A Consensus-based Guideline Defining the Clinical Target Volume for Pelvic Lymph Nodes in External Beam Radiotherapy for Uterine Cervical Cancer

Takafumi Toita1,*, Tatsuya Ohno2, Yuko Kaneyasu3, Takashi Uno4, Ryouichi Yoshimura5, Takeshi Kodaira6, Kazuhisa Furutani6, Goro Kasuya1, Satoshi Ishikura7, Toshiharu Kamura8 and Masahiro Hiraoka9

1Department of Radiology, Graduate School of Medical Science, University of the Ryukyus, Okinawa, 2Gunma University Heavy Ion Medical Center, Gunma University, Maebashi, 3Department of Radiation Oncology, Graduate School of Biomedical Sciences, Hiroshima University, Hiroshima, 4Department of Radiology, Graduate School of Medicine, Chiba University, Chiba, 5Department of Radiology, Tokyo Medical and Dental University, Tokyo, 6Department of Radiation Oncology, Aichi Cancer Center, Nagoya, 7Outreach Radiation Oncology and Physics, Clinical Trials and Practice Support Division, Center for Cancer Control and Information Services, National Cancer Center, Tokyo, 8Department of Obstetrics and Gynecology, Kurume University School of Medicine, Fukuoka and 9Department of Radiation Oncology and Image-applied Therapy, Kyoto University Graduate School of Medicine, Kyoto, Japan

*For reprints and all correspondence: Takafumi Toita, Department of Radiology, Graduate School of Medical Science, University of the Ryukyus, 207 Uehara, Nishihara-cho, Okinawa 903-0215, Japan. E-mail: b983255@med.u-ryukyu.ac.jp

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Objective: To develop a consensus-based guideline as well as an atlas defining pelvic nodal clinical target volumes in external beam radiotherapy for uterine cervical cancer.

Methods: A working subgroup to establish the consensus-based guideline on clinical target volumes for uterine cervical cancer was formulated by the Radiation Therapy Study Group of the Japan Clinical Oncology Group in July 2008. The working subgroup consisted of seven radiation oncologists. The process resulting in the consensus included a comparison of contouring on CT images among the members, reviewing of published textbooks and the relevant literature and a distribution analysis of metastatic nodes on computed tomography/magnetic resonance imaging of actual patients.

Results: The working subgroup defined the pelvic nodal clinical target volumes for cervical cancer and developed an associated atlas. As a basic criterion, the lymph node clinical target volume was defined as the area encompassed by a 7 mm margin around the applicable pelvic vessels. Modifications were made in each nodal area to cover adjacent adipose tissues at risk of microscopic nodal metastases. Although the bones and muscles were excluded, the bowel was not routinely excluded in the definition. Each of the following pelvic node regions was defined: common iliac, external iliac, internal iliac, obturator and presacral. Anatomical structures bordering each lymph node region were defined for six directions; anterior, posterior, lateral, medial, cranial and caudal. Drafts of the definition and the atlas were reviewed by members of the JCOG Gynecologic Cancer Study Group (GCSG).

Conclusions: We developed a consensus-based guideline defining the pelvic node clinical target volumes that included an atlas. The guideline will be continuously updated to reflect the ongoing changes in the field.

Key words: cervical cancer – radiation therapy – clinical target volume – contouring

INTRODUCTION

In recent years, external beam radiotherapy techniques have advanced considerably. An example of this is how the treatment planning for uterine cervical cancer has transitioned from a two-dimensional (2D) approach based on bony landmarks to a three-dimensional (3D) technique. The 3D
treatment planning involves the direct input of target volumes and organs at risk (OAR) using cross-sectional images from computed tomography (CT) and magnetic resonance imaging (MRI). Technical advances in the radiation delivery devices as well as ancillary equipments such as radiotherapy treatment planning systems and on-board imaging devices enable the precise delivery of external beam radiotherapy. Intensity-modulated radiation therapy (IMRT) has proven to have a significant dosimetric advantage in comparison with conventional treatment planning for various malignancies including gynecologic cancers (1).

Although improvements have been made in treatment equipments and techniques, determination of both target volumes and OAR has not been well standardized. In particular, contouring of the clinical target volume (CTV) of regional lymph nodes requires thorough understanding of both the distribution patterns of microscopic metastases and anatomic features on cross-sectional images. Lack of a standardized contouring protocol may result in considerable variation in contouring (2). Therefore, a global consensus is needed for the standard CTV for regional nodes in cervical cancer in order to optimize the delivery of high precision external beam radiotherapy including IMRT.

