る$N_{D,w}$の不確かさを見積もった結果、直接$N_{D,w}$を用いて校正点で水吸収線量を評価する場合は、その不確かさが1.5%にまで低減されることが判明した。

D. 考察

本研究により、$N_{D,w}$に基づくトレーサビリティが確立すると、国際的斉一性やモニター校正の不確かさ低減の観点から、治療線量の高精度化にとって大きなメリットがあることが示された。

しかしながら、このメリットを医療現場に浸透させるには、$N_{D,w}$を全国に供給する体制づくりや線量評価プロトコルの改訂作業等が必要不可欠である。こうした取組みは、関係機関が連携しオールジャパン体制で進める必要がある。その核として本研究班の存在は極めて有意義であると考えられる。

E. 結論

水吸収線量トレーサビリティの確立は治療線量の高精度化に資することが明らかとなった。これを全国の放射線治療施設に張り巡らせることが今後の大きな課題である。

F. 研究発表

1. 論文発表

なし

2. 学会発表

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G. 知的財産権の出願・登録状況
(予定を含む)

1. 特許取得

なし

2. 実用新案登録

なし

3. その他

なし

研究成果の刊行に関する一覧表

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CLINICAL INVESTIGATION **Lung**

VARIATIONS IN TARGET VOLUME DEFINITION FOR POSTOPERATIVE RADIOTHERAPY IN STAGE III NON–SMALL-CELL LUNG CANCER: ANALYSIS OF AN INTERNATIONAL CONTOURING STUDY

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Purpose: Postoperative radiotherapy (PORT) in patients with completely resected non–small-cell lung cancer with mediastinal involvement is controversial because of the failure of earlier trials to demonstrate a survival benefit. Improved techniques may reduce toxicity, but the treatment fields used in routine practice have not been well studied. We studied routine target volumes used by international experts and evaluated the impact of a contouring protocol developed for a new prospective study, the Lung Adjuvant Radiotherapy Trial (Lung ART).

Methods and Materials: Seventeen thoracic radiation oncologists were invited to contour their routine clinical target volumes (CTV) for 2 representative patients using a validated CD-ROM–based contouring program. Subsequently, the Lung ART study protocol was provided, and both cases were contoured again. Variations in target volumes and their dosimetric impact were analyzed.

Results: Routine CTVs were received for each case from 10 clinicians, whereas six provided both routine and protocol CTVs for each case. Routine CTVs varied up to threefold between clinicians, but use of the Lung ART protocol significantly decreased variations. Routine CTVs in a postlobectomy patient resulted in V_{20} values ranging from 12.7% to 54.0%, and Lung ART protocol CTVs resulted in values of 20.6% to 29.2%. Similar results were seen for other toxicity parameters and in the postpneumectomy patient. With the exception of upper paratracheal nodes, protocol contouring improved coverage of the required nodal stations.

Conclusion: Even among experts, significant interclinician variations are observed in PORT fields. Inasmuch as contouring variations can confound the interpretation of PORT results, mandatory quality assurance procedures have been incorporated into the current Lung ART study. © 2010 Elsevier Inc.

Non–small-cell lung cancer, Resection, Postoperative radiotherapy, Target volumes, Interobserver variability.

INTRODUCTION

The role of postoperative radiotherapy (PORT) in patients with completely resected non–small-cell lung cancer is still controversial. Despite increasing local control rates (1–3), a large meta-analysis has shown a detrimental impact of PORT on overall survival, particularly in patients with no mediastinal involvement (4). However, the meta-analysis has been criticized because the studies included may have led to higher morbidity and mortality rates resulting from the use of two-dimensional radiotherapy techniques, high doses and fraction sizes, and large-field radiotherapy that incorporated the entire mediastinum using suboptimal radiotherapy techniques and lacking modern verification procedures or trial quality assurance (QA) (5–7).

Recently, data from the Surveillance, Epidemiology, and End Results (SEER) database and an unplanned subgroup analysis of a Phase III trial suggested that PORT using more recent techniques may improve survival in patients with resected N2 disease (8, 9). This has renewed interest in evaluating PORT in this patient category. A new international Phase

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III trial, the Lung Adjuvant Radiotherapy Trial (Lung ART), has been activated to compare PORT with no PORT in patients with completely resected N2 disease, irrespective of the use of chemotherapy (10). However, the cornerstone of radiotherapy is the use of consistent and reproducible target definitions, and current literature suggested that many groups were using target volumes defined in the era of two-dimensional radiotherapy (7, 11). In addition, large interobserver variations in target volumes have been observed in patients presenting with lung tumors that were visible on CT or positron emission tomography (PET)—CT scans (12–15). It is conceivable that the lack of identifiable tumor after a radical resection may potentially result in even greater variations. In the Lung ART study, the use of conformal radiotherapy is mandatory, and the target volumes are tailored based on both radiologic and surgical findings. As a prelude to Lung ART, the present study was designed to identify potential variations in target definitions in an international setting. In addition, the ability of the Lung ART protocol to reduce the potential variations in defining clinical target volumes (CTVs) was studied.

