PHYSICS CONTRIBUTION

MAPPING PELVIC LYMPH NODES: GUIDELINES FOR DELINEATION IN INTENSITY-MODULATED RADIOTHERAPY


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Purpose: To establish guidelines for delineating the clinical target volume for pelvic nodal irradiation by mapping the location of lymph nodes in relation to the pelvic anatomy.

Methods and Materials: Twenty patients with gynecologic malignancies underwent magnetic resonance imaging with administration of iron oxide particles. All visible lymph nodes were outlined. Five clinical target volumes were generated for each patient using modified margins of 3, 5, 7, 10, and 15 mm around the iliac vessels. The nodal contours were then overlaid and individual nodes analyzed for coverage. The volume of normal tissue within each clinical target volume and planning target volume was also measured to aid selection of the margin that could provide maximal nodal, but minimal normal tissue, coverage.

Results: In total, 1216 nodal contours were evaluated. The nodal coverage was 56%, 76%, 88%, 94%, and 99% using vessel margins of 3, 5, 7, 10, and 15 mm, respectively. The mean volume of bowel within the planning target volume was 146.9 cm³ with a 7-mm margin, 190 cm³ with a 10-mm margin, and 266 cm³ with a 15-mm margin. Minor modification to the 7-mm margin ensured 99% coverage of the pelvic nodes.

Conclusion: Blood vessels with a modified 7-mm margin offer a good surrogate target for pelvic lymph nodes. By making appropriate adjustments, coverage of specific nodal groups may be increased and the volume of normal tissue irradiated decreased. On the basis of these findings, recommended guidelines for outlining pelvic nodes have been produced. © 2005 Elsevier Inc.

Pelvic lymph nodes, Clinical target volume, Intensity-modulated radiotherapy, Iron oxide particles.

INTRODUCTION

Whole pelvic nodal radiotherapy (RT) has a key role in the management of many pelvic malignancies and may improve both locoregional control and survival. The lymph nodes are included in the radiation target volume when the tumor stage and grade indicate a significant risk of microscopic nodal metastases or if overt node involvement is already present. Treatment, which is traditionally delivered using a four-field technique defined by bony landmarks, is associated with a dose-limiting incidence of acute and late toxicity (1–3). In addition, despite large volumes of normal tissue being encompassed, conventional planning increases the risk of a geographic miss (4, 5).

Planning studies comparing intensity-modulated RT (IMRT) with conventional approaches for pelvic RT have demonstrated the volume of small bowel, rectum, and bladder receiving high doses can be reduced by 20–50% (6–8). The initial clinical studies treating gynecologic malignancies with IMRT have reported a corresponding reduction in acute and late GI toxicity (9, 10). However, one factor that has prevented widespread implementation of pelvic IMRT has been the lack of a validated method for defining the nodal clinical target volume (CTV).

The probability of a node containing metastases is assessed with CT and MRI using size criteria, usually a nodal short axis diameter >1 cm, but the sensitivity of this method is only 40–70% (11–13). Unenlarged nodes may still contain tumor deposits; therefore, it is necessary to include all lymph nodes within the draining regions in the CTV. Most “normal size” lymph nodes are too small to be visualized directly with standard imaging, and delineation of the CTV depends on their relationship to other pelvic structures.

Anatomic studies have demonstrated that pelvic lymph nodes lie adjacent to major blood vessels. These are relatively well visualized on conventional imaging and can, with a margin, be used as a surrogate target for lymph
nodes. Debate is ongoing about whether the use of a uniform margin around the blood vessels is the appropriate method to define the CTV for nodal regions. The question as to what margin will ensure the maximal nodal, but minimal normal tissue, coverage has not been satisfactorily answered, and different groups have used margins varying from 5 to 20 mm (6, 9, 14, 15).

Ultrasmall particles of iron oxide (USPIO) are a novel class of MRI contrast agent developed for the assessment of lymph nodes. Initial clinical studies have reported USPIO-enhanced MRI improves the sensitivity, whilst maintaining a high specificity, for the detection of nodal metastases for head-and-neck, lung, and pelvic tumors (16–21). The nanoparticles, which are administered intravenously, are taken up by macrophages within benign lymph nodes. The magnetic susceptibility effects of the iron oxide causes a marked loss in the signal intensity of normally functioning nodes on T2- and T2*-weighted sequences, resulting in a black appearance. This makes the nodes easily visible on the post-contrast images (Fig. 1).

