Usefulness of 4D-CT for Radiation Treatment Planning of Gastric MZBCL/MALT

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4DCT/Gastric lymphoma/Treatment planning/IGRT.

It is well known that significant variations in stomach size, shape, and respiratory motion lead to uncertainties in target localization during treatment for gastric lymphoma. In this study, the usefulness of 4D-CT for radiation planning of gastric MZBCL/MALT was evaluated. Treatment planning using 4DCT (plan A) and conventional planning with a uniform margin (plan B) were compared using dose volume histograms (DVH) of the planning target volume (PTV) and the organ at risk, as well as the dose coverage of the clinical target volume (CTV) assessed by weekly online cone beam CT (CBCT) during the treatment course. In addition, regarding the image quality of CBCT, the interobserver agreement for the delineated volume of the CTV on CBCT was analyzed. The mean PTV of plan A was significantly smaller than that of plan B (p = 0.008). The mean doses to the liver and heart in plan A were significantly lower than those in plan B (p = 0.02 and 0.03, respectively). The reductions of V20 of each kidney in plan A compared with those in plan B were 4.8 ± 2.4% in the right kidney and 16.3 ± 10.4% in the left. There was no significant difference in the dose coverage of the CTV between the plans during the treatment course. The interobserver agreement for the volume of the CTV was moderate correlation. Treatment planning using 4DCT for gastric MZBCL/MALT was useful for effective and safe irradiation with minimizing exposure of the organ at risk.

INTRODUCTION

Extranodal marginal zone B-cell lymphoma mucosa-associated lymphoid tissue type (MZBCL/MALT) in the stomach is extremely sensitive to moderate-dose radiation. Therefore, radiotherapy (RT) is often selected as the advanced therapy for patients with MZBCL/MALT refractory to H. pylori eradication therapy and those negative for H. pylori infection.1–4) Effective radiation requires encompassing the whole stomach in the field, as well as the adjacent perigastric lymph nodes if they are involved. However, it is well known that significant variations in stomach size and shape, digestive movement, and respiratory motion lead to uncertainties with regard to target localization and reproducibility during simulation of and treatment for gastric MZBCL/MALT. The simplest approach is to add an adequate margin to the clinical target volume (CTV), defined as the whole stomach with or without adjacent perigastric lymph nodes. In some previous studies of RT for gastric lymphoma, the planning target volume (PTV) has been defined as the CTV plus an approximately 20 mm margin in all directions.1–3) However, the optimal irradiation technique that can be effectively and safely irradiated with adequate margins and a lower radiation dose to the organ at risk (OAR), i.e., kidney, liver, or heart, has not been well established.

In the free breathing state, respiration is the dominant source of intrafraction organ motion during RT. Respiratory synchronized four-dimensional CT imaging (4DCT) has been proposed as a technique to minimize motion uncertainties by providing information about respiratory-induced organ motion during treatment planning.5,6) Because respiratory motion affects the expansion of the irradiated target, 4DCT scans may aid in radiation targeting.7–9)

In the present study, we performed the following evaluations to investigate whether or not a 4DCT study is a reliable benchmark for determining radiation treatment margins in the setting of gastric MZBCL/MALT.

1) The dose distributions of the PTV and OAR for two different PTV margins, corresponding to the 4DCT-based margin and the uniform margin of 20 mm, were analyzed using dose-volume histograms (DVH) and compared.
(2) To investigate whether or not adequate planning margins were applied, the dose coverage of the CTVs assessed by weekly online cone beam CT (CBCT) during the treatment course for two different plans, corresponding to the 4DCT-based margin and the uniform margin of 20 mm, were analyzed using DVH and compared. In addition, regarding image quality of CBCT for image-guided radiotherapy (IGRT) on gastric irradiation, interobserver variability for delineation of the CTV on CBCT was evaluated.

MATERIALS AND METHODS

Included in the study were 7 patients with gastric MZBCL/MALT treated at our institution between April 2008 and March 2010. All patients were treated with RT because they were refractory to H. pylori eradication therapy or negative for H. pylori infection. Before RT, written informed consent to participate in the study was obtained from all patients.

