表3　順次 vs. 同時化学放射線療法についての第3相試験

報告者・年	化学療法	放射線療法 (Gy)	症例数	MST (M)	4年生存率 (%)
Furuse WJTOG, 1997[10]	MVP (seq)	56	158	13.3	10.1
	MVP (conc)	56split	156	16.5	17.9
Curran RTOG 2003[11]	VP (conc)	60	205	14.6	12.0
	VP (seq)	60	203	17.0	21.0
	PVP (conc)	69.6HF	203	15.2	17.0
Fournel France 2005[12]	VinoP (seq)	66	101	14.5	14.2
	PVP (conc)	66	100	16.3	20.7

MVP：mtomycin/vindesine/cisplatin, VP：VBL/cisplatin, PVP：etoposide/cisplatin, VinoP：vinorelbine/cicplatin, HF：hyperfraction, Seq：順次, conc：同時

め，grade 3以上の食道炎の発症は4%から18%に増加した。化学療法の併用，特に同時併用は有効性も高いが，有害事象も有意に増加するため，適応症例の選択が重要である。年齢に関して高齢者のみを対象とした比較試験はないが，年齢別のsubset analysisによると，化学療法併用は70歳以上ではかえって治療成績が不良であったという報告[8]がある。しかし一方PSの良い高齢者（fit elderly）では生存率に差がないという報告[15]もあり，特にPSを考慮して適応を選択する必要があると考える。

3）併用化学療法：第2世代 vs. 第3世代

現時点における標準的併用化学療法は前述のようにCDDP＋第2世代full doseのレジメンであるが，根治照射の対象とならない進行肺癌において有用性の示されたプラチナ製剤＋第3世代新薬〔パクリタキセル（PTX），ドセタキセル（DTX），イリノテカン（CPT11），ビノレルビン（VNR）など〕を組み入れる試みが積極的に行われている。しかしfull doseの第3世代レジメンは放射線と同時併用した場合毒性が増強するため実施困難とされ，減量するか分割投与する方法が試みられている。しかしカルボプラチン（CBDCA）とPTXを分割しweeklyに投与する同時化学療法の比較試験（LAMP trial[16]，CBDCA39801[17]）の結果などは第2世代レジメンを上回る成績ではなかった。

日本において第2世代レジメンと第3世代レジメンの比較第3相試験が2つ施行された。Okayama Lung Cancer Study Group（OLCSG）ではCDDP＋DTX（DP）をMVPと比較した優越性試験が行われ，その最終報告が2008年ASCOにて発表された[18]。primary endpointである2年生存率はMVP群48.1%に対し，DP群が60.3%と有意に良好な結果であったが，5年生存率には有意差を認めなかった。血液毒性はMVP群で強く，食道炎・肺炎はDP群で多く認められた。また，WJTOGでは，CBDCA＋CPT11，CBDCA＋PTXをMVPと比較した非劣性試験（WJTOG0105）が行われた。すでに奏効率には差がなかったことが報告されており[19]，2009年ASCOでの最終報告が待たれる。

今後放射線との併用で期待されるその他のレジメンとしては，CDDP＋VNR，CDDP＋TS1などがある。前者は国立がんセンター単施設での第1相試験ではあるが，CDDP 80mg/m^2＋VNR 20mg/m^{2}とfull doseに近い用量が推奨用量と報告され[20]，短期成績も良好で今後のさらなる検討が期待される。

4）分子標的薬剤の併用

非小細胞肺癌への有効性が期待され，進行・再発肺癌において有用性が示されている分子標的薬剤としては，①EGFR-TKI（tyrosine kinase inhibitor）の中のgefitinib（Iressa®），erlotinib（Tarceva®），②抗EGFR抗体であるcetuximab（Erbitux®），③抗VEGF抗体であるbevacizumab（Avastin®）などがある。これらは，生物学的に放射線との併用効果も期待されており，化学放射線治療への上乗せ効果についても検討されつつある。

