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FULL PAPER

Dosimetric impact of gastrointestinal air column in radiation treatment of pancreatic cancer

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Objective: Dosimetric evaluation of air column in gastrointestinal (GI) structures in intensity modulated radiation therapy (IMRT) of pancreatic cancer.
Methods: Nine sequential patients were retrospectively chosen for dosimetric analysis of air column in the GI apparatus in pancreatic cancer using cone beam CT (CBCT). The four-dimensional CT (4DCT) was used for target and organs at risk (OARs) and non-coplanar IMRT was used for treatment. Once a week, these patients underwent CBCT for air filling, isocentre verification and dose calculations retrospectively.
Results: Abdominal air column variation was as great as ±80% between weekly CBCT and 4DCT. Even with such a large air column in the treatment path for pancreatic cancer, changes in anteroposterior dimension were minimal (2.8%). Using IMRT, variations in air column did not correlate dosimetrically with large changes in target volume. An average dosimetric deviation of mere −3.3% and a maximum of −5.5% was observed.
Conclusion: CBCT revealed large air column in GI structures; however, its impact is minimal for target coverage. Because of the inherent advantage of segmentation in IMRT, where only a small fraction of a given beam passes through the air column, this technique might have an advantage over 3DCRT in treating upper GI malignancies where the daily air column can have significant impact.
Advances in knowledge: Radiation treatment of pancreatic cancer has significant challenges due to positioning, imaging of soft tissues and variability of air column in bowels. The dosimetric impact of variable air column is retrospectively studied using CBCT. Even though, the volume of air column changes by ± 80%, its dosimetric impact in IMRT is minimum.

INTRODUCTION

Radiation treatment of upper gastrointestinal (GI) tract malignancies requires consideration of many parameters for accurate delivery of prescribed dose to the appropriately defined target. In particular, these include respiratory motion, gastric motility, air volume, as well as other variabilities inherent in the set-up and delivery of external beam radiation treatment. Four-dimensional CT (4DCT) scan has been proposed for treatment planning purposes to account for the motion associated with breathing in treating upper GI tumours.[1–5] Structural changes due to inter-fractional gastric motion during radiation therapy can be delineated with use of surgical clips in the gastric mucosa detected on CT scan[3] and intra- and inter-fractional target deformation due to gastric motion have been described using CT images with corresponding estimations for necessary target volume changes.[4,5] However, even surgical clips may not be suitable with large variability due to gastric motion, where landmarks and clinical judgement prevails. Adaptive treatment approaches have been proposed for the changes in anatomical structures due to various parameters but have not exclusively pointed to changes in air column.[6,7] It is known that neither static CT nor 4DCT simulation scans will capture the potential variability of the air column that can be seen on a daily basis.[6,7] Air volume variability in the stomach and bowel is commonly observed in clinical practice on imaging studies and such variability in the air column can be seen during the course of radiation treatment for abdominal malignancies.

Furthermore, implementation of intensity modulated radiation therapy (IMRT) has been used for treating GI malignancies that has led to tighter margins around tumour volumes with optimal goals of dose escalation, increased conformality of target volumes and minimization of radiation dose to normal tissues/organs at risk (OAR). However,

this technique generally requires that the target volumes be well understood so that they are not inadvertently missed.[8–10] For the reasons of dose escalation and improved conformality, IMRT approaches for treating pancreatic cancer have been proposed and explored[11,12] except the motion management in photon beam. Such exploration involves non-coplanar beam arrangements but the advantage is not clearly understood.[13] Concerns arise from the complexities in accurately treating pancreatic cancer due to factors such as gastric air column and related organ motion.[7,14] The anatomical position of the pancreas inside the abdominal cavity related to the aforementioned changes inevitably leads to movement in the target volume position and location of OARs with respect to isocentre location. Consequently, image guidance plays a key role in accurately treating pancreatic cancer with IMRT.[15] Image guidance also provides leg work for adaptive therapy which has been advocated.[6] Now with the acquisition of frequent cone beam CT (CBCT) during the course of radiation therapy, such variability can be monitored and image-based setup adjustments can be made.

Even though CBCT can provide the confidence in our isocentre position localization, the abdominal structural deformation due to gastric air volume and subsequent dosimetric consequences on pancreatic cancer target volumes is not fully understood. Our goal here is to compare the "planned dose" to "actual dose" delivered to target volumes in the treatment of pancreatic cancer that has poor prognosis. This study used IMRT with CBCT for image-guided radiation therapy to improve dose delivery thus probably outcome.