4D planning of gastric MZBCL/MALT

Simulation procedures

The patients were instructed to avoid eating and drinking for 3 hours before simulation and eventual treatment in order to reduce the day-to-day variations in stomach size and digestive movement of during RT. The patients underwent simulation in the supine position with a customized vacuum immobilization device (Vac-Loc; MedTec, Orange City, IA) using a four-slice CT scanner (Lightspeed; GE Medical Systems, Waukesha, WI). Images were reconstructed at 2.5 mm intervals. After the simulation helical CT (HCT) scanning, 4DCT scanning was performed to analyze organ positions at all phases of respiration with the patient in the same treatment position. The Varian Real-Time Position Management System (RPM; Varian Medical Systems, Palo Alto, CA) was used to reconstruct the 4DCT respiratory phases. The respiratory pattern and the CT images were then transferred to an Advantage Workstation (GE Medical Systems), where the images were sorted according to the breathing phase during which they were acquired. Images were sorted into 10 phase groups, with one 3DCT image set for each phase group. The HCT and all 10 CT image sets of 4DCT data were imported into a 3D treatment planning system (Eclipse; Varian Medical Systems) and all CT data sets were fused using a rigid-volume image registration algorithm for bone registration to vertebral bodies.

After image registration, the CTV was defined as the entire stomach and any suspicious perigastric lymph nodes; this area was then contoured in simulation CT and the CT image sets corresponding to the 10 different breathing phases. The internal target volumes (ITVs) on 4DCT were then formed by merging all CTVs in the 10 phases. The organs at risk were defined as the right kidney, left kidney, liver, and heart. These organs were contoured in simulation CT as well as in the CT image sets for the 10 phases. Then two different PTVs were defined: One was the ITV on 4DCT plus an 8 mm margin as interfraction organ motion and setup error in all directions (PTV-A), and the other was the CTV on the HCT plus a 20 mm margin in all directions (PTV-B).

Planning procedures

All patients were treated with a 3D conformal radiation therapy (3D-CRT) plan using a 10-MV X-ray. A beam arrangement consisting of anterior, posterior, right, and left lateral fields was deemed most appropriate considering the location of the PTV and its proximity to the normal tissues. The fields were weighted appropriately to spare the kidneys as much as possible. MLC apertures were created that encompassed the PTV by 5 mm in all directions. In each patient, two different 3D-CRT plans, labeled A and B, were generated based on PTV-A and PTV-B, respectively. The plans were normalized to the isocenter, and the dose was prescribed to the isodose level that encompassed 95% of the PTV (D95), typically a 95% isodose. The prescription dose for each patient was 30 Gy in 15 fractions.

Dose distributions for each plan were analyzed using DVH. PTV and OAR doses were compared between plans A and B with the following parameters:

1. Mean PTV volume
2. The volume of the PTV receiving at least 95% of the prescription dose (V95)
3. The dose received by 95% of the PTV (D95)
4. Percent volume of each individual kidney receiving 20 Gy or more (V20)
5. Percent volume of the liver receiving 30 Gy or more (V30)
6. Mean dose of liver and heart

Challenging of IGRT on gastric irradiation

A Varian Clinac iX linear accelerator (Varian Medical Systems), equipped with an on-board imager (OBI) system that includes a kilovoltage X-ray tube and a flat-panel detector mounted to each side of the gantry perpendicular to the treatment beam, was used in this study. A CBCT image set was acquired weekly for each patient during the treatment course using OBI system. In this study, a CBCT image set was acquired using high quality mode (standard mode with bow-tie filter (125 kVp, 80 mA, 25 ms, source-to-imager distance of 150 cm) and full-fan mode (the imager is centered with X-rays axis and field-of-view < 25 cm). The CBCT images were transferred to the planning system and rigidly registered to the 4DCT and HCT with respect to bony anatomy. To evaluate the image quality of CBCT for IGRT on gastric irradiation, two radiation oncologists (M. M. and K. O.) independently delineated a CTV corresponding to each CBCT (CTVCBCT). Then the interobserver agreement for the delineation of the CTVCBCT was analyzed by the comparison of the volume of CTVCBCT. Next, to compare between plans A and B in the dose coverage of the CTVCBCT...
during the treatment course, a radiation oncologist (M. M.) delineated a new CTV\textsubscript{CBCT} to adjust the CTVs on plans A and B for changes due to organ motion. The resulting volumes were projected back to plans A and B. The dose distribution of CTV\textsubscript{CBCT} was analyzed using DVH, and the \( V_{95} \) and \( D_{95} \) of CTV\textsubscript{CBCT} were compared between plans A and B.