頭頸部腫瘍において化学放射線治療への上乗せ効果が証明されたcetuximabについては，局所進

表4　3D-CRT＋化学療法同時併用による線量増加の第1，2相試験

試験	試験デザイン	症例数	線量（Gy）	MTD (Gy/fr)	ENI	化学療法	MST (M)
North Carolina [25]	I/II	62	60～74	74/37	＋45Gy	導入＋同時 CBDCA/PTX	24
NCCTG N0028[26]	I	15	70～78	74/37	－	同時 CBDCA/PTX	(37)
CALGB 30105[27]	Randomized II	43	74	－	－	導入＋同時 CBDCA/PTX	24.2
		26	74	－	－	導入＋同時 GEM	17.0
RTOG0117[24]	I/II	63	74～75.25	74/37	－	同時 CBDCA/PTX	(21.6)

ENI：elective nodal irradiation

行非小細胞肺癌においても化学放射線同時併用への同時併用の第2相試験（RTOG0324）が行われ，MST22.7カ月と良好な成績であり[21]，さらに第3相試験が予定されている。一方，gefitinibの同時併用についての第2相試験（CALGB30106）ではPS 2の症例ではMST 19カ月と比較的良好な成績であったが，PS 0～1症例では12カ月とむしろ不良であった[22]。今後は遺伝子変異の有無など感受性を考慮した個別化治療，費用対効果比も含めて，検討していくべき重要な分野である。

5）胸部放射線治療の進展：限局照射野による線量増加の試み

放射線治療についての現在の標準治療は1回2Gyの通常分割照射法で60Gy/30frを最低合計線量とするよう推奨されている。しかし，局所制御率はいまだ良好とはいえず，近年のコンピュータ治療計画の進歩も寄与して，3D治療計画を用いた線量増加の試みが行われている。RTOGではまず，化学療法を同時には行わずに予防的縦郭リンパ節照射（elective nodal irradiation：ENI）を省いた限局照射野（involved field radiotherapy：IFRT）で三次元原体照射法（three dimensional conformal radiotherapy：3D-CRT）を用いた線量増加第1，2相試験（RTOG9311）が行われた。肺のV20が25%未満では許容線量は83.8Gy/39fr，25～36%では77.4Gy/36frであった[23]。ついで化学療法同時併用（CBDCA＋PTX weekly）による線量増加第1,2相試験（RTOG0117）が同じく3D-CRTを用いたIFRTで行われ，V20を30%以下として許容線量は74Gy/34frとなった[24]。現在までに報告されている化学放射線同時併用時の線量増加第1，2相試験について代表的なものを表4[24-27]に示す。

このような線量増加の意義について，RTOGではCBDCA/PTX weekly同時併用，3D-CRT,IFRTを用いた60Gy/30frと74Gy/34frの比較第3相試験（RTOG0617）が2007年末より進行中である。日本においても，いくつかの第1，2相線量増加試験が進行・計画中でそれらの結果が期待される。

線量増加にあたっては，IFRTが用いられることが多いが，その根拠は主にretrospectiveなデータに基づいている。前述のIFRTを用いたRTOG9311では，中央経過観察期間16カ月で照射野外の縦郭リンパ節再発は9%と，局所制御率を考慮すれば低値であったと述べている[23]。中国においてIFRTでの線量増加とENIを含む通常線量の比較試験が行われ，IFI群において5年局所制御率（51% vs. 36%，p＝0.032）と2年生存率（39.4% vs. 25.6%，p＝0.048）の延長を認め，放射線肺炎の発症は低かった（17% vs. 29%，p＝0.044）と報告されている[28]が，症例数が少ないためかP値もぎりぎりであり，さらなる検討が望まれる。

❸ 術前・術後照射

1) IIIA/N2 症例の術前化学放射線治療

前述したように，IIIA/（non-bulky）N2 症例は切除可能と不能の境界領域であり，治療法の選択に議論が多い。この領域では，術前化学放射線療法を行った上で外科治療を追加する意義があるかについて，米国で intergroup trial（INT0139/RTOG9309）が行われた。病理学的に確認された 396 例の IIIAN2 例で，CDDP + VP16 +同時 RT45Gy 後に手術を加える群と 61Gy まで照射する群が比較された[29]。無再発生存期間中央値では手術群が有意に良好（14.0Mvs. 11.7M, p = 0.017）であったが，5 年生存率では同等（27.2% vs. 20.3%, p = 0.10）であり，治療関連死亡は手術群で有意に高く（7.9% vs. 2.1%），特に肺全摘群における手術死亡率は 26%と高率であった。これらの結果から IIIA/N2 期症例に対し，化学放射線治療後に手術を加える trimodality therapy は現在のところ標準的治療とはいい難いが，症例を選択すれば有用である可能性はあり，今後の研究がさらに必要な領域である。