METHODS AND MATERIALS

Study design

Seventeen radiation oncologists in Europe, Asia, Australasia and North America who were considered to be experts in the treatment of lung cancer were invited to participate in this study. Radiation oncologists who were invited to participate had to be members of the International Association for the Study of Lung Cancer and to be also actively involved in research in radiotherapy for lung cancer. All were attached to academic centers, had experience in treating patients with postoperative radiotherapy, and had access to CT-based treatment planning for this purpose. Each participating expert was asked to contour his/her current routine CTV for 2 patients eligible for PORT. For contouring purposes, a CD-ROM–based validated contouring program was provided (16), which contained complete CT datasets (slice thickness 2.5 mm) of both patients and a tutorial regarding use of the contouring program in PowerPoint format (MS Office). In addition, relevant patient details were provided in the first mailing. The CTVs were contoured using standardized window level settings and saved to the CD-ROM, which was then mailed to the study coordinator. Subsequently, details of the contouring protocol for Lung ART were mailed to experts approximately 2 weeks after response to the initial mailing, to derive a second set of contours (protocol CTV) of the same 2 patients. Contours from each observer were copied (made anonymous) to a template CT dataset of the corresponding patient (Fig. 1).

Patient 1 (post-lobectomy). The first patient had undergone a radical right upper lobectomy with a mediastinal lymph node dissection for a stage $pT_2N_2M_0$ tumor. Histology revealed a 3-cm adenocarcinoma with extension to the visceral pleura. Hilar nodes showed no metastases, but two out of seven explored ipsilateral mediastinal nodes (stations 4 and 7 right) showed tumor deposits (17) (Fig. 2). Adjuvant treatment consisted of administration of four cycles of systemic chemotherapy, after which the patient was referred for PORT.

Patient 2 (post-pneumonectomy). The second patient had received induction chemotherapy (three cycles of a platinum-based combination) for a 5-cm nodule in the right upper lobe extending to the visceral pleura, with both ipsilateral hilar and subcarinal nodal disease. As response evaluation revealed a partial response of the tumor and no hilar abnormalities, a right pneumonectomy and mediastinal dissection was performed. Nine lymph nodes were explored: three intrapulmonary and hilar nodes, two subcarinal nodes (station 7), and four paratracheal nodes (2 station 4R and 2 station 2R). Histology revealed a poorly differentiated large-cell carcinoma measuring 4 cm in diameter with 50% necrosis. Metastases were found in a subcarinal node and a right paratracheal node (station 4R). All resection margins were free of tumor, and the patient was referred for PORT for a stage $pT_2N_2M_0$ tumor.

Lung ART contouring protocol (Appendix A). The CTV includes the bronchial stump, the ipsilateral hilar node region, and any possible extension to the mediastinal pleura adjacent to the resected tumor bed. In addition, the mediastinal CTV is to include all the lymph nodes that lie between two noncontiguous nodal stations that have contained metastases at any stage. Based on the surgical literature, subcarinal (LN7) and ipsilateral paratracheal nodes (LN4) are always included in the CTV (Fig. 2). In the case of leftsided tumors, the subaortic and para-aortic nodes (LN 5 and 6) should be included in the CTV (Fig. 2). When metastases are identified in a nodal station, the next nodal station superior to it is included in the CTV, as is the nodal station immediately inferior to the lower involved mediastinal node. However, in some cases the volumes delineated for the CTV could become too large. For instance, in the case of LN7 involvement, LN8 should theoretically be included so that the lower limit will be at the gastroesophageal junction. Therefore, it was decided to define the boundaries more clearly in a table (Appendix B).

Analysis of clinical target volumes

Volumes of the routine and protocol contoured targets of each observer were determined, using a tracing tool in ImageJ (http://rsb.info.nih.gov/ij/). The outlines of all axial two-dimensional contours were traced, and the number of encompassed internal pixels (pixelsize 0.87*0.87 mm) and the number of contoured slices (slice thickness 2.5 mm) were calculated. In addition, both length in three orthogonal directions and center-of-mass (COM) coordinates of each CTV were determined. To determine the coverage of nodal stations to be included in the CTV, a gold standard for mediastinal nodal regions was generated by two clinicians (F.S. and S.S.) at the VU University Medical Center for both patients according to the definitions by Chapet *et al.* (18) using Eclipse v8.1 software (Varian Med. Systems, Palo Alto, CA).