**Statistical analysis**

For statistical analysis, SPSS software (version 15.0, SPSS, Chicago, IL, USA) was used. Data are expressed as mean ± SD. Statistical analysis was performed using the Mann-Whitney \( U \) test. A \( P \) value of .05 or less was considered to indicate a significant difference. The interobserver variability for the delineations of the CTV\textsubscript{CBCT} was analyzed by calculating the interclass correlation coefficient (ICC) for single measurements (0–0.20, poor correlation; 0.21–0.40, fair correlation; 0.41–0.60, moderate correlation; 0.6–0.80, good correlation; and 0.81–1.00, excellent correlation).

**RESULTS AND DISCUSSION**

The mean PTV volume of plans A and B were 867.8 ± 120.9 and 1291.4 ± 111.6 cm\(^3\), respectively. The PTV volume of plan A was significantly smaller than that of plan B (\( p = 0.008 \)). Table 1 compares the results of analysis using DVH between the plans. The \( V_{95} \) and \( D_{95} \) of the PTV differed only slightly between the plans. The \( V_{20} \) of each kidney and the \( V_{30} \) of the livers in plan A tended to be lower than those in plan B, but there was no significant difference. The mean doses of the liver and heart were significantly lower in plan A than in plan B (\( p = 0.02 \) and 0.03, respectively).

Figure 1 indicates the \( V_{20} \) of each kidney for all 7 patients. In comparison with plan B, plan A was able to reduce the \( V_{20} \) of each kidney. On average, for the right and left kidneys, the corresponding reductions in \( V_{20} \) of plan A were 4.8 ± 2.4\% and 16.3 ± 10.4\%, respectively.

In each patient, weekly CBCTs were performed three times. The interobserver agreement for the volume of CTV\textsubscript{CBCT} was moderate correlation (ICC = 0.53). The mean \( V_{95} \) and the mean \( D_{95} \) of CTV\textsubscript{CBCT} for plans A and B are shown in Table 2. The mean \( V_{95} \) and the mean \( D_{95} \) of CTV\textsubscript{CBCT} on plan B were each closer to 99\%, and those on plan A were closer to 97\%. There were no significant differences between the plans in the mean \( V_{95} \) and the \( D_{95} \) of CTV\textsubscript{CBCT}. Therefore, we considered the dose coverage of CTV\textsubscript{CBCT} on both plans to be excellent, and the dosimetric differences between the plans were negligible. Figure 2 shows the frontal radiation fields of both plans projected the CTV\textsubscript{CBCT}.

For gastric MZBCL/MALT, target localization and reproducibility during simulation and treatment are complicated by uncertainties arising from variations in stomach filling and respiratory motion. The PTV must account for all intra-

<table>
<thead>
<tr>
<th>Plan</th>
<th>PTV volume (cm(^3))</th>
<th>PTV ( V_{95} ) (%)</th>
<th>PTV ( D_{95} ) (%)</th>
<th>Rt kidney ( V_{20} ) (%)</th>
<th>Lt kidney ( V_{20} ) (%)</th>
<th>Liver ( V_{30} ) (%)</th>
<th>Liver mean dose (Gy)</th>
<th>Heart mean dose (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>867.8 ± 120.9</td>
<td>99.6 ± 0.3</td>
<td>99.7 ± 1.2</td>
<td>2.7 ± 2.4</td>
<td>15.9 ± 15.1</td>
<td>5.00 ± 1.9</td>
<td>13.4 ± 1.6</td>
<td>5.4 ± 2.1</td>
</tr>
<tr>
<td>B</td>
<td>1291.4 ± 111.5</td>
<td>99.7 ± 0.4</td>
<td>100.1 ± 1.1</td>
<td>5.7 ± 3.6</td>
<td>23.6 ± 23.8</td>
<td>10.9 ± 5.9</td>
<td>18.4 ± 2.6</td>
<td>7.6 ± 2.7</td>
</tr>
</tbody>
</table>

Values are average ± standard deviation. * Statistically significant difference (\( p < .05 \))

**Table 1.** The comparisons of PTV volume, PTV \( V_{95} \), \( D_{95} \), and normal-tissue dose between plan A and plan B.