2) 術後照射

術後放射線療法（postoperative radiotherapy：PORT）の有用性については，PORT Meta-analysis Trialists Group により 1998 年に 9 つの第 3 相試験 2,128 症例の meta-analysis の結果が報告された[30]。術後照射の追加により全生存期間はむしろ短縮し，術後 2 年生存率は PORT 群 48%，無治療群 55%であった。その傾向は I, II 期および N0, 1 例で顕著であったが，III 期，N2 症例では差は明らかではなかった。同グループにより再検討された追加報告でも同様の結果であった[31]。以上より I, II 期，N0, 1 症例に対しては，術後照射を行うべきではないとされている。N2 症例に対しては予後を悪化することはないが有用性も明らかではないとされた。その後，米国の SEER database からの大規模な報告[32]や，ANITA（Adjuvant Navelbine International Trialist Association）trial の subset analysis[33]では pN2 症例に限ると術後照射により生存期間が延長したという報告がなされた。これらのことから，pN2 症例に対する術後照射の有用性は再検討の余地があると考えられ，EORTC において pN2 症例に対する PORT の意義についての第 3 相試験が進行中である（Lung-Art trial）。

❹ 三次元治療計画・治療技術

1) 呼吸移動対策

肺癌の放射線治療における種々の物理的問題点の中でも，呼吸性移動への対応は非常に重要である。X 線シミュレーターで呼吸性移動を観察・評価する事も簡便で有用な方法であるが，CT 治療計画装置の導入に伴い X 線シミュレーターを持たない施設もある。そのような場合や，さらに高精度な呼吸移動対策を要する場合には近年の機械工学・コンピュータ技術の進歩によって種々の対策法が開発されており，施設の状況に応じて適切に取り入れていく必要がある。対策法の詳細は他を参照されたい[34]が，① 呼吸性移動による internal margin（IM）を正確に評価し，移動範囲を包容する方法と，② IM を減少させる方法に大別される。①としては slow scan CT，吸気呼気融合 CT，4D-CT などがあり，②には，呼吸ゲート法，息止め法，呼吸抑制法，動体追跡法などがある。両者を組み合わせることにより，より正確にかつ照射範囲を限局する照射が可能になる。SBRT においてはもちろん必須であるが，今後は進行肺癌における線量増加試験などでも肺など周囲正常臓器への線量を減少させつつ腫瘍への線量を増加させていくために必要になると思われる。前述の RTOG0617 ではいずれかの呼吸移動対策を必要条件としている。

2) 不均質補正の導入

CT を用いた三次元治療計画を行う意義のひとつに，不均質補正を用いて線量計算を行うことにより，より実際に近い線量分布が得られることがある。特に肺などの電子密度の低い臓器を含む肺癌放射線治療においてはその意義は大きく，JASTRO ガイドラインにおいても superposition 法相当以上のアルゴリズムを用い，不均質補正を行うことを推奨している[35]。しかしこの際に，2 次元治療計画や不均質補正を用いない三次元治療計画での治療経験との違いを認識し，各施設での品質管理・品質保証を十分に行う必要がある。例えば肺野を含む照射野では線量分布が不均一となり，同じ線量を処方する場合，不均質補正なしと比較して線量（MU 値）が低くなる可能

表5　NCCN v.1.2009 によるリスク臓器の線量制約

リスク臓器	放射線単独治療		化学放射線治療	
	パラメータ	制限値	パラメータ	制限値
脊髄	Dmax	＜50Gy	Dmax	＜45Gy
肺	V20	＜40%	V20	＜35%
心臓	V40	＜100%	V40	＜50%
	V50	＜50%		
食道	V60	＜50%	V55	＜50%
腕神経叢*	Dmax	＜66Gy	Dmax	＜66Gy