METHODS AND MATERIALS

Pancreatic cancer in our centre was relatively rare, thus accruing a large number of patients was not possible. Nine consecutive patients treated for pancreatic cancer with IMRT were chosen under the Institutional Review Board exempt status for retrospective analysis. During the CT simulation process, each patient was properly immobilized in a vacloc and scanned using a 4DCT (Picker CT Scanner). As per departmental protocol, no explicit instructions were given to patients in regards to oral intake (foods or liquid) prior to the simulation or for their treatments. Target volumes and OARs were delineated. Patients were planned using Eclipse treatment planning system (Varian Medical Systems, Palo Alto, CA) with analytical anisotropic algorithm v. 11.1 for inhomogeneity correction. IMRT plans using typically a 7 to 9 non-coplanar beam arrangement were created. These plans were designed with target goals to achieve 95% planning target volume (PTV) coverage with at least 95% of the prescribed dose while sparing OARs as much as possible, which is common practice.[16] Even though such criterion is not recommended in ICRU-83[17] for IMRT where D_{50} is advised. All patients had prescription doses of 50 or 50.4 Gy (mean dose 50.1 Gy) to the PTV2, which covered areas of either gross disease or where there was clinical suspicion of microscopic spread. In nearly all cases, uninvolved regional lymphatics were covered by a second lower dose target volume, PTV1, with a prescribed dose of 45 Gy. These patients with lower two dose levels were treated with a simultaneous integrated boost technique using 25 total fractions treated 5 days per week.

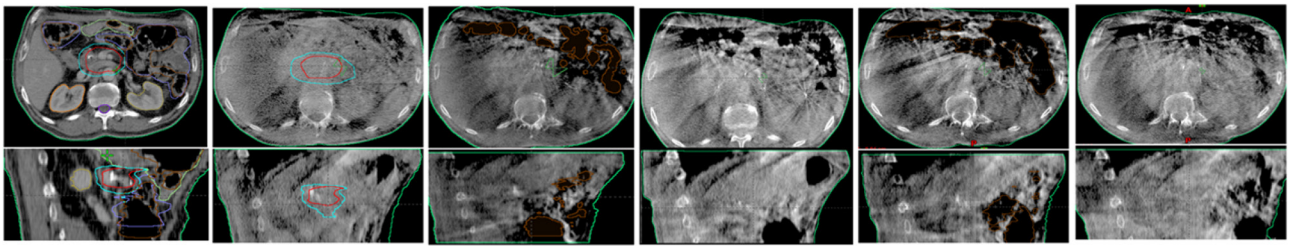
Patients were treated daily after obtaining kilovoltage (kV) orthogonal imaging for isocentre localization matched on target. Each patient also underwent multiple CBCTs for isocentre and volume verification during the course of treatment. The institutional practice was to match image set with CBCT and shift >5 mm in any direction was applied before patient treatment. There was no 6 degree of freedom table at our institution. Anywhere from 3 to 6 CBCTs were obtained on each patient with a total of 41 CBCTs acquired and an average number of CBCTs per patient of 4.6. For each CBCT, the images were exported to the treatment planning system for image fusion with the actual simulation CT. These acquired CBCTs were then used for repeated target delineation. Air column was contoured slice by slice and volume was then estimated. The treatment planning was performed without optimization so comparison could be made with the initial simulation CT scans.

Each CBCT image was fused to the simulation CT using bony anatomy as well as identified soft tissues. Once a CBCT was fused accurately, the target volumes were traced onto each CBCT by superimposing or blending the image sets. The "external" or "body" contour was recreated for each case as well as the "air volume", consisting of gastric air and bowel gas. This volume was contoured individually onto each CBCT and recorded in cubic centimetres. From the fusion, the location of the original plan's isocentre was also drawn on each CBCT to give a surrogate point for isocentre placement.

CBCT images have been used successfully for dose calculation with proper CT number to electron density conversion as described in literature.[18–24] Different CT-electron density file of a CT phantom with various kV and filter on imaging system was acquired as described elsewhere.[25] These files were appropriately used after importing the images for dose calculation in this study. The on-board imaging based CBCT v.n 2.1 (Varian Medical System) was used in this study. Dosimetric accuracy of CT-based planning has been completed during treatment planning system (TPS) commissioning based on CT-electron density curve to within ± 2% for various clinical cases. The same is expected of CBCT data when a different CT-electron density file is used.