Dosimetric analysis

To evaluate the influence of contouring variation on dose–volume histogram (DVH) statistics before and after use of the protocol, a dosimetric analysis was performed based on both the smallest and the largest target volume. Planning target volumes (PTVs) were generated by expanding CTVs with a margin of at least 5 mm in the mediolateral and dorsoventral directions and of 10 mm in the craniocaudal direction to account for tumor motion and variations in patient setup. A routine conformal treatment plan consisting of five fields using 6- to 15-mV photons was designed in Eclipse v8.1, based on a gold standard CTV contoured by the principal investigator (S.S.). The Lung ART protocol prescribed a dose of 54 Gy in daily fractions of 2.0 Gy. This plan was then projected on each PTV (smallest and largest routine and protocol PTV) and adjusted such that the 95% isodose volume tightly conformed the PTV while respecting dose constraints to organs at risk according to International Commission on Radiation Units and Measurements objectives (19). Specifically, it was aimed to limit the percentage volume of lung tissue outside the PTV planned to receive 20 Gy to 35% ($V_{20} \leq 35\%$) and the maximum spinal cord dose to 50 Gy. The DVHs were calculated to evaluate variability in toxicity

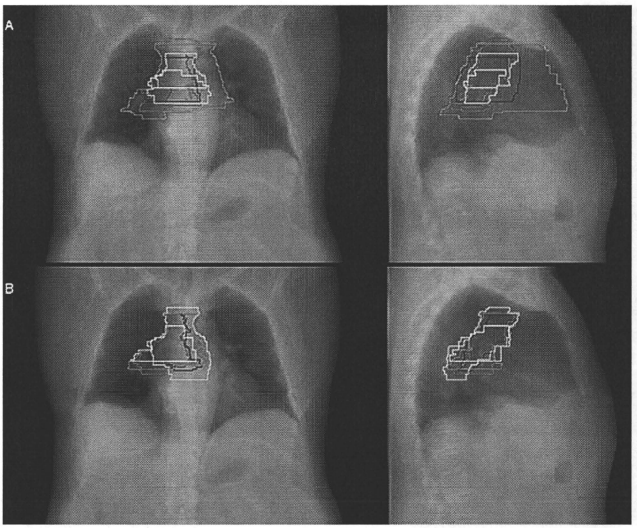

Fig. 1. Routine clinical target volumes (CTVs) (upper panel) and protocol CTVs (lower panel) from six observers projected on a digital reconstruction of a computed tomography dataset from the postlobectomy patient.

profile, and the following parameters were assessed: mean lung dose, total lung volume minus PTV receiving either ≥20 Gy (V_{20}) or ≥5 Gy (V_5), total cardiac volume percentage receiving ≥45 Gy (V_{45}), maximum spinal cord dose, and esophageal length receiving ≥45 Gy.

Statistical analysis

The variance between routine and protocol CTVs of different observers was assessed by constructing a mixed-effects model for each endpoint (*i.e.*, volume, length, or COM position). Contouring procedure and patient identifier were taken as fixed effects, whereas the observer identifier was taken as the random grouping variable. Significance was reported at levels 0.05 and 0.007, with the latter being the adjusted value for multiple testing using the Bonferroni method. Differences in nodal coverage between routine and protocol CTVs were evaluated using an F test in Excel (Microsoft Office 2003).

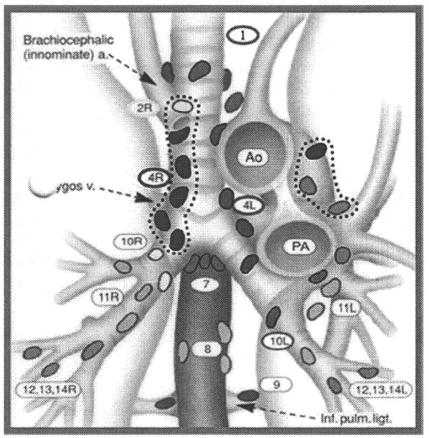

Fig. 2. Nodal staging system (Mountain-Dresler).

RESULTS

Number of datasets received

For each case, a total of 10 clinicians generated routine clinical target volumes (CTV); they included the principal investigator, who had knowledge of the protocol. Both routine and protocol CTV's for both patients were available from six expert observers. One participating clinician returned only a protocol CTV for both cases because the center did not perform routine PORT.