* 腕神経叢の値は NCCN では記載されていないため，RTOG0617 の線量制約より引用

性がある事や，リスク臓器への線量制約の値も異なってくることなどに注意が必要である。

3) DVH による正常組織の線量制約

三次元治療計画の意義のもうひとつに dose volume histogram（DVH）から導かれたパラメータを用いて正常組織の有害事象の発症を予測することがある程度可能になったことがあげられる。特に肺癌放射線治療における放射線肺炎に関しては研究が多く，実臨床に取り入れられている。Washington 大学の Graham らは非小細胞肺癌 99 例（照射単独 58%）において V20（20Gy 以上照射される肺の全肺容積に対する割合）が 32%を超えると重症な放射線肺炎の発症例を認め，40%を超えると発症率が高くなり 17 例中 3 例の死亡例を認めたと報告している[36]。当院の症例で検討した化学放射線同時併用 71 例ではさらに発症率が高く，V20 が 31%を超えた 7 例中 2 例に放射線肺炎による死亡を認めたため，化学放射線同時併用時には V20 が 30%以下になるようにしている[37]。その他食道や心臓などでも DVH パラメータと有害事象の関連性の検討が行われ，それらを用いた正常組織の線量制約を行うことにより，より安全に放射線治療が行えるようになっている。線量制約の制限値については DVH の計算法（たとえば肺の場合の全肺容積は全肺－GTV や全肺－PTV の報告がある），放射線総線量，分割法，併用化学療法などによっても異なると考えられるため，一定したものがまだないが，一例として，2009 年度版 NCCN ガイドライン[38] のものを表 5 に示す。各施設の治療法に合わせて，DVH による線量制約を用いていくことが望まれる。

■ おわりに

非小細胞肺癌の放射線治療の中で，根治目的の治療にかかわる部分について，現在の標準治療と今後の展望について概説した。I 期肺癌については，SBRT の初期成績は良好で，さらなる追跡と前向き臨床試験の結果が待たれる。III 期局所進行肺癌については，80～90 年代にかけて化学放射線併用療法による治療成績の向上が得られたが，まだ治療成績は良好とはいえない。併用する新規抗がん剤・分子標的薬剤の有用性の検討と共に，放射線治療としては，近年の著しい治療技術の発展によって安全に行うことが可能となった線量増加などに期待が寄せられている。

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Summary

Radiotherapy for non-small cell lung cancer

We reviewed the role of radiotherapy in the management of non-small cell lung cancer (NSCLC) . For stage I NSCLC, the initial results of stereotactic body radiotherapy (SBRT) have been promising and larger prospective trials are ongoing. For locally advanced NSCLC, concurrent chemoradiotherapy (CCRT) is the current standard of care for patients with good performance status. However, the prognosis of those patients is still poor. Radiotherapy combined with new third generation chemotherapy regimens and molecular target agents, and radiation dose escalation using novel IGRT techniques are under investigation.

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CLINICAL INVESTIGATION

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. © 2009 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