The purposes of this study were first to map the distribution of normal pelvic lymph nodes in relation to the blood vessels using the USPIO contrast agent; second, to use these data to determine the margin needed around the blood vessels to allow full coverage of the lymph nodes while achieving maximal sparing of normal tissue; and third, to propose guidelines for pelvic lymph node definition that can be applied to standard CT imaging for three-dimensional planning techniques.

Fig. 1. Axial magnetic resonance images of pelvis with lymph nodes indicated (arrows). (a) T2-weighted images without contrast. (b) Lymph nodes have high signal on T2*-weighted images before contrast. (c) Decrease in signal intensity on T2*-weighted images after ultrasmall particles of iron oxide administration improved visibility of lymph nodes.

Fig. 2. Gradient echo T2*-weighted axial pelvic magnetic resonance image after ultrasmall particles of iron oxide administration. Margins of 3, 5, 7, 10, and 15 mm drawn around pelvic blood vessels, and nodal contours overlaid in yellow.

Fig. 3. Axial magnetic resonance image of external iliac region composed of lateral nodes (EL lat) lateral to external iliac artery (a), anterior nodes (EL ant) anteromedial to external iliac vein (v), and medial nodes (EL med) medial and directly posterior to vein. Obturator (obt) nodes lie between internal and external iliac vessels.
METHODS AND MATERIALS

Twenty patients with gynecologic (12 cervical and 8 endometrial) tumors underwent preoperative assessment of their pelvic lymph nodes with USPIO contrast medium (Sinerem, Guerbet, Roissy, France and Combidex, Advanced Magnetics Inc., Cambridge, MA). The local research ethics committee approved the study, and the Medical Controls Agency (United Kingdom) approved off-license use of USPIO. All patients were >18 years old and provided written informed consent. MRI of the pelvis was performed with axial T2-weighted fast spin echo and T2*-weighted gradient-echo (GE) sequences taken at 4-mm increments. After the scan, intravenous USPIO was administered, and the nodal imaging sequences were repeated after 24–36 h. The post-contrast T2* images were co-registered with the precontrast T2-weighted and T2* scans. This enabled positive identification of the lymph nodes by demonstrating a change in signal intensity between the matched images. When delineating nodes, agreement was required between two observers—a radiation oncologist and a radiologist. All pelvic nodes were contoured and measured on the postcontrast T2* images (Fig. 2).

Lymph nodes were assigned to a nodal group depending on their position in relation to the blood vessels. The common iliac nodes are adjacent to the common iliac vessels from the aortic bifurcation to the division of the common iliac artery into the external and internal iliac branches. The internal iliac nodes lie in relation to the internal iliac vessels and their branches and tributaries. The external iliac nodes surround the external iliac vessels until they pass through the inguinal ligament. This group is subdivided into the medial, anterior, and lateral subgroups (Fig. 3). The medial external iliac nodes are medial and directly posterior to the external iliac...
vein; the anterior external iliac nodes sit in the sulcus between the artery and vein and anteromedial to the artery; and the lateral external iliac nodes extend laterally from the external iliac artery. The obturator nodes lie within the triangle between the external and internal iliac vessels. The presacral nodes are situated directly anterior to the sacrum and are subdivided into the subaortic nodes, below the aortic bifurcation over the sacral promontory, and the perirectal nodes, found within the mesorectal fascia in the sacral hollow.

The pelvic blood vessels were outlined, and three-dimensional margins of 3, 5, 7, 10, and 15 mm were used, creating five CTVs for each patient. In the lower pelvis, the obturator nodes would inevitably be inadequately covered by vessel expansion alone. To encompass this region, the medial contour around the external iliac vessel was continued posteriorly, parallel to the pelvic sidewall, until it joined the internal iliac contour (Fig. 4d). This created a single volume on each side of the pelvis that would incorporate the obturator region with varying width. Muscle and bone were excluded from each volume. The lymph node outlines were then overlaid on each CTV to determine which margin would result in best coverage of the node (Fig. 2).