Analysis of clinical target volumes

Regarding experts who returned routine and protocol datasets, for the postlobectomy patient, the median routine CTV was 90.2 cc (range, 36.2–678.4 cc), and the median corresponding protocol CTV was 91.3 cc (range, 60.0–112.4 cc). For the postpneumectomy patient, the median routine CTV was 115.5 cc (range, 48.5–712.1 cc), and the median corresponding protocol CTV was 93.3 cc (range, 78.3–125.3). Regarding all experts, routine CTVs varied up to threefold between clinicians, but this variance was significantly reduced

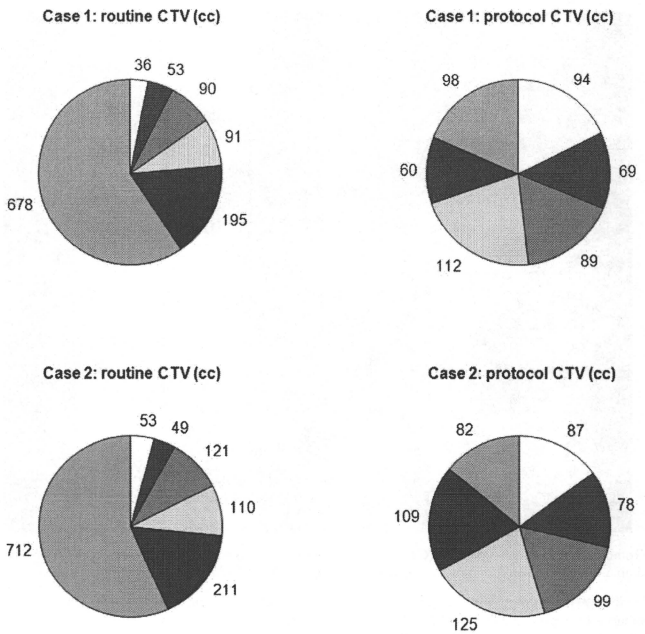

Fig. 3. Routine vs. protocol clinical target volumes (CTVs) (cc) from six observers for the postlobectomy patient (upper panel) and the postpneumectomy patient (lower panel).

for both cases when clinicians used the Lung ART protocol ($p < 0.007$) (Fig. 3). In addition, both the variance in cranial-caudal COM positions ($p < 0.007$) and contoured target lengths along the cranial-caudal Z axis were significantly reduced ($p < 0.05$) using the protocol. All results maintained significance when data of the observer with the most deviating CTV were excluded from analysis.

In both patients, the Lung ART protocol required the CTV to include nodal stations 2 right (LN2R), 4 right (LN4R), 7 (LN7), and ipsilateral hilus. Median coverage of LN4R and LN7 by routine CTVs were 82% (range, 44–97%) and 94% (range, 20–100%), respectively, for the postlobectomy patient. Use of the protocol resulted in an increased median coverage of LN4R ($p < 0.05$) (Fig. 4). Although median coverage did not significantly improve in LN7, the range between observers was much smaller with the protocol (73–100%) compared with routine (20–100%) contoured CTVs (Fig. 4). Similar results were seen in the postpneumectomy patient (Fig. 4). Median coverage of LN2R by routine CTVs was poor in both cases, with values of 0% (range, 0–47%) and 38% (range, 0–62%) in the postlobectomy and postpneumectomy patients, respectively. The results did not significantly improve using the protocol (Fig. 4).

Dosimetric analysis

The difference in 95% isodose volume between the smallest and the largest CTV was reduced from 1,802 cc to 216 cc in the postlobectomy patient and from 1,342 cc to 53 cc in the postpneumectomy patient. Variations in routine CTVs led to important differences in the risk of radiation-induced toxicity; *i.e.*, the V_{20} ranged from 12.7% to 54% in the postlobectomy patient, whereas corresponding values in the postpneumectomy patient ranged from 1.5% to 20.6% (Table 1). Similarly, large variations between experts were observed in mean lung dose, lung V_5, and cardiac V_{45} in both cases. When the protocol was used, differences between observers were significantly reduced, resulting in a more consistent toxicity profile (Table 1). The differences in both spinal cord doses and esophageal length receiving > 45 Gy between routine and protocol CTVs were not as striking as seen with the other parameters.