Next, the previously used IMRT plans from each case were copied and pasted onto the patients' CBCT scans, effectively creating a radiation treatment plan with the same beam arrangement on each CBCT image set (Figure 1). A new set of CT number and electron density curve for the CBCT was used for dosimetry. The fields were aligned onto the CBCT's at the isocentre that was placed from the planning CT registration. Monitor Units (MU) from individual treatment beams were obtained and recorded from the initial IMRT plans. To ensure the accuracy and validity of this process, the newly created IMRT plans were calculated using the same fluence and fixed MUs from the original treatment plans as this was delivered to the patient on a daily basis. The CBCT dose calculation was not optimized, rather treatment planning system derived fluence and MU were used for dose calculation. Finally, anterior to posterior (AP) separation was measured on all CT data sets at the isocentre so that CBCT

Figure 1. Axial (top row) and sagittal (bottom row) images of a pancreatic cancer patient. The left most image is the simulation CT followed by the weekly CBCT images. Note that the gastric content is variable weekly from simulation to treatment. Red colour GTV and teal PTV contour. CBCT, cone beam CT; GTV, gross tumour volume; PTV, planning target volume.



dimensions could be compared to those of the planning CTs to see any gross changes in body structure or weight loss.

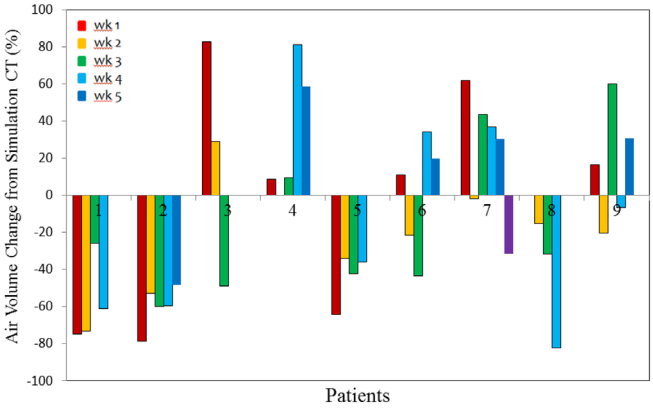
RESULTS

The volume of the air column measured from the simulation CTs was variable among our patients with a range of 152 to 852 cm^3. The average air column on the nine planning CTs was 400 ± 210 cm^3 (one SD). The variability of the measured air volume from CBCTs was larger with a range of 144 to 1100 cm^3. The average air column on the 41 CBCTs was 347 ± 282 cm^3. When comparing each patient's air volume from the initial simulation CT to individual CBCTs, air volumes ranged as much as ± 80% as shown in Figure 2 for all patients.

To understand how air column changes related to physical dimensions, we measured AP thickness on all CT scans, including the simulation and CBCTs. The average patient AP separation at isocentre was 22.4 cm (range 20.4–25.3 cm) on the simulation scans. The average patient AP separation of the CBCTs at isocentre was also 22.4 cm (range 20.0–25.4 cm). This range of AP dimensions corresponded to a maximum difference of 2.8% when comparing each patient's AP separation on initial planning CT to that patient's averaged CBCT AP separation value.

Dose volume histogram (DVH) analysis was used to evaluate target volume coverage. We evaluated the high dose PTV2 from the initial treatment plans and compared this to the coverage this volume received on the individual CBCT plans. For the initial plans, 100% of the PTV was covered by 91.7% of the prescription dose. When this was compared to the plans created on the CBCTs, it was found that 100% of the PTV was covered by 88.4% of the prescribed dose thus a reduction of 3.3%. Comparing the PTV coverage on DVH between the actual plans and the CBCT plans across the nine individual patients, the largest difference in relative dose coverage was −5.5% (SD = 4.8) and smallest difference between actual and CBCT plans was +0.1% (SD = 0.8). The average difference in relative dose from the CBCT plans compared to the actual plans was 3.3% reduction across our cohort of patients. To see if there was a correlation between the dose covering 100% of the PTV and air volume in cm^3 of the 50 plans (9 from the initial simulation CT and 41 CBCT plans), these two variables were plotted relative to each other. The resultant trend line was nearly constant and linear as described by the equation $y = 0.0019 \times +88.0$, $R^2 = 0.0149$ shown in Figure 3. This dose reduction is probably due to air column. But this indicates that there is no correlation between dose covering 100% and air volume.

Figure 2. Variability of air volume on serial CBCTs compared to simulation CT for each patient. Colour bars represent weeks. CBCT, cone beam CT.



DISCUSSION

Pancreatic cancer has relatively poor prognosis that may be due to clinical and technical difficulties. Radiation therapy for GI malignancies can be difficult due to internal changes to the patient's anatomy caused by multiple factors including air in the GI tract. Variability of gastric and bowel gas is inherent and thus creates potential uncertainties in daily setup variances along

Figure 3. Correlation between the dose covering 100% of the PTV and air volume in cm^3 taken from the 50 treatment plans (9 from the initial simulation CT's and 41 CBCT's). CBCT, cone beam CT; PTV, planning target volume.