Each CTV was expanded uniformly by an additional 10 mm to generate the planning target volumes (PTV). The rectum was delineated from the anal margin to the sigmoid flexure, and the whole bladder was contoured. The bowel (comprising the large and small intestine) was outlined on all slices up to the level of the aortic bifurcation. The volume of each normal structure overlapped by the CTV and PTV was measured.

Each nodal group was examined to assess whether a simple modification to the CTV could improve nodal coverage and achieve maximal sparing of normal tissues. To determine the volume width necessary to cover the obturator region adequately, the distance from the pelvic sidewall to the medial border of each obturator node was also measured. This information was used to generate the proposed guidelines for delineating the pelvic nodal CTV.

**RESULTS**

In total, 1216 nodal contours were evaluated in 20 patients. The median number of nodal contours identified was 58 per patient (range, 30–101). The distribution of the nodal groups is presented in Table 1. The external iliac group had the greatest number of nodes identified, with a total of 627 contours, evenly distributed among the three subgroups as 196 medial, 241 anterior, and 190 lateral external iliac nodes. We visualized 303 obturator, 144 internal iliac, and 135 common iliac nodal contours, although only 13 patients had imaging to assess this region adequately. Only 7 presacral nodes were identified, 3 overlying the sacral prominence and 4 in the perirectal fascia. The median short axis diameter of the lymph nodes was 3.6 mm. Very few nodes were enlarged, with only 30 (2.5%) measuring >8 mm and 7 (0.6%) >10 mm.

The number of nodes fully encompassed by a margin around the blood vessels increased correspondingly with the margin size. The percentage of lymph node contours covered by a 3-, 5-, 7-, 10-, and 15-mm margin was 56%, 76%, 88%, 94%, and 99%, respectively (Table 2).

**Normal tissue coverage**

The volume of normal tissue within each CTV and PTV is shown in Table 3. The PTV created with the 15-mm

<table>
<thead>
<tr>
<th>Lymph node group</th>
<th>Contours per patient (n)</th>
<th>Short axis diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Mean Range</td>
</tr>
<tr>
<td>Common iliac*</td>
<td>135</td>
<td>10.4 2–22</td>
</tr>
<tr>
<td>Medial external iliac</td>
<td>196</td>
<td>9.8 2–19</td>
</tr>
<tr>
<td>Anterior external iliac</td>
<td>241</td>
<td>12.1 4–20</td>
</tr>
<tr>
<td>Lateral external iliac</td>
<td>190</td>
<td>9.5 3–23</td>
</tr>
<tr>
<td>Obturator</td>
<td>303</td>
<td>15.2 3–43</td>
</tr>
<tr>
<td>Internal iliac</td>
<td>144</td>
<td>7.2 1–22</td>
</tr>
<tr>
<td>Presacral</td>
<td>7</td>
<td>0.4 0–2</td>
</tr>
<tr>
<td>Total</td>
<td>1216</td>
<td>60.8 30–101</td>
</tr>
</tbody>
</table>

* Common iliac region imaged in 13 patients.