DISCUSSION

Studies planned to evaluate PORT should use not only modern radiotherapy techniques but also consistent target volume definition. The latter is particularly relevant because the lack of standardized protocol definitions in the past may

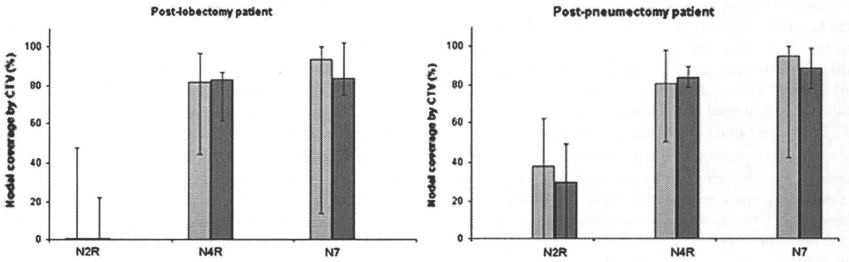

Fig. 4. Nodal coverage (%) by routine and protocol clinical target volumes in the postlobectomy patient (left) and the postpneumectomy patient (right).

have contributed to inconclusive results (10, 20); i.e., the total dose was often not standardized and excessively high (5), with variable field sizes influencing both local recurrence rates and radiotherapy-induced mortality (6). The results of the present study show that even among thoracic radiation oncology experts, large variability was observed in routine target definition for PORT, and the up to threefold variation resulted in important differences in DVH parameters. The potential influence of pulmonary and cardiac toxicity, arising from unnecessarily large fields, on the risk of radiotherapy-induced mortality is now well appreciated (6). Similar concerns are experienced with the use of adjuvant chemotherapy, which is presently the standard of care in patients with non–small-cell lung cancer and resected N1 and N2 disease (21). Follow-up after more than 5 years after adjuvant chemotherapy revealed an increase in mortality (22), a development that highlights the potential for long-term hazards after any adjuvant therapy for such patients.

Before the commencement of the Lung ART trial, protocol target volumes were developed by the Lung ART writing committee based on patterns of local recurrence after surgery (23, 24), lymphatic pathways, and results of the omission of elective nodal irradiation (25, 26). The present study revealed that use of the Lung ART protocol resulted in a large degree of consensus between clinicians. However, residual interobserver variability may still exist as a result of misinterpretation, lack of clear formulation, or ignorance of the protocol. This is supported by the finding that use of the protocol did not improve coverage of the upper para-aortal nodes (LN2R). Consequently, a clear definition of the boundaries of this particular region should be specified in the protocol.

Recent major intergroup trials have also included dummy runs as a part of QA analysis (27–32), but these studies differ from ours in that we investigated interobserver variability both before and after the protocol was provided, allowing for evaluation of the impact of the protocol. In addition, earlier dummy runs were performed using hard copies, whereas we used a CD-ROM–based contouring program containing complete CT datasets that can be run automatically on each Windows-based computer. Our previous study validating this CD-ROM tool has established a more realistic assessment of clinical variations than with hard copies, and it was shown that most clinicians were able to complete the exercise (16).

One limitation of our study is that none of the invited experts from North America finally participated in this study. Furthermore, experts were arbitrarily identified from members of International Association for the Study of Lung Cancer and European Organisation for Research and

Table 1. Variability in planning parameters between the smallest and largest target volumes

	Postlobectomy patient				Postpneumectomy patient			
	Routine		Protocol		Routine		Protocol	
	Range	Difference	Range	Difference	Range	Difference	Range	Difference
Planning target volume (cc)	148–1,342	(1,194)	297–382	(85)	187–1,262	(1,075)	275–308	(33)
95% Isodose volume (cc)	300–2102	(1,802)	518–734	(216)	446–1,788	(1,342)	556–609	(53)
Lung								
Mean lung dose (Gy)	8.0–26.1	(18.1)	11.6–15.3	(3.7)	3.4–13.4	(10.0)	4.0–4.1	(0.1)
V_{20} (%)	12.7–54.0	(41.3)	20.6–29.2	(8.6)	1.5–20.6	(19.1)	2.1–2.9	(0.8)
V_5 (%)	34.7–79.5	(44.8)	52.2–63.1	(10.9)	31.6–59.3	(27.7)	30.4–35.7	(5.3)
Heart								
V_{45} (%)	0–20.5	(20.5)	1.6–5.1	(3.5)	4.3–37.0	(32.7)	7.1–10.0	(2.9)
Spinal cord								
D_{max}	45.3–49.5	(4.2)	47.8–50.0	(2.2)	50.0–51.0	(1.0)	44.8–48.7	(3.9)
Esophagus								
Length receiving 45 Gy (cm)	4.5–11.5	(7.0)	6.8–9.5	(2.8)	5.8–12.0	(6.3)	7.5–10.8	(3.3)

