. Strategies which could result in an increased rate of conversion to resectable disease, such as neoadjuvant mFOLFIRINOX or dose-escalated neoadjuvant radiation, are highly appealing. In our small study, 2 of the 3 initially borderline resectable patients ultimately underwent resection.

Both double-scatter and pencil-beam proton techniques have been demonstrated to provide improved integral dose to critical normal tissues while maintaining target coverage goals, which may lead to improved rates of acute and late toxicities for patients (8,19,20). A previous phase II trial at our institution demonstrated no grade 2 or higher GI toxicities or increased surgical complications among a cohort of 15 patients treated for locally advanced pancreatic cancer with dose-escalated proton radiation to 59.4 GyRBE. Our cohort of 15 patients also lends evidence that dose escalation with proton radiotherapy is safe, as only a single grade 3 toxicity of nausea was reported, and this resolved completely with cessation of concurrent chemotherapy; in fact, it resolved prior to the conclusion of radiotherapy once this step was taken.

Ultimately, conclusions regarding toxicity and survival outcomes are limited by our small treatment population; however, treatment per protocol appears to be well-tolerated, although a 1-year survival benefit was not seen compared to historical standards. The few patients who did undergo resection following neoadjuvant treatment did not experience untoward operative or perioperative complications.

There is considerable interest but currently limited *in vivo* data regarding the safety and efficacy of dose-escalated particle therapies, such as proton and carbon ion radiation, in pancreatic cancer. To our knowledge, despite our small sample size, this the largest study of dose-escalated, non-stereotactic treatment of pancreatic cancer in the literature. The early closure of this single-institution study was the result of the opening of a multi-institutional study with a similar protocol, which our institution has transitioned to. The PCG will continue to test the utility of dose-escalated proton therapy as patients accrue to the multicenter PAN0098-18 trial.

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Footnote

Reporting Checklist: The authors have completed the TREND checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-21-593/rc

Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-21-593/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-21-593/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of the University of Florida (IRB201702633) and the informed consent was taken from all individual participants.

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