**Table 2. Lymph node contours covered by margin around blood vessels**

<table>
<thead>
<tr>
<th>Lymph node group</th>
<th>3 mm (%)</th>
<th>5 mm (%)</th>
<th>7 mm (%)</th>
<th>10 mm (%)</th>
<th>15 mm (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common iliac (n = 135)</td>
<td>41 (30.3)</td>
<td>90 (66.7)</td>
<td>123 (91.1)</td>
<td>135 (100)</td>
<td>135 (100)</td>
</tr>
<tr>
<td>Medial external iliac (n = 196)</td>
<td>122 (62.2)</td>
<td>167 (85.2)</td>
<td>193 (98.4)</td>
<td>196 (100)</td>
<td>196 (100)</td>
</tr>
<tr>
<td>Anterior external iliac (n = 241)</td>
<td>124 (51.4)</td>
<td>190 (78.8)</td>
<td>227 (94.2)</td>
<td>241 (100)</td>
<td>241 (100)</td>
</tr>
<tr>
<td>Lateral external iliac (n = 190)</td>
<td>16 (8.4)</td>
<td>41 (21.6)</td>
<td>76 (40)</td>
<td>123 (64.7)</td>
<td>178 (93.7)</td>
</tr>
<tr>
<td>Obturator (n = 303)</td>
<td>275 (90.1)</td>
<td>295 (97.3)</td>
<td>302 (99.7)</td>
<td>303 (100)</td>
<td>303 (100)</td>
</tr>
<tr>
<td>Internal iliac (n = 144)</td>
<td>105 (72.9)</td>
<td>135 (93.8)</td>
<td>142 (98.6)</td>
<td>144 (100)</td>
<td>144 (100)</td>
</tr>
<tr>
<td>Presacral (n = 7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>3 (42.9)</td>
<td>3 (42.9)</td>
<td>3 (42.9)</td>
</tr>
<tr>
<td>Total (n = 1216)</td>
<td>683 (56.2)</td>
<td>918 (75.7)</td>
<td>1066 (87.7)</td>
<td>1145 (94.2)</td>
<td>1200 (98.7)</td>
</tr>
</tbody>
</table>
margin included 266 cm³ of bowel, 41 cm³ of bladder, and 17 cm³ of rectum. A 10-mm margin reduced the normal tissue encompassed to 190 cm³ of bowel, 28 cm³ of bladder, and 10 cm³ of rectum. In view of the large volume of bowel within the 15-mm PTV, the lymph nodal coverage was assessed further to assess whether a margin could maximize normal tissue sparing without compromising nodal coverage.

**Lymph node groups**

The coverage of each nodal group by the different vessel margins was assessed (Table 2). Even a 15-mm margin failed to cover fully the lateral external iliac and presacral nodes. Excluding these two groups, all other nodes were included by a 10-mm expansion and 95% nodes by a 7-mm expansion. The 150 nodal contours incompletely encompassed by a 7-mm margin were scrutinized to determine which simple adjustments to this volume would increase nodal coverage. Of these nodes, 93 (62%) were readily visible on the T2 precontrast scans. The results of the required modifications are summarized below for each nodal group, with the provision that all enlarged, and therefore visible, nodes were also included in the CTV (Table 4).

**Common iliac nodes.** Although the common iliac nodes are usually situated in direct contact with the vessels, they may also lie some distance away in the posterior and lateral spaces. Because of this, a nonuniform margin is necessary. The CTV should be drawn 7-mm anterior and medial to the vessels; however, posterolaterally, it must be extended to the psoas muscle and vertebral body (Fig. 4a).

**Internal iliac nodes.** The internal iliac vessels have many branches, and all need to be included in the CTV. A 7-mm margin around these vessels will provide coverage of 100% of the nodes provided the lateral border reaches to the pelvic sidewall (Fig. 4b).

**External iliac nodes.** The external iliac nodes consist of three connecting subgroups—the lateral, anterior, and medial groups. Although a 7-mm margin uniformly around the external iliac vessels covers all the medial and anterior nodes, the lateral external iliac nodes are poorly covered, with only 40% completely encompassed. Additional extension of only the anterior margin by another 10 mm (a total of 17 mm from the vessel) anterolaterally along the iliopsoas muscle would include >99% of the external iliac nodes. A nonuniform margin around the vessel should, therefore, be used (Fig. 4c).

**Obturator nodes.** The obturator nodes would not be included by uniform expansion of the vessel contour, unless a very large margin were used. In this study, the potential CTVs were designed to cover this region with varying widths by joining the corresponding medial and lateral borders of the internal and external iliac contours, creating a single volume on each side of the pelvis. All obturator nodes were covered by joining the contours created with the 7-mm vessel margin. The average distance from the pelvic sidewall required to cover the nodes was 8 mm (range, 2–21 mm; SD, 3.6). Therefore, a volume along the pelvic sidewall to encompass 95% of the lymph nodes needs a width of 15 mm, and 99% nodes would be covered with an 18-mm-wide strip (Fig. 4d).

**Presacral nodes.** Very few sacral nodes were identified in this study. A uniform vessel margin is not an appropriate method to cover these nodes, and it is necessary to cover the presacral region specifically, if indicated by the tumor site.

