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Phase I trial

Phase I study of neoadjuvant accelerated short course radiation therapy with photons and capecitabine for resectable pancreatic cancer

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ABSTRACT

Purpose: In this phase I study, we sought to determine the feasibility and tolerability of neoadjuvant short course radiotherapy (SC-CRT) delivered with photon RT with concurrent capecitabine for resectable pancreatic adenocarcinoma.

Materials and methods: Ten patients with localized, resectable pancreatic adenocarcinoma were enrolled from December 2009 to August 2011. In dose level I, patients received 3 Gy × 10. In dose level 2, patients received 5 Gy × 5 (every other day). In dose level 3, patients received 5 Gy × 5 (consecutive days). Capecitabine was given during weeks 1 and 2. Surgery was performed 1–3 weeks after completion of chemotherapy.

Results: With an intended accrual of 12 patients, the study was closed early due to unexpected intraoperative complications. Compared to the companion phase I proton study, patients treated with photons had increased intraoperative RT fibrosis reported by surgeons (27% vs. 63%). Among those undergoing a Whipple resection, increased RT fibrosis translated to an increased mean OR time of 69 min. Dosimetric comparison revealed significantly increased low dose exposure to organs at risk for patients treated with photon RT.

Conclusions: This phase I experience evaluating the tolerability of neoadjuvant SC-CRT with photon RT closed early due to unexpected intraoperative complications.

Adjuvant therapies, including chemotherapy and chemoradiation (CRT), have been explored to improve upon surgical outcomes for pancreatic cancer. Prospective [1] and retrospective data [2] have been mixed in demonstrating an improvement in overall survival and locoregional control with the addition of adjuvant 5-fluorouracil and CRT.

The risk of delaying postoperative CRT has prompted interest in neoadjuvant CRT for resectable pancreatic cancer [3,4]. However, standard fractionated neoadjuvant CRT has been associated with significant gastrointestinal toxicity [3]. Shorter courses of preoperative CRT have been explored with the goal of decreasing toxicity while maintaining local control [5]. Moreover, given the questionable survival benefit of CRT and the systemic nature of pancreatic cancer, shorter courses may minimize the delay to adjuvant chemotherapy.

Extrapolating from short course preoperative radiotherapy in rectal cancer [6], the results of a Phase I experience demonstrating the feasibility and tolerability of preoperative CRT with 1 week of proton beam therapy and capecitabine followed by early surgery for resectable pancreatic cancer has been previously published [7]. A phase II prospective study evaluating the efficacy of this regimen has recently completed accrual. Due to the tolerability of the proton experience, but limited availability of protons, in this prospective phase I study, we sought to determine the feasibility and tolerability of preoperative CRT with 1 week of photon radiotherapy and capecitabine followed by early surgery.

Methods and materials

Patient eligibility

Patients with resectable pancreatic cancer were prospectively enrolled in a clinical trial approved by the institutional review board. Patient eligibility included cytologic or histologic proof of pancreatic ductal adenocarcinoma prior to treatment. Patients with

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ampullary cancer, biliary cancer, or duodenal cancer were excluded. All patients were required to have staging work-up with a physical examination, chest CT, and abdominal CT with intravenous contrast (or abdominal MRI with gadolinium) with no evidence of distant metastases. Screening diagnostic laparoscopy was not required. All patients were 18 years or older with no upper age restriction. Patients with ECOG Performance score 0 or 1 were eligible.

Laboratory evaluation included CA 19-9, electrolytes, complete blood count, liver function tests, and renal function tests (Supplemental Appendix 1). Any patients with serious concomitant systemic disorders, life expectancy <3 months, any serious, uncontrolled, concurrent infections, prior chemotherapy or radiation for the patient's pancreatic tumor, treatment of other cancers within the last 5 years (except cured non-melanoma and treated in situ cervical cancer), any prior fluoropyridimine therapy (unless administered in an adjuvant setting and completed $\geqslant$6 months earlier), known DPD deficiency, major surgery or participation in any investigational drug study within 4 weeks of study entry, were excluded.

