Original Article

Feasibility and reproducibility of substituting oral contrast with water for duodenal volume delineation in patients undergoing pancreatic stereotactic body radiotherapy

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Background: This is the first known report evaluating the feasibility of substituting oral contrast with water in efforts to delineate the duodenum for pancreatic stereotactic body radiotherapy (SBRT).

Methods: From January 2015 to August 2016, 13 patients were simulated after ingestion of 8 ounces of water approximately 15–20 min prior to their simulation scan. We examined the feasibility of contouring the duodenum thereafter, and measured the duodenal volume as well as its variation. Comparison was made to 40 patients treated from January 2009 to February 2012 on a prospective trial who used oral contrast. Group comparisons were performed by the Mann-Whitney U test.

Results: The duodenum was identified in all 13 patients who used water instead of oral contrast without subjective difficulty. In this group, the median duodenal volume was 72.86 cm^3 (range, 44.61–130.90 cm^3). In the oral contrast group, median duodenal volume was 86.21 cm^3 (range, 50.11–157.89 cm^3) There were no significant differences between groups (P=0.115). The approach was reproducible, as all patients were able to drink the same amount of water 15–20 min prior to each SBRT fraction to keep duodenal volumes subjectively similar to volumes on the simulation CT scan.

Conclusions: This novel approach is effective and reproducible in delineating the duodenum for treatment planning and daily setup.

Keywords: Stereotactic body radiotherapy (SBRT); pancreatic cancer; toxicity; duodenum; stereotactic ablative radiotherapy

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Introduction

There is currently a major focus of investigation of stereotactic body radiotherapy (SBRT) for pancreatic neoplasms. However, resulting from the close anatomic pancreaticoduodenal relationship, SBRT planning and delivery are challenging vis-à-vis potential for duodenal toxicity (1,2). Additionally, owing to the relatively rapid development and institution of pancreatic SBRT, technical nuances of SBRT setup and simulation have been understudied and are largely institution-dependent (3).

Currently, per initial studies, four-dimensional simulation is most often preceded by fiducial placement

and intake of oral contrast. However, these methods have several noteworthy shortcomings. First, rapid intake of an oral contrast bolus may not provide desired results, owing to expected versus observed transit time. If there is too short of a time differential between intake and simulation scan, the duodenum becomes over distended and substantially irreproducible between simulation and SBRT delivery (alternatively, contrast remains in the stomach). If the interval is too long, most contrast material goes through the duodenum and target delineation becomes difficult. Next, fiducial markers do not circumvent the need to add nontrivial margins around the target volume. There is often soft tissue distortion around the area from many extra-respiratory sources; thus, even with kilovoltage cone-beam image guidance, neither bony nor fiducial registration accurately provides a surrogate for the "true" target (4).

A major cause of this soft tissue misalignment is from the duodenum, as during simulation the duodenum can be artificially distended to some degree from oral contrast. During treatments, however (depending on the prandial status), the duodenum is more collapsed. This potentially leads to substantially higher doses delivered during treatment, owing to the sharp dose drop-off within each millimeter from the field. Potential solutions to this problem, including re-planning and gated treatment, are incompletely understood and are currently used based on physician preference only (5,6). We intent to discover an oral contrast that patient can use for daily radiation therapy.

Methods

This study examined 13 unresectable/borderline resectable pancreatic cancer patients simulated with water (January 2015 to August 2016) with comparison to 40 unresectable/borderline resectable patients treated on a prospective trial (NCT01068327) that utilized oral contrast. With the exception of the material ingested, all logistic elements and treatment planning was identical per institutional protocol.

Prior to simulation, all patients underwent fiducial marker implantation (two 2 mm x 5 mm VISICOIL gold seeds were implanted approximately 2 cm apart adjacent to the tumor). Simulation with a free-breathing CT and four-dimensional CT (4DCT), occurring at a minimum of 7 days after fiducial placement, was carried out using body fixation and immobilization devices (Medical Intelligence, Schwabmunchen, Germany). Intravenous contrast was given unless renal function precluded administration. The 13 patients that were evaluated for this report ingested 8 ounces of water, 15–20 min prior to simulation, similar to those that swallowed oral contrast.

The duodenum was defined as the duodenal bulb to the point the transverse duodenum crossed the left lateral border of the aorta; this (as well as contouring of other organs-at-risk) was performed in accordance with Radiation Therapy Oncology Group (RTOG) guidelines (7). Dose constraints used were per our institutional trial (NCT01068327) which were initially designed according to many sources, including previous studies (8-10), SBRT dose tolerance publications (11), the RTOG 0631 protocol (12), and previous dosimetric studies of SBRT for pancreatic cancer.

The gross tumor volume (defined as visible disease) was contoured using either Eclipse or BrainLab software, with 5 mm expansion to form the planning target volume (PTV). No prophylactic radiation to the regional lymphatic drainage area, similar to published work (8-10). The prescribed dose was required to cover 95% of the PTV at minimum.