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**Table 3. Volume of normal structures within clinical target volumes (CTV) and planning target volumes (PTV)**

<table>
<thead>
<tr>
<th></th>
<th>Total volume</th>
<th>3 mm (%)</th>
<th>5 mm (%)</th>
<th>7 mm (%)</th>
<th>10 mm (%)</th>
<th>15 mm (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Mean volume of normal structure within CTV (cm³)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bowel</td>
<td>643.7</td>
<td>5.9</td>
<td>16.8</td>
<td>32.4</td>
<td>63.2</td>
<td>123.3</td>
</tr>
<tr>
<td>Bladder</td>
<td>131.0</td>
<td>0.7</td>
<td>2.1</td>
<td>3.9</td>
<td>7.4</td>
<td>14.3</td>
</tr>
<tr>
<td>Rectum</td>
<td>44.4</td>
<td>0.2</td>
<td>0.5</td>
<td>0.9</td>
<td>2.2</td>
<td>5.4</td>
</tr>
<tr>
<td><strong>B. Mean volume of normal structure within PTV (cm³)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bowel</td>
<td>643.7</td>
<td>95.6</td>
<td>120.7</td>
<td>146.9</td>
<td>190.3</td>
<td>265.9</td>
</tr>
<tr>
<td>Bladder</td>
<td>131.0</td>
<td>13.1</td>
<td>16.7</td>
<td>21.2</td>
<td>28</td>
<td>40.6</td>
</tr>
<tr>
<td>Rectum</td>
<td>44.4</td>
<td>3.9</td>
<td>5.5</td>
<td>7.2</td>
<td>10.4</td>
<td>17.1</td>
</tr>
</tbody>
</table>

**Table 4. Recommend modifications to margins**

<table>
<thead>
<tr>
<th>Lymph node group</th>
<th>Recommended margins*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common iliac</td>
<td>7-mm margin around vessels; extend posterior and lateral borders to psoas and vertebral body</td>
</tr>
<tr>
<td>External iliac</td>
<td>7-mm margin around vessels; extend anterior border by additional 10-mm anterolaterally along iliopsoas muscle to include lateral external iliac nodes</td>
</tr>
<tr>
<td>Obturator</td>
<td>Join external and internal iliac regions with 18-mm-wide strip along pelvic sidewall</td>
</tr>
<tr>
<td>Internal iliac</td>
<td>7-mm margin around vessels; extend lateral borders to pelvic sidewall</td>
</tr>
<tr>
<td>Presacral</td>
<td>10-mm strip over anterior sacrum</td>
</tr>
</tbody>
</table>

* Also include any visible nodes.
and stage. A 10-mm strip over the sacral prominence connecting the common iliac contours would include the subaortic presacral nodes. Similarly, a volume should be drawn anterior to the sacrum to cover the lower sacral nodes, but there were insufficient nodes in this study to draw conclusions on the width required.

**Recommendations for pelvic nodal CTV delineation**

The guidelines for delineating the pelvic lymph node CTV are summarized below:

1. Uniformly draw a contour around the pelvic blood vessels by 7 mm.
2. Include all visible nodes and exclude muscle and bone from the volume.
3. Ensure the lateral border of the volume extends to the psoas muscle and pelvic sidewall.
4. Continue the medial border around the external iliac vessels posteriorly, parallel to the sidewall, until it joins the medial contour of the internal iliac vessels to encompass the obturator region. This creates a strip medial to the pelvic sidewall that should be at least 18 mm wide.
5. To include all the lateral external iliac nodes, extend the contour around the external iliac artery anterolaterally along the iliopsoas muscle by an additional 10 mm.
6. To cover the presacral region, connect the volumes on each side of the pelvis with a 10-mm strip over the anterior sacrum.

**DISCUSSION**

Intensity-modulated RT has great potential for normal tissue sparing and dose escalation when treating pelvic tumors. The CTV usually comprises the primary tumor, or tumor bed, structures at risk of direct tumor spread, such as the parametrium, and the draining lymph node regions. The pelvic lymph nodes, however, are difficult to delineate, because most cannot be visualized on CT or MRI, but still may contain metastases. Consistent and accurate target volume definition is essential, because salvage treatment for relapsed disease due to a geographic miss is rarely successful (22).