Radiation therapy

Three radiation oncologists accrued to this study. All patients underwent three-dimensional (3D) simulation with intravenous and oral contrast. "Four-dimensional" CT simulation to account for respiratory motion of the target volume was recommended but not required. Computerized dosimetry and CT planning were required for all treatments. Gross tumor volume (GTV) was contoured with the pancreatic protocol CT available, and was defined as the gross primary tumor and any lymph nodes (LNs) enlarged over 1 cm during simulation. Tumor volume was defined on the basis of CT and MRI imaging findings, operative notes, and cholangiography findings. Clinical target volume (CTV) was contoured to include the following modest elective LN coverage: celiac axis, superior mesenteric artery, pancreaticoduodenal, and para-aortic LNs (Supplemental Appendix 2, Fig. 1). A planning target expansion was customized using the estimated set-up variation. Generally, at the physician's discretion, a 7–10 mm margin in all directions except 5 mm posteriorly, was used to define the planning target volume (PTV). The radiation dose escalation schema and planning dose constraints are summarized in Supplemental Appendix 3, Tables 1 and 2, respectively. At dose level 1, a total dose of 30 Gy in 10 fractions (3 Gy/day) was prescribed to the 95% isodose and administered 5 days per week over 2 weeks. At dose levels 2 and 3, a total dose of 25 Gy in 5 fractions was prescribed to the 95% isodose and administered at 5 Gy per fraction as outlined below. Both intensity modulated radiation therapy (IMRT) and 3-D conformal techniques were permitted.

Chemotherapy

For each dose level, capecitabine was given Monday through Friday for week 1 and week 2 for a total of 10 days. Capecitabine dose was 1650 mg/m^2 administered in two divided doses.

Supportive treatment

All patients were counseled to take ondansetron 8 mg by mouth 30–60 min prior to radiation therapy. Additionally, patients were initiated on a proton pump inhibitor if they were not already taking one.

Surgery

Patients underwent surgery 1–3 weeks after the completion of chemotherapy. Surgical resection was performed by 5 pancreaticobiliary surgeons. All but one surgeon have enrolled patients onto the parallel study of proton radiotherapy and employed identical surgical techniques. Pathology was processed and scored per standard institutional practices.

Postoperative chemotherapy

Patients were recommended to have chemotherapy with gemcitabine for 4–6 months per institutional policy, to start 4–10 weeks after surgery. Patients were followed every 6 months for 5 years after surgery in order to follow progression free and overall survival status.

Dose limiting toxicity

A dose limiting toxicity (DLT) was defined as occurring within 3 weeks of the start of radiation therapy. Specifically, a DLT included any (1) grade 3 non-hematologic or hematologic toxicity requiring >7 day interruption in drug therapy OR >3 day interruption in CRT; (2) grade 4 non-hematologic toxicity; or (3) grade 4 neutropenia or thrombocytopenia; (4) treatment related deaths; (5) delays in surgery beyond 3 weeks due to treatment-related toxicities. Additionally, a 30% increase in any surgical complication rates beyond those previously established at MGH was considered a DLT (readmission rate: 16%; pancreatic fistula/intra-abdominal rate: 27%, major intra-abdominal bleeding requiring return to OR: 1.6%, delayed gastric emptying: 4.4%, and superficial wound infection rate: 8%). Beginning at level I, 3 patients were scheduled to be treated at dose level I and II, and 6 patients were scheduled to be treated at dose level III.

Evaluation of unexpected surgical complications

We evaluated unexpected intraoperative complications seen in this study, and compared them to surgical complication rates previously reported in the companion phase I study of neoadjuvant accelerated short course radiotherapy with protons and capecitabine [7]. The primary unexpected surgical complications evaluated were the presence of intraoperative fibrosis, as reported by the surgeon, and the resultant prolongation of operative room time. The presence of intraoperative retroperitoneal fibrosis was compared between the 8 patients enrolled in this current photon study who underwent surgical resection and the 15 patients enrolled in the companion phase I proton study. Because all patients enrolled in the proton study were mandated to require pancreaticoduodenectomy, operating room (OR) time was compared between the 5 patients enrolled in this current photon study who underwent pancreaticoduodenectomy with recorded OR times and the 15 patients enrolled in the phase I proton study.

Dosimetric comparison

Dose–volume histogram (DVH) data were collected for patients treated prospectively on this current study (n = 10) and the patients treated on the phase II proton study (treated in 25 Gy in 5 fractions), which has recently completed accrual (n = 50). DVH analysis was performed both with the entire cohort of patients enrolled in the current study, and excluding the 3 patients treated at dose level I (30 Gy in 10 fractions) to account for any potential confounding effect of treatment dose. DVH between these two patient cohorts was performed using the Wilcoxon–Mann–Whitney test. All analyses were performed in Stata 11.1 (StataCorp, College Station, TX). All statistical tests were two sided and statistical significance was defined as a P value of <0.05.