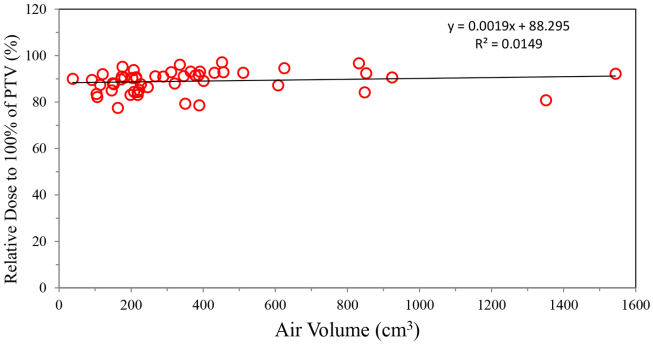
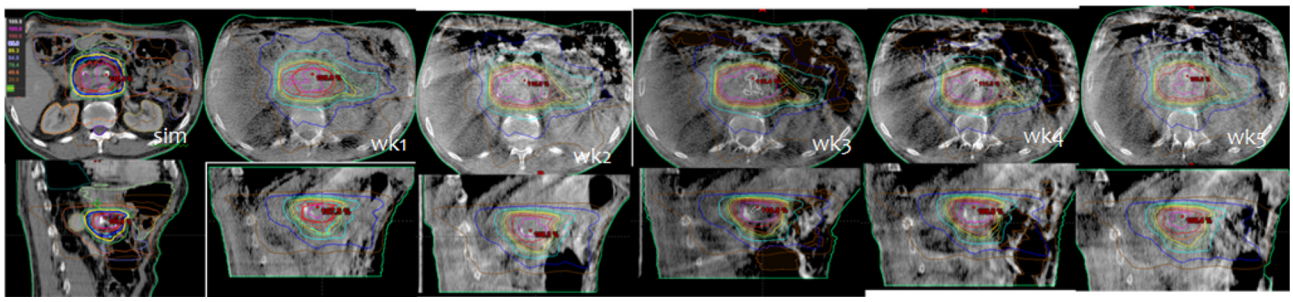


Figure 4. Isodose distribution in axial (top row) and sagittal (bottom row) view of the above pancreatic cancer patient. The left most image is CT-simulated image treatment plan. The rest are the weekly CBCT images on which dose calculation was performed based on the image fusion.



with the PTVs and OARs as shown in Figure 4. This variability of targets and OARs due to air column is of particular concern when attempts are made for dose escalator to spare normal tissues and reducing margin around target for decreased toxicity. In treating pancreatic cancer, IMRT has been suggested as an alternative to three-dimensional conformal radiation therapy (3DCRT) by optimization to achieve increased target dose and reduce normal tissue complications.[11,12] Furthermore, in dose escalation studies with hypofractionated stereotactic body radiation therapy (SBRT) for the treatment of pancreatic cancer, it has been shown that air volume differences between treatments can have a significant impact on the dose delivered to the target volumes.[26] The central focus of this research was to evaluate the impact of air column on the dose coverage to target volumes for patients with pancreatic cancer treated with IMRT where the air column is variable in position and amount daily.

To evaluate potential dosimetric differences that could occur from changes in air column during IMRT for pancreatic cancer, we compared actual treatment plans from nine patients to the CBCT scans acquired on nearly a weekly basis during treatment. These CBCTs were initially intended to aid in image guidance for target localization. To make this comparison between a CT scan used for treatment planning and CBCT used for image guidance, dose calculation linearity between a conventional planning CT and a CBCT had to be established. CBCT-based dose calculations can be complicated by inaccuracies in the conversion of CT values to electron densities due to difference in scatter contribution and CBCT acquisition parameters. Furthermore, the significant degree of variance when calculating dose between the two modalities (CT and CBCT) would distort the results of any such comparison. However, the magnitude of dose differences from CT number in soft tissues has been found to be relatively minimal[25] and dose calculation based on individual electron density curves could be fairly accurate.