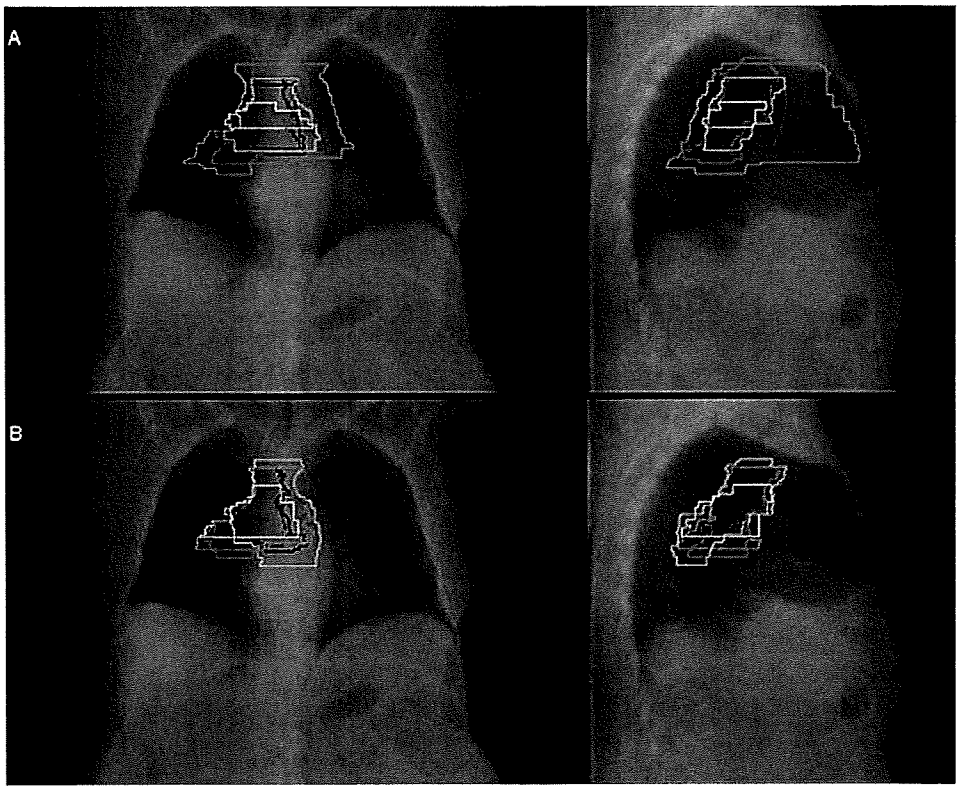

Fig. 1. Routine clinical target volumes (CTVs) (upper panel) and protocol CTVs (lower panel) from six observers projected on a digital reconstruction of a computed tomography dataset from the postlobectomy patient.

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).

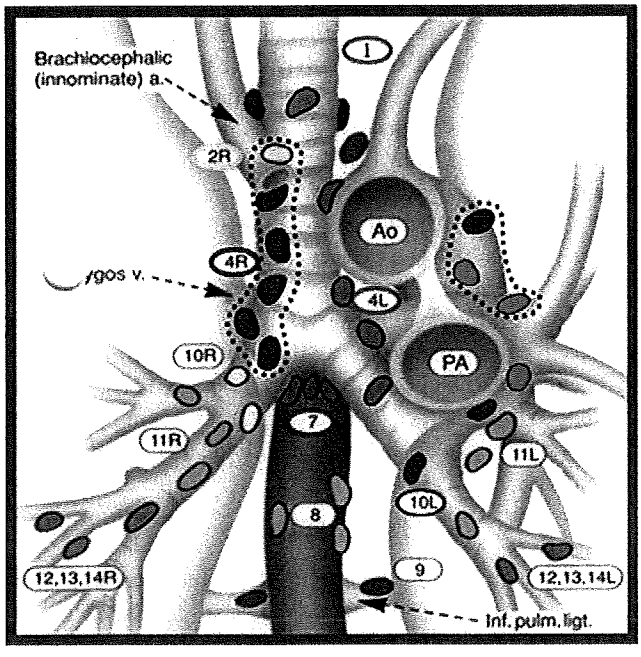

Fig. 2. Nodal staging system (Mountain-Dresler).