The 13 patients receiving water during simulation were instructed to take the same amount at the same time prior to each SBRT session. Daily image guidance with kilovoltage cone-beam CT (CBCT) was performed, and owing to the quality of the imaging, re-contouring of the duodenum on each pre-treatment CBCT was not possible. Each treatment was performed using the Varian TrueBeam linear accelerator with a board-certified radiation oncologist supervising each session.

SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) was utilized for statistics, and $P<0.05$ was considered statistically significant. Comparisons of the duodenal volume were performed by the Mann-Whitney U test.

Results

Clinical characteristics of both the populations receiving water and oral contrast are displayed in *Table 1*. In all patients, in the absence of a quantitative measure, the duodenum was able to be subjectively identified on the simulation CT (*Figure 1*). In the water group, the median volumes of duodenum and stomach were 72.86 cm^3 (range, 44.51–130.90 cm^3) and 350.27 cm^3 (range, 66.37–1,314.19 cm^3), respectively. In the oral contrast group, median volumes were 86.21 cm^3 (range, 50.11–157.89 cm^3) and 341.03 cm^3 (range, 134.65–1,134.88 cm^3). There were no significant differences between groups in median duodenal and gastric volumes (*Figure 2*, P=0.115 for

Table 1 Clinical characteristics of the study population

Parameter	Water	Oral contrast
Age (years)		
Median (range)	69 (47–84)	64 (35–87)
Gender		
Male	9 (69%)	24 (60%)
Female	4 (31%)	16 (40%)
Tumor location		
Head/neck	10 (77%)	40 (100%)
Body/tail	3 (23%)	0 (0%)
Stage		
IIA	4 (31%)	1 (3%)
IIB	6 (46%)	17 (43%)
III	1 (8%)	22 (55%)
IV	2 (15%)	0 (0%)
Pathology		
Adenocarcinoma	13 (100%)	40 (100%)
Dose/fractionation		
3 Gy ×10	2 (15%)	0 (0%)
5 Gy ×5	0 (0%)	9 (23%)
6 Gy ×5	0 (0%)	4 (10%)
7 Gy ×5	8 (62%)	13 (33%)
8 Gy ×5	3 (23%)	14 (35%)
Duodenal volume, cm^3		
Median (range)	72.86 (44.61–130.90)	86.21 (50.11–157.89)

duodenum and 0.813 for stomach). All patients were able to drink the same amount of water 15–20 min prior to each fraction of SBRT to keep the duodenum volume subjectively the same as it was on the simulation CT scan.

Discussion

SBRT is an emerging treatment option for pancreatic cancer, used primarily for locally advanced (unresectable) diseases, as it can potentially provide local tumor control without significant disadvantages for patients' quality of life (13). Feasibility and efficacy has been shown in neoadjuvant settings (14), elderly patients (15), those with many comorbidities (16), and re-irradiation cases (17).

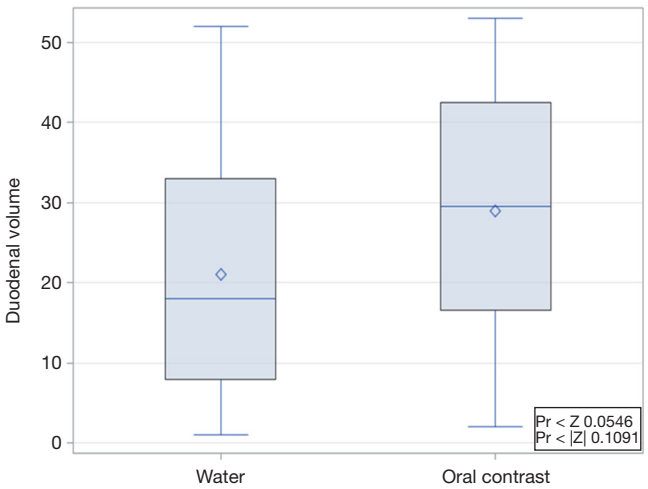

Figure 1 Comparison of duodenal volume in the water and oral contrast groups.

Our institution has employed a novel strategy for these patients that has resulted in high reproducibility and ultimately, low observed duodenal toxicities. In patients both on- and off-protocol, we have observed no grade 2+ duodenal toxicities which have been attributed to SBRT thus far in utilization of this strategy. The commonly duodenal-associated toxicities were grade-1 dyspepsia, poor appetite, nausea, and abdominal discomfort/pain. Recently, we performed a secondary dosimetric analysis to examine any possible associations among dosimetric parameters, histologic damage to the duodenum, and clinical toxicities in patients who had pancreaticoduodenectomy from our institutional phase I neoadjuvant SBRT trial. Our study showed that duodenal histologic damage but not the clinical toxicities correlate with the mean duodenal dose, V20-V35, and the PTV mean/maximum doses. In this cohort, four grade-2 and one grade-3 acute toxicities were observed (18).