Treatment of Cancer who were active in lung cancer and who were known to the study group. In addition, the participating experts themselves did not perform treatment planning; therefore, interinstitution variability in dose statistics could not be assessed. Instead, dosimetric impact of contouring variability was evaluated by designing a standard plan in our own institution, although we believe that this was of minor influence, as contouring variation seems to be the largest source of systemic errors in lung cancer (33). Furthermore, the results are based on a routine conformal plan consisting of five fields, whereas the use of three fields (which is allowed in the protocol) may have resulted in a more forgiving situation, leading to less striking differences between routine and protocol target volumes. In addition, this study did not account for interobserver variability with respect to shape of the contours, which has been reported to be imprecise between observers (34). Other factors besides the Lung ART protocol could have contributed to the reduction in contouring variability over a period of time, including test–retest reliability. We were unable to study the latter because the logistic difficulties involved in obtaining the full cooperation of all the invited experts were considerable.

This dummy run test was part of the first phase of an external QA program, and the results were sent to the QA team for protocol validation. The magnitude of the observed differences led to a decision to invest in a web-based dummy run for the Lung ART trial. This ongoing study will address the above issues in a more representative population of thoracic radiation oncologists. The next step will include collection of the plans and its verification images for the first patient from each participating center. Subsequently, 15% of the plans will be collected by the QA team to ensure protocol adherence in centers where plans of the first patients were adequate, whereas plans of the patients included in the RT arm will be considered for revision in centers where plans were not adherent to the protocol.

CONCLUSIONS

The large interobserver variation in target definition seen among experts is a confounding factor in clinical outcomes of multicenter clinical trials, emphasizing the need for standardization. A protocol defining target definitions was shown to serve this purpose and is therefore incorporated in the QA program of the Lung ART.

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APPENDIX A: CONFORMATIONAL POSTOPERATIVE RADIOTHERAPY

According to randomization, patients will receive or not receive postoperative radiotherapy (PORT). We recommend that patients randomized in the treatment arm start PORT as soon as possible after randomization. No concomitant chemotherapy is allowed. At least 10 days' interval between the last day of chemotherapy and PORT is requested. This interval may be extended in case radiosensitizing drugs such as gemcitabine have been used, or when the patient does not have full haematologic recovery from the chemotherapy.

Radiotherapy technique

High-energy photons (≥6 MV) should be used. The planned dose to the International Commission on Radiation Units and Measurements reference point is 54 Gy in 27 fractions of 2.0 Gy. The radiotherapy will be given once each day, 5 days per week. The use of conformal techniques is mandatory. A planning computed tomography (CT) scan in treatment position should be used, with a maximal slide thickness of 5 mm for the whole thorax. The use of intravenous contrast is recommended. All target volumes as well as the critical organs should be delineated on this CT scan. Dose–volume histograms (DVH) of all target volumes—resected clinical tumor volume (rCTV), clinical target volume (CTV), and planning target volume (PTV)—and of all critical organs (lungs, cardiac volume, and spine, with or without esophagus) as described in the following section are required. All patients should be treated with a minimum of three fields. All fields should be treated daily.

Definition of volumes

rCTV in the mediastinum. This corresponds to lymph nodes involved according to the pathologic report of the lymph node exploration. The bronchial stump, the homolateral hilar node region, and the eventual extension to mediastinal pleura facing the resected tumor bed completely resected will always be included in the rCTV.

CTV in the mediastinum. In the CTV will be included the rCTV plus a margin corresponding to the upper and lower lymph node station to the involved lymph node area. All the lymph nodes that lie between two noncontiguous node stations that are involved will be included in the CTV. Because of the frequent involvement of subcarinal (LN7) and paratracheal nodes (LN4) on surgical series, these stations will also be systematically included in the CTV.

In the case of a leftsided tumor, the subaortic and the paraaortic nodes (LN 5 and 6) should also be included in the CTV because they are very often involved (as shown in Appendix B). The homolateral supraclavicular region will not be included systematically in the CTV.

PTV. Owing to organ movements and to setup uncertainties, an additional margin of at least 0.5 cm (lateral, anterior, and posterior) and 1 cm (superior and inferior) is recommended. The margins may be individualized according to 4D-CT scan data and/or measurements of the daily setup error. For patients who have had a positron emission tomography (PET)—CT scan before treatment, all data will be collected concerning positive nodes. However, only surgical positive nodes will be included in the rCTV.