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

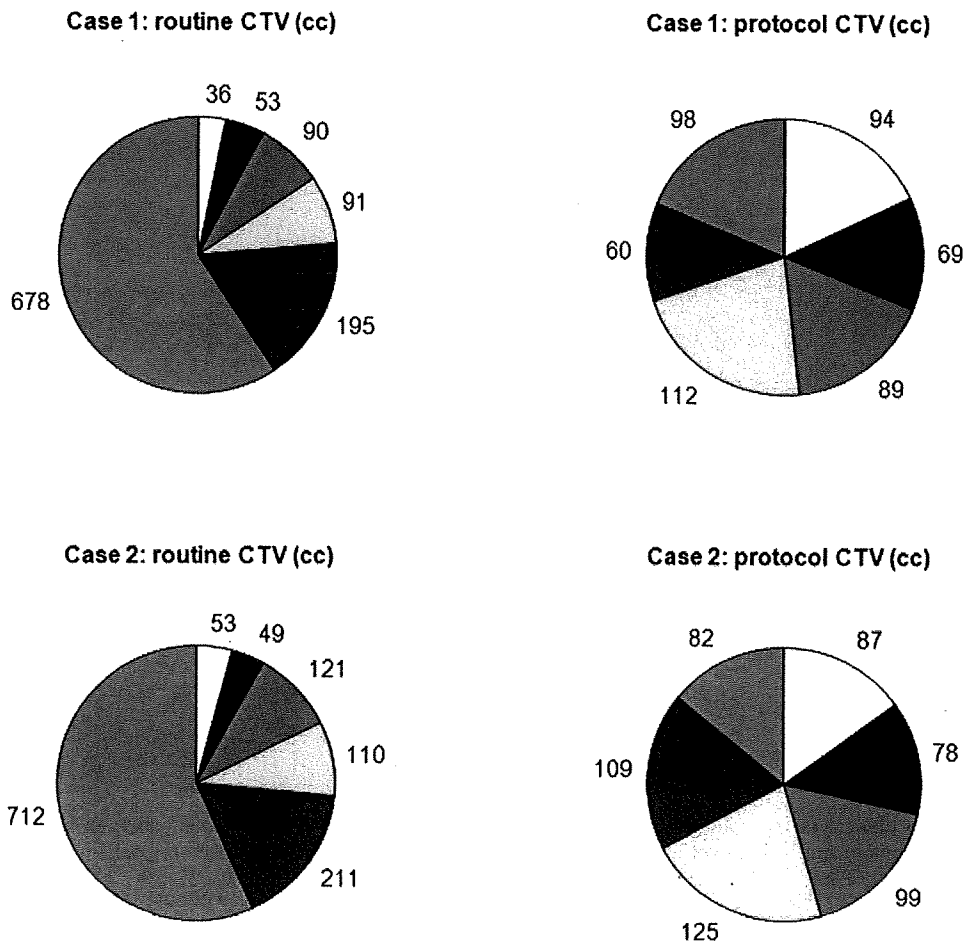

Fig. 3. Routine vs. protocol clinical target volumes (CTVs) (cc) from six observers for the postlobectomy patient (upper panel) and the postpneumectomy patient (lower panel).

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

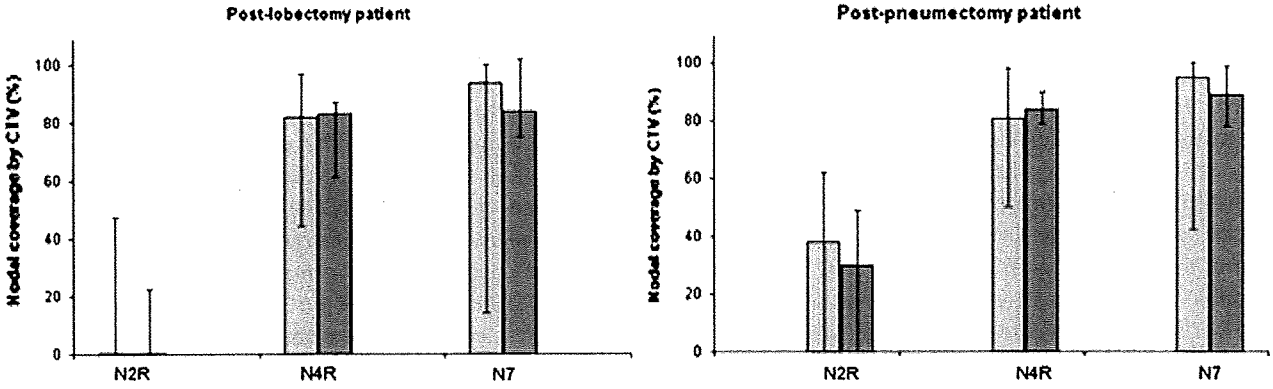

Fig. 4. Nodal coverage (%) by routine and protocol clinical target volumes in the postlobectomy patient (left) and the postpneumectomy patient (right).

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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Quality Assurance in the Prospective Multi-institutional Trial on Definitive Radiotherapy Using High-dose-rate Intracavitary Brachytherapy for Uterine Cervical Cancer: The Individual Case Review

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Objective: To assess compliance with the radiotherapy protocol of a multi-institutional prospective study (JAROG0401/JROSG04-2), which investigated the efficacy and toxicity of definitive radiotherapy using high-dose-rate intracavitary brachytherapy (HDR-ICBT) for early-stage uterine cervical cancer patients.
Methods: Individual case reviews (ICRs) were performed on all 60 study participants. Radiotherapy data were submitted to the quality assurance (QA) committee, which performed ICRs on 16 QA items according to previously selected criteria. The items focused on quality of external beam radiotherapy (EBRT), HDR-ICBT and both. Each item was determined to be either acceptable or a deviation. The QA committee performed ICR three times as planned, two during the patient accrual and the final one just after the final patient accrued. The QA results of the first and second reviews were reported back to the investigators after each ICR.
Results: In 40 cases (67%), all 16 QA items were classified as acceptable. One deviation was found in 16 cases, two deviations were identified in 3 cases and three deviations were noted in 1 case. The most frequently observed deviation was missing the rules for determining point A (10 cases). The items described by quantitative values, such as prescribed doses, certain time intervals and overall treatment time, were well followed. The proportion of deviations gradually decreased during the ICR process.
Conclusions: The present ICR demonstrated the favorable radiotherapy compliance with the JAROG0401/JROSG04-2 protocol. The QA process using ICRs can potentially be used to improve the quality of radiotherapy, including HDR-ICBT in the multi-institutional prospective studies for cervical cancer.