Using water, target, duodenal, and gastric volume delineation is comparably similar to that with oral contrast, as the hypodense nature of water and the higher-density duodenal wall provide a high-quality barometer for delineating the clinical borders of the duodenum and stomach. Moreover, this setup is associated with high reproducibility for each treatment, although it is an admittedly a subjective measure. In addition, due to tumor motion with an average peak-to-peak amplitude of 15 mm in the craniocaudal direction, 5 mm in the anteroposterior direction and 3 mm in the lateral direction has been reported by Heerkens *et al.* (19), gating delivery as well as

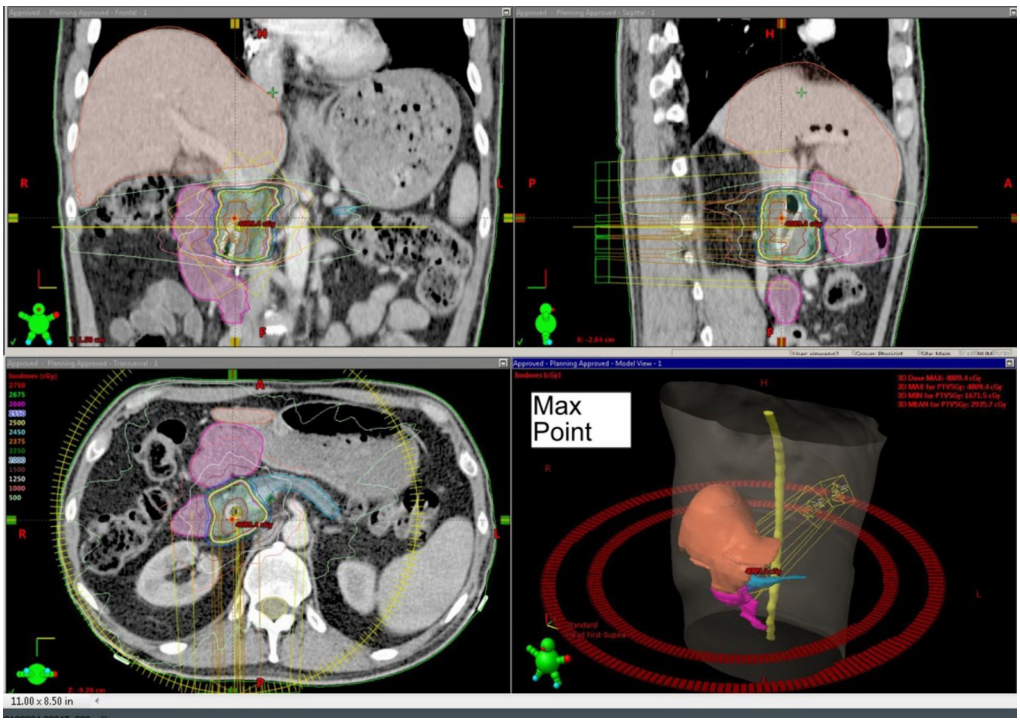

Figure 2 Simulation CT scan images showing outline of the duodenum in a patient who ingested water prior to simulation.

intestinal filling with water with the presented drinking protocol may reduce variability. Lastly, we performed dosimetric analysis and found that the median duodenal max and mean doses in the water group were significantly smaller than those in the contrast group (max: 31 *vs.* 37 Gy, P=0.005; mean: 12 *vs.* 17 Gy, P=0.009). The median gastric max dose in the water group was significantly smaller than that in the contrast group (25 *vs.* 33 Gy, P=0.017). However, there was no difference between groups in the stomach median mean dose (4 *vs.* 6 Gy, P=0.750). The superior dosimetric profile for the water group can be explained as improved planning technique as patients in the water group are planned more recently. Furthermore, it is important to consider that the "*in vivo* dosimetry" during actual treatments may result in an even more superior profile for the water group. This is due to the fact that oral contrast is typically not ingested prior to each treatment and the duodenum is presumably collapsed during SBRT delivery, as opposed to daily pre-SBRT ingestion of water.

There are limitations to our study. First, the retrospective nature and low sample sizes can never exclude selection bias; but this issue will likely not be studied prospectively; and the group receiving water were consecutive patients with the comparator arm a group of prospectively-collected patients. Second, the limitations of the quality of kilovoltage CBCT in providing accurate estimates (of what subjectively constituted a "similar-looking duodenum" as the simulation CT) is clearly apparent. Rather, it should be prominently mentioned that the goal of this communication is to put forth a novel technique that should be "subjectively corroborated" by other investigators and utilized in their own clinical practices in order to individually assess whether this method is of utility for their patients.

In summary, to our knowledge, this method has not been described before and is used rarely (if at all) at the present time. Nevertheless, we encourage further use and study of this method for the known technical challenges posed by pancreatic SBRT.

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Footnote

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

Ethical statement: The study was approved by University of Nebraska Medical Center Institutional Review Board (IRB# 646-16-EP) and informed consent was waived by the IRB because it is a retrospective study.

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