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Duodenal Toxicity After Fractionated Chemoradiation for Unresectable Pancreatic Cancer

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Summary

This study examined the clinical and dosimetric factors associated with duodenal toxicity after fractionated radiation therapy for unresectable carcinoma of the pancreas. Although toxicity was correlated with a number of factors, the strongest correlation was seen with the volume of duodenum receiving 55 Gy, establishing this as an important dosimetric constraint to guide future attempts at therapeutic dose escalation.

Purpose: Improving local control is critical to improving survival and quality of life for patients with locally advanced unresectable pancreatic cancer (LAPC). However, previous attempts at radiation dose escalation have been limited by duodenal toxicity. In order to guide future studies, we analyzed the clinical and dosimetric factors associated with duodenal toxicity in patients undergoing fractionated chemoradiation for LAPC.

Methods and Materials: Medical records and treatment plans of 106 patients with LAPC who were treated with chemoradiation between July 2005 and June 2010 at our institution were reviewed. All patients received neoadjuvant and concurrent chemotherapy. Seventy-eight patients were treated with conventional radiation to 50.4 Gy in 28 fractions; 28 patients received dose-escalated radiation therapy (range, 57.5-75.4 Gy in 28-39 fractions). Treatment-related toxicity was graded according to Common Terminology Criteria for Adverse Events, version 4.0. Univariate and multivariate analyses were performed to assess prognostic influence of clinical, pathologic, and treatment-related factors by using Kaplan-Meier and Cox regression methods.

Results: Twenty patients had treatment-related duodenal toxicity events, such as duodenal inflammation, ulceration, and bleeding. Four patients had grade 1 events, 8 had grade 2, 6 had grade 3, 1 had grade 4, and 1 had grade 5. On univariate analysis, a toxicity grade ≥ 2 was associated with tumor location, low platelet count, an absolute volume (cm^3) receiving a dose of at least 55 Gy ($V_{55\ Gy} > 1\ cm^3$), and a maximum point dose >60 Gy. Of these factors, only $V_{55\ Gy} \geq 1\ cm^3$ was associated with duodenal toxicity on multivariate analysis (hazard ratio, 6.7; range, 2.0-18.8; $P = .002$).

Conclusions: This study demonstrates that a duodenal $V_{55\ Gy} > 1\ cm^3$ is an important dosimetric predictor of grade 2 or greater duodenal toxicity and establishes it as a dosimetric constraint when treating patients with unresectable pancreatic cancer with concurrent chemoradiation.

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Conflict of interest: none.

Supplementary material for this article can be found at www.redjournal.org.

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Introduction

Local tumor progression in patients with locally advanced unresectable pancreatic cancer (LAPC) remains a significant problem, worsening patient quality of life and reducing survival. Although metastatic progression is the dominant pattern of failure for most patients with LAPC, local tumor progression has been reported in 25% to 62% of patients (1-3) and is the initial site of failure in approximately 1 in 4 cases after definitive chemoradiation (1, 2). As such, there is significant interest in strategies to improve local tumor control for patients with LAPC.

Previous attempts at local therapeutic intensification for patients with LAPC have focused on radiosensitization and radiation dose escalation. Studies have examined intensified concurrent chemotherapy regimens (2-4) and the escalation of radiation dose through conventional fractionation (5, 6), intraoperative radiation (7), or, most recently, the use of stereotactic hypofractionated radiation therapy (8). Unfortunately duodenal toxicity has limited these efforts (4-7, 9).

Investigators have recently reported the dosimetric and clinical parameters associated with duodenal toxicity after hypofractionated radiation therapy for LAPC (9). However, there are very few data available quantifying the risk of duodenal toxicity after standard fractionation chemoradiation therapy for LAPC (10). In this study, we performed a detailed analysis of clinical, dosimetric, and treatment-related factors associated with late duodenal toxicity among a cohort of patients treated with standard fractionation chemoradiation for LAPC.