Key words: cervical cancer – radiotherapy – quality assurance – clinical trial

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INTRODUCTION

Standard definitive radiotherapy for uterine cervical cancer consists of whole pelvic external beam radiotherapy (EBRT) and intracavitary brachytherapy (ICBT). Several randomized controlled trials (RCTs) have demonstrated that high-dose-rate ICBT (HDR-ICBT) has equivalent safety and efficacy to low-dose-rate ICBT (LDR-ICBT) (1,2). HDR-ICBT has been popular in most Asian and European countries for several decades, and its use has gradually increased in the USA in recent years (3,4).

Despite the widespread use of HDR-ICBT, the optimal schedule (e.g. total dose and fractions in combination with EBRT) has not been standardized globally. A substantial difference in total dose has been observed between Japan and the USA (3–5): total radiation doses used in Japan are approximately one-third lower than those given in the USA, both in clinical practice (3–5) and as published in national guidelines (5,6). Several Japanese investigators have demonstrated comparable clinical outcomes (7) to those of series performed in the USA, which consisted of patients treated with LDR-ICBT (8). This suggests that Japanese schedules that include lower radiation doses can be used to achieve local control rates equivalent to those produced using US schedules. However, the majority of these data are from retrospective analysis; thus, we considered it imperative to conduct multi-institutional prospective trials to assess the efficacy and toxicity of the Japanese radiotherapy schedules in patients with uterine cervical cancer. We initiated our first trial (JAROG0401/JROSG04-2) for early-stage cervical cancer patients in 2004.

Large clinical study groups in Europe and the USA, such as the European Organization for Research and Treatment of Cancer (EORTC), Gynecologic Oncology Group (GOG) and Radiation Therapy Oncology Group (RTOG), have established well-organized radiotherapy quality assurance (QA) program (9,10). Recently, radiotherapy QA processes have also been investigated by Japanese clinical study groups (11–13). To maintain consistency in radiotherapy quality, radiotherapy parameters were carefully considered throughout the protocol development process of our trial. Additionally, individual case reviews (ICRs) were planned primarily to evaluate protocol compliance with respect to several important radiotherapy parameters, particularly for HDR-ICBT. This manuscript describes our initial experience using ICR in our prospective multi-institutional trial (JAROG0401/JROSG04-2) for cervical cancer to assess compliance with the radiotherapy protocol.

PATIENTS AND METHODS

Summary of JAROG0401/JROSG04-2

This multi-institutional prospective study was designed to evaluate toxicity and efficacy of definitive radiotherapy using the Japanese standard schedule/dose for patients with Stage I or II cervical cancer (Table 1). From September 2004 to July 2007, the planned numbers of 60 patients were successfully accrued into this study from 13 institutions. The present QA study includes data from these 60 patients.

ICR Summary

The QA committee included radiation oncologists from participating and non-participating institutions. Participating institutions were requested to submit treatment data for all treated patients. Table 2 describes the submitted materials and items. Radiotherapy records describing treatment parameters were submitted as hard copies, whereas other radiological data and figures (e.g. dose distributions) were collected as digital data formatted on CD-ROMs. The QA committee performed ICRs on 16 QA items according to previously selected criteria (Table 3). The items focused on quality of EBRT, HDR-ICBT or both. Each item was determined to be acceptable or a deviation. QA committee meetings were conducted for three times to complete the ICR. The first meeting was held in February 2006 to evaluate the first 15 cases, the second occurred in December 2006 for the next 20 cases and the third was held in October 2007 for