APPENDIX B

Surgically involved mediastinal nodes	LN stations to be included in the CTV
1–2R	1–2R, 4R, 7, 10R Maximal upper limit: 1 cm above sternal notch but homolateral subclavicular node station may be treated if needed Maximal lower limit: 4 cm below the carina*
1–2L	1–2L, 4L, 7, 10L Maximal upper limit: 1 cm above the sternal notch but homolateral subclavicular node station may be treated if needed Maximal lower limit: 4 cm below the carina*
3 (Right -sided tumor)	3, 4R, 7, 10R Maximal upper limit: 1 cm above the sternal notch Maximal lower limit: 4 cm below the carina*
3 (Left-sided tumor)	3, 4L, 7, 10L Maximal upper limit: 1 cm above the sternal notch Maximal lower limit: 4 cm below the carina*
4R	2R, 4R, 7, 10R Maximal upper limit: sternal notch Maximal lower limit: 4 cm below the carina*
4L	2L, 4L, 7, 10L Maximal upper limit: sternal notch Maximal lower limit: 4 cm below the carina*
5	2L, 4L, 5, 6, 7 Maximal upper limit: top of aortic arch Maximal lower limit: 4 cm below the carina*
6	2L, 4L, 5, 6, 7 Maximal upper limit: sternal notch Maximal lower limit: 4 cm below the carina*
7 (Right-sided tumor)	4R, Maximal upper limit: top of aortic arch Maximal lower limit: 5 cm below the carina*
7 (Left-sided tumor)	4L, 5, 6, 7 Maximal upper limit: top of aortic arch Maximal lower limit: 5 cm below the carina*
8 (Right-sided tumor)	4R, 7, 8 Maximal upper limit: top of aortic arch The lower limit should be the gastroesophageal junction
8 (Left-sided tumor)	4L, 5, 6, 7 8 Maximal upper limit: top of aortic arch The lower limit should be the gastroesophageal junction

Abbreviations: LN = lymph node; CTV = clinical target volume.
* Unless other nodes are involved.

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

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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 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 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

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

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

a, artery; a/v, artery and vein; m, muscle.
[a]Even in patients with low adipose connective tissue in this space, posterior margin should also extend to posterior edge of vertebral body.

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 ultrasmall 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.

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

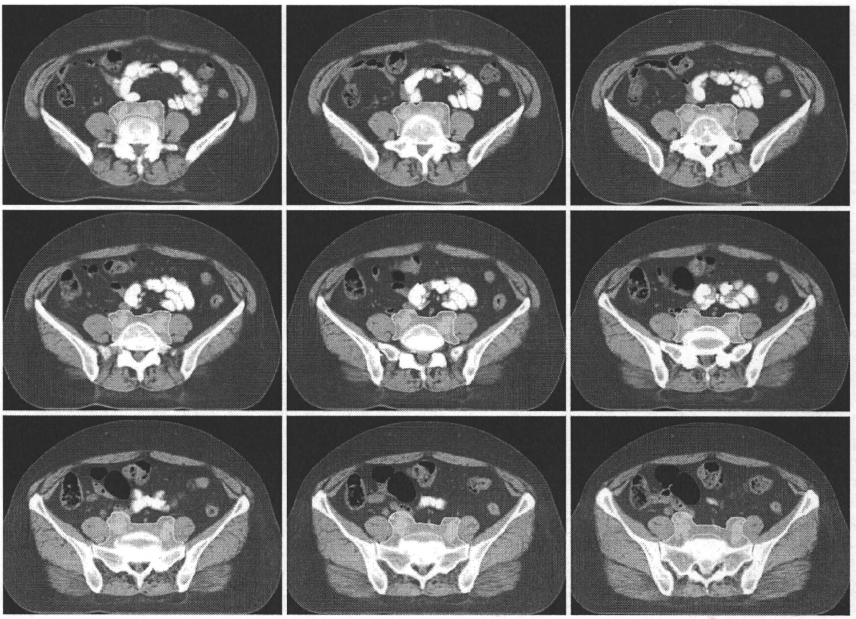
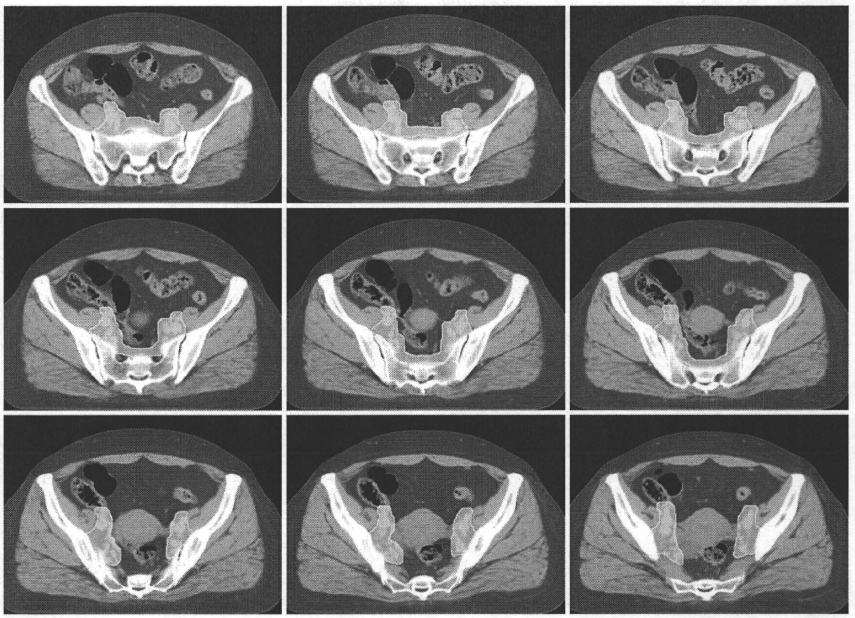