In Europe, the nodal CTV was first standardized for head and neck cancers (3,4). CTV standardization has also progressed in prostate cancer (5) and anorectal cancers (6) in the USA. For uterine cancers, the Radiation Therapy Oncology Group (RTOG) (7) and UK investigators (8,9) have also recently published their guidelines.

A working subgroup to establish a guideline delineating the CTV for cervical cancer was organized within the Radiation Therapy Study Group (RTSG) of the Japan Clinical Oncology Group (JCOG). The guideline is intended for use by Japanese clinicians. Additionally, the guideline is also designed to be utilized by researchers conducting prospective multi-institutional studies using high precision external beam radiotherapy including IMRT for uterine cervical cancer. This paper describes the process by which the guideline was developed and presents the guideline for contouring pelvic node CTV in cervical cancer.

PATIENTS AND METHODS

A working subgroup to establish consensus-based guideline on CTV for uterine cervical cancer was formulated by the JCOG RTSG in July 2008. The working subgroup consisted of seven radiation oncologists practicing in Japan. The committee met twice and extensive discussions were conducted via electronic mail (e-mail) throughout the entire process. The working group first addressed pelvic nodal CTV.

First, a set of hard copies of actual CT images of a cervical cancer patient were sent to each member. Each performed a contouring procedure of the pelvic nodal CTV on the CT images. At the first meeting held in November 2008, the members brought the contoured images and compared to identify areas of discrepancy in the nodal CTV delineation. A preliminary draft of the guideline was then formulated based on published studies (T.T.). Previously published guidelines on CTV delineation (7–9), imaging studies (10–14), as well as gynecologic surgery series (15–17) (reviewing the distribution of pelvic nodal metastases), and papers and textbooks of pelvic anatomy related to images (18,19) were reviewed. The draft included basic criteria, definitions and a preliminary atlas of the nodal CTV. In the draft, the nodal CTV was subdivided into five regions, i.e. common iliac, external iliac, internal iliac, obturator and presacral. Anatomical structures bordering each lymph node region were defined for six directions; anterior, posterior, lateral, medial, cranial and caudal (14). An atlas of the nodal CTV was drawn using a commercial radiotherapy planning system (Eclipse; External Beam Planning 8.1.20, Varian Medical Systems) according to the stated definitions. The preliminary draft was intensively reviewed and discussions held over several months through multiple e-mail discussions. The document was extensively revised. Next, CT/MRI image sets of cervical cancer patients who were assessed as having pelvic node metastases (short axis diameter of $>10\text{mm}$) were collected from the committee members’ institutions. With these data, anatomic distributions of metastatic nodes within each lymph node region on transverse images were analyzed to assess whether the preliminary CTV definition was adequate. On the basis of these results, a final draft of the guideline was confirmed in the second face-to-face working group meeting in April 2009. The version was presented and reviewed at the JCOG RTSG meeting in June 2009, and the JCOG Gynecologic Cancer Study Group (GCSG) meeting in July 2009. The draft was reviewed and minor revisions were proposed by radiation oncologists and gynecologic oncologists at these meetings. In response to those, minor revisions were made, and any discrepancies remaining were discussed and consolidated. A final draft of the guideline on nodal CTV contouring was established in September 2009.

RESULTS

As a basic criterion, the lymph node CTV was defined as the area encompassed by a $7\text{mm}$ margin around the applicable pelvic vessels (artery and vein). In addition to the aforementioned areas, some modifications were made in each nodal area. Since there are no visible major vessels in the presacral area, the definition for the presacral node region was based on the bony and muscle anatomy.

The CTV was modified to exclude bones and muscles. We determined that the bowel could not be excluded routinely due to the daily changes in its shape and position. Table 1 shows the nodal CTV definitions which describe the anatomical boundary of each subcategorized node group in the pelvis. Definitions were made for the following six directions on the 3D images: anterior, posterior, lateral, medial, cranial...
and caudal. Figure 1 is an atlas of the pelvic nodal CTV contouring which applies these definitions (Fig. 2). Digitally reconstructed radiograph with pelvic node CN and vessels are shown in Figure 2.

DISCUSSION

We established a guideline and an atlas that defined the pelvic nodal CTV in external beam radiotherapy for cervical cancer. This document underwent extensive revision by a committee consisting of seven radiation oncologists considered experts in cervical cancer treatment in Japan. In addition, this guideline was also critically reviewed by radiation oncologists other than the committee members and the gynecologic oncologists in the JCOG. Therefore, this may be considered a consensus-based guideline in Japan.