Several institutions have undertaken studies to investigate the use of CBCT for IMRT planning and the linear relationship of CBCT IMRT planning with conventional CT methods. One such study compared CBCT planning to conventional CT planning for IMRT in patients with head and neck cancer.[27] Hounsfield Unit (HU) mapping from conventional CTs were applied to the CBCTs prior to dose calculation. This revealed the overall differences between the dose calculation based on the mapped CBCT scans and the conventional CT scans were generally within 1%. Another institution evaluated dose accuracy using site-specific calibration and investigated HU to electron density conversion stability.[24] Different anatomical sites were analysed including the abdomen and pelvis. HUs for various tissues were compared between CBCT and conventional CT as well as minimum, maximum and mean doses to target volumes. The authors concluded that there was a 2% difference between the two planning methods. HU mapping methodologies have been carried out on homogeneous and inhomogeneous phantoms with dosimetric consequence due to HU variations for CBCTs as well.[28] Results indicate variance from conventional CT scans of less than 1% and close agreement in isodose lines. A fourth group has done similar dosimetric comparisons and concluded that less than 1% difference was found in calculated dose to targets for a complex inhomogeneous phantom between CBCT images and planning CT images.[29] Just as in our study, all the facilities conducting the aforementioned research utilized Varian linear accelerators with CBCT image acquisition and Eclipse treatment planning system with analytical anisotropic algorithm for dose inhomogeneity corrections. Therefore, there is seemingly a consensus that CBCT images can be used to calculate dosimetric parameters accurately in radiotherapy planning, which is also in agreement with the data provided by Das et al[25].

Using CBCT for treatment planning in our study, we found there is a potentially substantial variation in air volume on any given scan. Patients in our series had changes in air volume as great as ± 80% on CBCT when compared to initial simulation CTs used for treatment planning. The AP dimension could be a quick indication of gastric volume. However, these changes in air column had a seemingly minimal effect on the measured AP dimension with both the average measurement on simulation CT and CBCT for all scans being the same at 22.4 cm. Furthermore, our results show that these differences in air volume over the course of treatment have a minimal impact on target volume coverage. The largest average difference in 100% of a PTV being covered was a 5.5% reduction in dose compared to the coverage delivered in the actual treatment plan. Across our total cohort of patients, the average difference in relative planned *vs* delivered dose was only −3.3%. Furthermore, no instructions were given to our patients for food or liquid oral intake prior to simulation or daily treatments. Given this, our results are consistent with others' findings when treating upper GI malignancies without

daily intake instructions and with no plan to try to control or alter stomach volume during radiation therapy.[30]

While these results show a minimal relative reduction in dose delivered, we believe with 3DCRT planning techniques the dosimetric impact would be more concerning. As 3D planning delivers radiation dose from fixed field sizes with the same intensity using beam weighting, therefore such plans may more easily skew the dose when traveling through large volumes of air. On the other hand, our plans were all done with an IMRT technique, and IMRT offers the advantage of dose delivery based on beamlet segmentation. Similar findings were observed by Houweling et al[7] who compared photon, proton and carbon ion and concluded that photon beam is more robust to interfractional changes in pancreatic cancer using modulated beam. With beamlets, only a small fraction of the beam passes through at any given area of the air column and the air would thus have less potential impact on overall dose distribution. While this might be a potential advantage for using IMRT in upper GI treatment planning, others have found that using breath holding techniques in conjunction with IMRT might actually lead to considerable dose variation between fractions due to other variables in daily treatment.[31] Care must be taken for protecting OARs if these techniques are concurrently employed.

There are several limitations to our study. The number of patients in this study on pancreatic cancer was limited due to relatively fewer patients at our institution, thus a very strong conclusion can be made. Additionally, this is a retrospective study and OARs were not individually delineated and analysed on our CBCTs, and because of this there is no dosimetric comparison to be made to the actual treatment planning DVHs for OARs. This is due to our priority in study for target volume coverage and difficulty to accurately delineate OAR boundaries on CBCTs given the poor image quality, lack of i.v. contrast and inherent loss of resolution. This study was limited to IMRT plans and we do not have a head-to-head comparison of IMRT to 3DCRT plans for the effects of air column on target dose. A future area of research to address these identified shortcomings could be to prospectively use an adaptive planning technique with weekly simulation CTs taken to create both IMRT and 3DCRT plans with full DVH analysis of targets and OARs.

CONCLUSIONS

In our series, variation in the abdominal air column was as much as ±80% between weekly CBCT and planning CT for a given patient. When treating pancreatic cancer with IMRT, these differences in air volume do not seem to affect patient AP dimension nor do they correlate with significant changes in PTV coverage (<3.3%). Because of the inherent advantage of beamlet segmentation in IMRT, where only a small fraction of a given beam passes through the air column at a time, this technique might have an advantage over 3DCRT in treating upper GI malignancies where the daily air column can vary.

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The data in this study were acquired at Indiana University where most of the authors used to work.

INFORMED CONSENT

This study was approved by Indiana University Institutional Review Board as exempt study. The data were retrospectively analysed without alteration of patient care. For this retrospective study, formal consent is not required.

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