Methods and Materials

Patient selection

After approval was received from our institution's internal review board, patients were identified through a search of the institution's Department of Radiation Oncology databases. In all, 161 patients with pancreatic cancer were identified who were treated with chemoradiation to doses of at least 50.4 Gy between July 2005 and June 2010 and did not undergo surgical resection or surgical bypass. Of these, 34 patients had less than 6 months of follow-up; after we confirmed no duodenal events were reported for this group, these 34 patients were excluded to reduce the bias of short follow-up. An additional 12 patients who were enrolled in a previously unreported phase 1 trial were removed from analysis. Finally, for 12 of the remaining 118 patients it was not possible to accurately delineate the duodenum due to the quality of the planning computed tomography (CT) scan, and they also were removed, leaving 106 patients available for analysis.

Treatment

All patients underwent simulated radiation treatment in the supine position with their arms up, immobilized using a customized Vak-Lok cradle (Civco, Kalona, IA). Noncontrast CT scans were performed, and data were transferred to a Pinnacle unit (Phillips Healthcare, Andover, MA) for treatment planning. Seventy-eight patients (73%) were treated to a total dose of 50.4 Gy in 28 fractions. Of these, 75 patients were treated with standard 3-dimensional (3D) conformal treatment techniques, and 3 patients were treated with intensity modulated radiation therapy (IMRT). An additional 28 patients received dose-escalated radiation therapy either to the entire tumor or to a focal area of arterial abutment to doses greater than 50.4 Gy (median, 63 Gy; range, 57.5-70.4 Gy) at the discretion of the treating physician, based on patient, tumor, and dosimetric considerations. All patients receiving dose-escalated radiation were treated with IMRT plans for part or all of their treatment. Typical plans used 5 to 9 beams with 6-MV photons, customized beam angulation, and weighting. In 23 patients, dose escalation was achieved through the use of a simultaneous integrated boost technique. A planning target volume (PTV) including the gross tumor, superior mesenteric artery, and celiac axis was treated to 50.4 Gy. A smaller PTV consisting of the gross tumor volume (GTV) with a 5-mm expansion was treated to doses higher than 50.4 Gy. In 5 patients, a sequential boost was performed in which the PTV, consisting of the GTV with a 5- to 8-mm expansion, was targeted with 3 to 11 additional fractions. In all patients treated with dose escalation, the duodenum was contoured and used as avoidance structure during treatment planning, with the goal of limiting the volume of duodenum receiving 60 Gy to less than 5 cm^3 ($V_{60\ Gy}$ <5 cm^3). This planning constraint was achieved in 25 of 28 patients (89%).

Follow-up and statistical analysis

Retrospective reviews of the treatment records of all 106 patients were performed, and details concerning patient sex, age, Karnofsky performance status, medical history, smoking history, anticoagulant use, platelet count, prothrombin time/international normalized ratio (INR), location of tumor, chemotherapy treatment, and radiation treatment were recorded. In addition, to obtain dosimetric data, we contoured the duodenum from the gastric pylorus to the distal end of the duodenal loop, 3 cm past the midline, on the treatment planning scan retrospectively in all 106 patients. Dose-volume histograms were then computed using a collapsed cone convolution algorithm in the Pinnacle system. Using the linear quadratic model and α/β ratio for the duodenum of 10, we calculated equivalent doses and then converted to a standardized 28-fraction treatment course for the 5 patients who received more than 28 fractions. The $V_{40\ Gy}$ (with $V_{40\ Gy}$ representing the absolute volume [cm^3] receiving a dose of at least 40 Gy), $V_{45\ Gy}$, $V_{50\ Gy}$, $V_{55\ Gy}$, and $V_{60\ Gy}$ doses were then recorded along with the mean dose to the duodenum.

Duodenal toxicity was scored according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. All of the recorded duodenal toxicity events were confirmed by endoscopic evaluation. The time to toxicity was defined in months after completion of radiation therapy, and patients were censored at the time of their last clinic visit. Median follow-up was 12.4 months (range, 6-51 months). Optimal cutoff points for dosimetric factors analyzed were determined using receiver operator curve (ROC) analysis and the Youden index (11). Univariate and multivariate analyses were performed to assess prognostic influence of clinical, pathologic, and treatment-related factors using the Kaplan-Meier and Cox regression methods. All data were computed using SPSS, version 15.0, software for Windows (SPSS, Chicago, IL; Microsoft, Redmond, WA). A P value of less than .05 was accepted as significant.