Margins are designed around blood vessels which serve as good surrogate targets for regional nodes (7,8,12,20). Chao and Lin (12) studied the pelvic node distribution in patients with uterine cervical cancer who underwent lymphangiography. They showed that 10–15 mm margins adequately covered the pelvic node regions. However, the working group felt that these margins were unnecessarily expansive. Taylor et al. (8) demonstrated using the intravenous ultra-small particles of iron oxide (USPIO) MRI that a 7 mm margin around the vessels achieved 88% nodal coverage in the assessed regions. The RTOG guideline also employed this basic definition of a 7 mm margin (7). In addition to that, Taylor et al. (8) modified the definition and achieved a coverage ratio of 99%. We considered this methodology to be clinically appropriate and adopted it into our definition.

As the RTOG guideline, the bones and muscles were excluded from the CTV in the present guideline (7). However, the bowel was not routinely excluded in contrast to the RTOG guideline. We accounted for daily changes in bowel configuration. Further studies are needed to address bowel exclusion with image-guided radiotherapy devices, such as the on-board cone beam CT system.

Table 1. Clinical target volume definition on pelvic nodes related to anatomic landmarks for cervical cancer

<table>
<thead>
<tr>
<th>Node chains</th>
<th>Cranial margin</th>
<th>Caudal margin</th>
<th>Anterior margin</th>
<th>Posterior margin</th>
<th>Lateral margin</th>
<th>Medial margin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common iliac</td>
<td>Aortic bifurcation or L4-5 space</td>
<td>Common iliac a bifurcation</td>
<td>7 mm anterior to a/v L5—sacrum (adequately involve adipose connective tissue between lateral surface of vertebral body and psoas m*)</td>
<td>7 mm lateral to a/v (expanding to psoas major m)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>External iliac</td>
<td>Common iliac a bifurcation</td>
<td>Superior aspect of femoral head</td>
<td>7 mm anterior to a/v (connecting to obturator region)</td>
<td>7 mm posterior to a/v (connecting to obturator region)</td>
<td>7 mm lateral to a/v (expanding to psoas major m or iliacus m)</td>
<td>7 mm medial to a/v uterus, ovary, bowel, ureter or bladder</td>
</tr>
<tr>
<td>Internal iliac</td>
<td>Common iliac a bifurcation</td>
<td>Cranial section of coccygeus m, spine of ischium or uterine a/v (connecting to parametrial region)</td>
<td>Cranial level: wing of sacrum</td>
<td>Cranial level: psaos m, iliacus m or lateral edge of sacroiliac joint</td>
<td>Middle-caudal level: anterior edge of piriformis m or inferior gluteal a/v</td>
<td>Middle level: Iliac bone, psaos m or medial edge of iliacus m</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Caudal level: obturator internus m or piriformis m</td>
</tr>
<tr>
<td>Obturator</td>
<td>Caudal section of sacroiliac joint (connecting to internal iliac region)</td>
<td>Superior part of obturator foramen</td>
<td>Cranial-middle level: connecting to external iliac region</td>
<td>Cranial-middle level: connecting to internal iliac region</td>
<td>Obturator internus m, iliacus m, psaos m or iliac bone</td>
<td>Bladder, uterus or bowel</td>
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<td></td>
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</tr>
<tr>
<td>Presacral</td>
<td>Common iliac a bifurcation</td>
<td>Lower level of S2 or cranial section of piriformis m</td>
<td>10 mm anterior to sacrum</td>
<td>L5—sacrum</td>
<td>Piriformis m (connecting to external or internal iliac region)</td>
<td>—</td>
</tr>
</tbody>
</table>

*Even in patients with low adipose connective tissue in this space, posterior margin should also extend to posterior edge of vertebral body.

a, artery; a/v, artery and vein; m, muscle.
For the common iliac region, two questions arose in the process of arriving at a consensus. The first issue pertained to defining the cranial margin. Ideally, the region should be defined based on the blood vessel anatomy at the level of common iliac arterial bifurcation. However, a key principle of the present guideline was not to deviate significantly from the conventional 2D whole pelvic field. The RTOG guideline also maintained a definition based on the bone anatomy (7). Therefore, we provided two definitions, one based on blood vessels and the other based on bone anatomy. A therapeutic challenge identified in several studies lies in treating nodal recurrence around the cranial margin of the pelvic field (21). The delivery of secondary radiotherapy with an appropriate target volume in such a situation is technically difficult. In addition, categorizing the recurrence as a regional (pelvic recurrence) or distant (para-aortic nodal) failure may not be possible when the previous pelvic field was constructed based on the bony anatomy. Therefore, we recommended that the definition based on vessel anatomy be solely employed in future revisions of the guideline. A second issue was the posterior margin of the CTV. In contrast to the RTOG guideline (7), the CTV in the present guideline involves adipose connective tissue between the iliopsoas muscles and the lateral surface of the vertebral body. This is based on our present analysis of CT/MRI images of the actual patients who had pelvic nodal metastases. The analysis revealed that some patients had lymphadenopathy in this area. In the atlas of Taylor et al. (8,9), the area is also included in the CTV for common iliac nodes. However, this area has not been covered to the same extent when a conventional 2D lateral field is used. Therefore, the clinical appropriateness of treatment planning using conventional 2D lateral portals should be re-evaluated in light of actual failure rates.