**Fig. 1.** The evaluations of \( V_{20} \) of each kidney for all 7 patients on both plans A and B. (A) Right kidney, (B) Left kidney. Plan A is able to reduce the \( V_{20} \) of each kidney in comparison with plan B.
fractional as well as interfractional organ motions throughout a treatment course. The intrafractional organ motion during RT is derived from respiration, cardiac motion, and digestive movement. In the free breathing state, respiration is the dominant source of intrafractional motion of the stomach during RT. Some investigators have examined the respiratory amplitude of the stomach using fluoroscopy with an oral barium sulfate suspension and inspiration and expiration films to aid in the localization of the stomach; as a result, PTV was defined as the outline of the stomach with a margin of 20 mm in all directions. However, regarding these techniques, it was not ensured that the stomach received an adequate dose at each treatment during RT. In a case report of a patient with diffuse large B-cell lymphoma of the stomach treated with RT, Isobe et al. evaluated a surgical clip in the stomach using fluoroscopy during the initial simulation and again during RT, 2 and 4 weeks later. The median displacement was 24 mm (range, 5–35 mm) in the right-left direction. In an evaluation of the respiratory amplitude of the upper abdominal organs during RT using a planning CT scan and a serial study CT scan during free breathing, Wysocka et al. found that the median respiratory amplitude of the stomach in the craniocaudal direction was 16.4 mm, with individual dispersion varying from 0–41.5 mm. These results highlight the extreme individual variation that can occur in some patients. Therefore, individual assessment of respiratory motion is warranted.

Respiration-synchronized 4DCT has enabled more accurate patient specific measurement of the ITV for targets that move with respiration, as well as the customization of target volume to minimize the dose to normal tissues while avoiding a geographic miss. Therefore, several investigators have recommended the use of 4DCT to decrease the interfractional variations and to increase the geometric accuracy of RT for lung cancer and liver cancer. However, 4DCT data have been useful for reducing the intrafractional motion component of the internal margin, but its interfractional component and setup margin have not changed. The interfraction organ motion caused by daily variations in stomach size and shape is more difficult to address but also needs to be taken into account during margin design. In an assessment of interfraction organ motion of the upper abdominal organs during RT, Wysocka et al. found that the median interfraction stability of the stomach during normal breathing was 7.2 mm in the craniocaudal, 3.9 mm in the anteroposterior, and 5.8 mm in the right-to-left directions. Therefore, in this study the PTV on 4DCT was defined as the ITV with an interfractional margin of 8 mm in all directions.

To our knowledge, no study has used 4DCT to plan the treatment of gastric MZBCL/MALT. In the present study, we evaluated the usefulness of 4DCT for the treatment planning of gastric MZBCL/MALT compared to treatment planning using a uniform margin. The mean PTV volume of the treatment planning using 4DCT was significantly smaller than that of the treatment planning with a uniform margin. In addition, a comparison of the results of DVH revealed that the mean doses of liver and heart with the treatment planning using 4DCT were significantly lower than those of the treatment planning with a uniform margin. There was no statistically significant difference between the plans in either the V20 of each kidney or the V30 of the liver. However, for most patients, the treatment planning using 4DCT enabled lower V20 of each kidney compared to that with the uniform-margin treatment planning. In addition, a comparison between the plans in the dose distributions of CTV assessed by weekly
CBCT showed that the mean $V_{95}$ and the mean $D_{95}$ of the CTV of treatment planning using 4DCT were almost the same as those of the treatment planning with a uniform margin, and the dose coverage of the CTV was excellent in both plans. Therefore, treatment planning using 4DCT can be useful for safe and effective RT, with low radiation doses to the OAR.

The present study has limitations. First, the small sample size, 7 patients, limits our ability to make firm recommendations regarding the usefulness of 4DCT for treatment planning. Secondly, CBCT based IGRT is problematic for low contrast soft tissue structures. In this study, CBCT images were acquired using high-quality mode to expect the improvement of the image quality. In a comparison of image quality between CBCT and 16-multislice CT scanner, Steinke et al.\textsuperscript{13}) found that high-contrast spatial resolution and low contrast resolution for CBCT were better or equal compared to the multi-slice CT, while noise appeared to be an on-going issue for CBCT. In this study, the interobserver agreement for the volume of CTV\textsubscript{CBCT} was moderate correlation. Therefore, CBCT for IGRT on gastric irradiation is moderately acceptable, however, further research in software and hardware is necessary to improve CBCT devices with respect to image quality. Finally, we assessed the dose coverage of the CTV (stomach with or without adjacent perigastric lymph nodes) using CBCT during RT only three times for each patient. The dose coverage of the CTV had to be confirmed with every treatment fraction because of the day-to-day variability of stomach shape. However, daily CBCT on every treatment fraction may prolong treatment time and take into account the increase in patient dose.

In summary, when treatment planning using 4DCT is available for gastric MZBCL/MALT, the stomach volume, with adequate margins that account for organ motion during respiration and unavoidable changes in volume, can be effectively and safely irradiated with minimizing exposure of the kidneys, liver, and heart.

**REFERENCES**


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