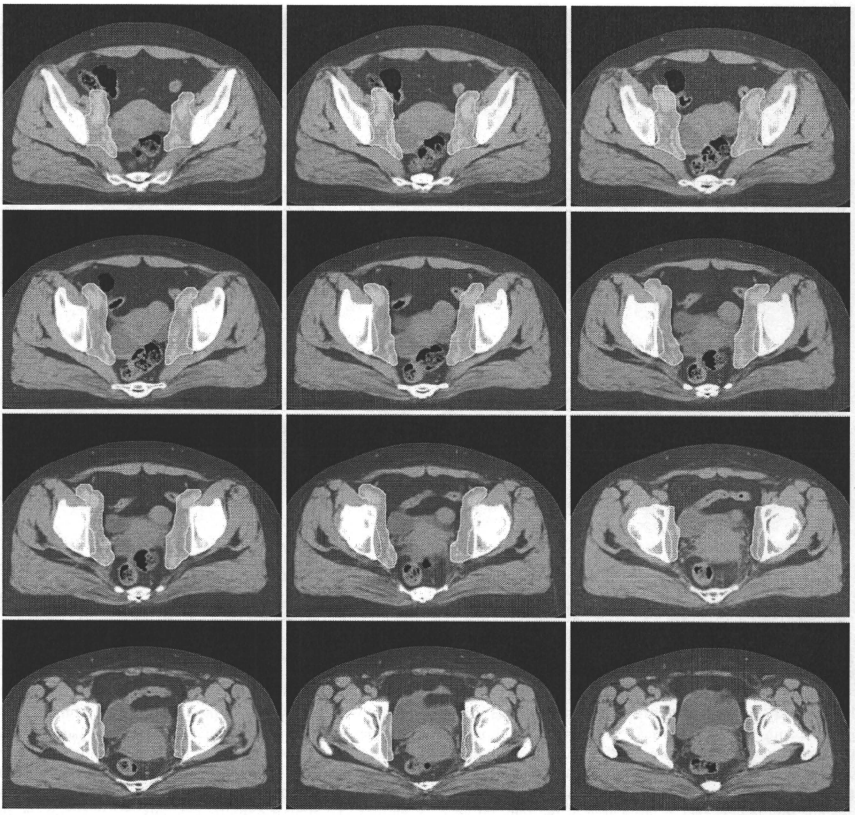
Figure 1. An atlas of clinical target volume (CTV) for pelvic lymph nodes for uterine cervical cancer.



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 foramens. 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 foramens (22). In cases of external beam radiotherapy, the conventional 2D pelvic fields also include the foramens. 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

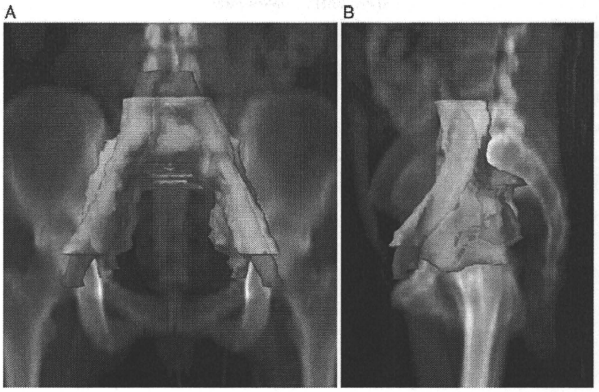


Figure 2. Digitally reconstructed radiographs showing CTV for pelvic lymph nodes (yellow) and vessels (orange); (A) anterior view and (B) lateral view.

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.

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