In the external iliac region, the caudal margin was defined as the level of the superior border of the femoral head. This definition is the same as that of the RTOG guideline (7). According to this anatomical definition, the margin should move caudally until it reaches the level at the junction with the femoral vessels or the level at the intersection with the transverse abdominal muscles. However, in this guideline, the superior border of the femoral head was selected as the caudal margin for the following two reasons. One reason is that the incidence of nodal metastases reported in surgical

Figure 1. An atlas of clinical target volume (CTV) for pelvic lymph nodes for uterine cervical cancer.
series is relatively low (15–17). Sakuragi et al. (16) analyzed the distribution patterns of metastatic nodes in 208 patients with Stage I/II cervical cancer treated with radical hysterectomy and pelvic node dissection. They reported that only 3.8% of the patients had pelvic nodal metastases in the external iliac region (16). Second, if the caudal margin extends to a lower level, a large area of the femoral head and neck would be included in the treated volume resulting from the CTV definition. Furthermore, this situation would be significant when the conventional technique is applied. In contrast, portals resulting from the present definition would be far from those produced using conventional 2D fields, which always include the lower aspect of the region. The appropriateness of the present definition should be evaluated clinically by investigating whether the rates of nodal recurrence increase in the excluded area. Exceptionally, when a patient has nodal metastases (either pathologically conformed or clinically) in the cranial level of this chain, we recommend nodal CN should be extended more caudally.

The present CTV definition of the internal iliac node region differs significantly from the guideline of the RTOG. Our analyses on the actual distribution of enlarged nodes demonstrated that a significant number of enlarged nodes were observed from the lateral margin of the adipose connective tissue to the medial surface of the psoas muscle, or at the level of the sacral wing tips, which were not included in the RTOG guideline (7). The conventional 2D fields usually cover this area. Taylor’s guideline also employed a similar definition to ours (8,9). Therefore, the current RTOG definition on lateral expansion of the CTV for the internal iliac node may be insufficient. In the present guideline, the parametrial lymph node region was not defined. This will be included in the guideline for primary tumor CTV.

Defining the caudal extent of the obturator node region was another area of discrepancy addressed by the present guideline. Referring to the anatomical definition, the obturator nodes distribute into the anatomical level where the obturator vessels penetrate the obturator foramen. The surgical procedure manual published by the Japanese Gynecologic Oncology Group (JGOG) indicates that the obturator node dissection should be performed caudally to the level of the obturator foramen (22). In cases of external beam radiotherapy, the conventional 2D pelvic fields also include the foramen. Therefore, in our current definition,
the upper level of the foramen is also included in the nodal CTV.

The presacral node region was defined similarly to previously published guidelines (7–9). A study with MRI using USPIO revealed that the lymph node was only sparsely distributed in this area and CTV coverage was not required extensively (8). The working group discussed why the conventional 2D lateral field covers extensively entire sacral surface. We concluded that conventional lateral field was primarily intended to achieve adequate coverage of the parametrial tissues. The parametrial tissues will be included in the CTV for primary tumor (9,23).

The present guideline was intended to be applied irrespective of pelvic nodal status. In head and neck cancers, the nodal CTV guideline was proposed separately for node-positive and post-operative patients (4). We expect this guideline could be applied to patients with pelvic nodal metastases with individual arrangement, e.g. appropriate margin within adhered muscles or bones.

The presently developed guideline provides standard definitions for nodal CTV in cervical cancer to aid in treatment planning for highly precise external beam radiotherapy including IMRT. The guideline may also be utilized in prospective multi-institutional clinical trials to avoid
variation in CTV determination. This guideline is a work in progress. It will continue to be modified as new clinical findings and opinions from functional imaging and sentinel lymph node studies become available. Guideline defining the CTV for primary lesions in the cervical cancer is currently under development.

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Conflict of interest statement

None declared.

References


Figure 2. Digitally reconstructed radiographs showing CTV for pelvic lymph nodes (yellow) and vessels (orange); (A) anterior view and (B) lateral view.