Magnetic resonance imaging with USPIO is a promising new method for differentiating benign from malignant lymph nodes. The technique also improves the visibility of nodes and provides information about lymph node morphology and function. This is the first study to demonstrate that magnetic resonance lymphography can also be used to aid RT target volume localization. The lymph node positions within the pelvis have been identified to generate practical recommendations for delineating the lymph node regions. The technique could also be applied to other anatomic sites.

The number of nodes visualized with USPIO is consistent with other surgical and radiographic series (23–26). Vinnicombe et al. (24) identified 45 nodes on CT scans after lymphangiography compared with only 10 on prelymphangiography CT images. Benedetti-Panici et al. (23) dissected a median of 38 pelvic nodes in a detailed anatomic study treating gynecologic cancers. In the current study, the average was 61 lymph nodal contours per patient, slightly more than on previous studies. It is possible that because larger nodes would have been visible on more than one image, the numbers may have been overestimated. The nodes, however, occurred in a highly consistent pattern, without great variations in the position of lymph nodes from the predicted anatomic location.

It is desirable to reduce the volume of irradiated normal tissue, but it is essential not to compromise the target coverage. Alternative methods for identifying the nodal CTV have been suggested by other groups (6, 27). Chao et al. (14) used CT lymphangiograms to document the nodal position in relation to the blood vessels. Our guidelines resulted in smaller volumes than those in previous reports. There are two possible reasons for this. First, we were able to identify normal-size nodes, with an average node diameter of only 3.8 mm. Such small nodes are not usually visible on CT. Second, evidence has shown that lymphangiography using lipiodol for ionizing radiation can increase the apparent size of the nodes, which would require a corresponding increase in the CTV (28). In terms of clinical significance, changing the margin from 10 mm to 7 mm reduced the volume of bowel, bladder, and rectum within the PTV in this study by 23%, 24%, and 31%, respectively, which is very likely to reduce the incidence of toxicity.

The conventional RT target volume covers all the pelvic nodes not only because identification of metastatic involvement is difficult, but also as an inevitable consequence of the standard dose distribution of the four-field “box” technique. With the complexity of dose patterns that can be achieved with IMRT, it is now possible to select which nodal groups need to be covered depending on the tumor site and stage. The proposed guidelines have been applied to generate an atlas of reference images defining each of the pelvic lymph node regions and enabling standardization of the target volumes for IMRT (Fig. 5).

For most pelvic tumors, the nodal CTV would typically comprise the common iliac, external iliac, internal iliac, and obturator nodes. Frequently, the upper presacral region is also included. A particular point of discussion is the necessity of including the distal lateral external iliac nodes. These nodes often lie distant from the vessels, and encompassing all the nodes will significantly move the position of the anterior field border, resulting in a large increase in the volume of small bowel within the target volume. Review of lymphangiograms has shown that conventional fields miss these nodes in 34–45% of cases (4, 5, 29). Despite this, the region is a rare site of recurrence. In the absence of other external iliac nodal enlargement, the incidence of distal lateral external iliac node involvement is low, and it may be justifiable to exclude these nodes from the CTV (30, 31). The selection of the appropriate nodal groups will depend on existing data from surgical and autopsy series, but more informa-
tion will increasingly be available from positron emission tomography and sentinel lymph node studies. It is also essential to collect data on the site of local recurrence in all patients treated with pelvic IMRT.

In addition to the selection of which nodal groups should be in the CTV, the increasing sophistication of imaging could enable further individualization of the target volumes. New techniques, including USPIO and positron emission tomography may be incorporated to modify the volume definition by identifying involved nodes. For example, USPIO assists in the visualization of normal nodes, as was done in this study, but can also localize those nodes with metastatic disease with a high sensitivity and specificity. Treatment with IMRT could integrate a boost to these nodes while excluding uninvolved areas.

CONCLUSION

Using MRI with USPIO, the pelvic lymph node distribution was mapped and a relation to the pelvic blood vessels defined. Because blood vessels are readily seen on standard CT imaging, these are suitable as a surrogate lymph node target. Guidelines for the accurate definition of different nodal CTV groups using a standardized target definition have been proposed.

REFERENCES