Table 1. Summary of JAROG0401/JROSG04-2

Purpose: To assess the efficacy and toxicity of definitive radiotherapy with HDR-ICBT using the Japanese standard schedule for patients with early-stage uterine cervical cancer
Eligible patients
1. Histologically conformed invasive squamous cell carcinoma of the intact uterine cervix
2. FIGO Stage Ib1, IIa, IIb
3. Tumor diameter <40 mm assessed by MRI (T2WI)
4. Without enlarged pelvic or para-aortic lymph nodes (<10 mm shortest diameter)
5. Age 20–80 years
6. PS (Zubrod) 0–2
Treatment
External beam radiotherapy (EBRT)
Whole pelvis: 20 Gy/10 fr
Whole pelvis with midline block: 30 Gy/15 fr (should be treated through AP–PA portals)
HDR-ICBT
24 Gy/4 fr at point A
⇒Total BED = 62 Gy_{10} (at point A)
Endpoints
Primary: 2-year pelvic disease progression-free survival
Secondary: adverse events (acute/late), 2-year overall survival, 2-year cause-specific survival, 2-year disease-free survival, site of failure
Planned sample size: 60

HDR-ICBT, high-dose-rate intracavitary brachytherapy; MRI, magnetic resonance imaging; PS, performance status; AP, anterior-posterior; PA, posterior-anterior; BED, biologically effective dose.

the remaining 25 cases. The QA results for the first and second reviews were reported to the participating investigators immediately after each meeting. Prior to the meetings, the principal investigator of this trial (T.T.) performed a preliminary evaluation of each of them. The preliminary evaluation was checked and approved by other committee members at the meeting. All graphical data (i.e. simulation X-ray, linacgraphy and dose distributions) were viewed and reviewed by the committee members at the meeting. For cases in which the ICR could not be conducted due to absence or inadequacy of the materials, the committee requested that the participating institutions submit the missing materials, and subsequently evaluated these cases at the next meeting.

Table 2. Data required for ICR submission

Pre-treatment pelvic MRI (T2WI)
External beam radiotherapy
Treatment chart (beam energy, SAD, field projection, field size, MU and daily treatment records)
Simulation films or digitally reconstructed radiographs
Verification portal films or EPIDs
Isodose distributions (central axis)
HDR-ICBT
Treatment chart for all insertions (activity, dwell times, dwell positions and point doses)
AP and lateral orthogonal films for all insertions
AP and lateral isodose distributions for all insertions

ICR, individual case review; SAD, source-axis distance; MU, monitor unit; EPID, electronic portal imaging device.

RESULTS

(1) Review summary

ICR results are shown in Table 4. In 40 cases (67%), all 16 QA items were evaluated as acceptable. A total of one deviation was found in 16 cases, two were identified in 3 cases and three were noted in 1 case. The ratio of patients with deviations gradually decreased with each consecutive QA committee meeting; 6/15 (40%) in the first meeting, 7/20 (35%) in the second meeting and 6/25 (14%) in the third meeting.

(2) Evaluation details for each item

(a) Time interval from patient entry to start of treatment

One case was determined to be a deviation because treatment was initiated $\geq$14 days after study entry. Median interval was 4 days with a range of 0–7 days.

Table 3. Radiotherapy ICR items and criteria

Items	Evaluation	
	Deviation	Acceptable
1) Time interval from patient entry to start of treatment	$\geq$8 days	$\leq$7 days
2) EBRT beam energy	<6 MV	$\geq$6 MV
3) Prescribed EBRT daily fraction dose	Other	2 Gy
4) Prescribed EBRT total dose	Other	50 Gy
5) Planned EBRT target volume	No	Yes
6) EBRT dose homogeneity in PTV[a]	<95% or >107%	95–107%
7) Timing of MB set-up	Other	20 Gy
8) MB set-up position and shape	Other	Prescribed shape and position[b]
9) All ports were treated each day	No[c]	Yes
10) Divergence between simulation films and verification films	>5 mm	$\leq$5 mm
11) Interval between EBRT 20 Gy administration and HDR-ICBT start	$\geq$10 days	<9 days
12) Single point A dose of HDR-ICBT (prescribed)	Other	6 Gy
13) Total point A dose of HDR-ICBT (prescribed)	Other	24 Gy
14) Point A determination protocol compliance[d]	No	Yes
15) Dose calculation of organs at risk (ICRU 38)	No	Yes
16) Overall treatment time	>8 weeks	<8 weeks

PTV, planning target volume; MB, midline block.
[a]Central axis plane.
[b]3–4 cm width and whole length from cranial to caudal borders of the field.
[c]Counted as a violation.
[d]Two rules were developed for point A definition.

Table 4. Radiotherapy ICR summary

Items	Evaluation	
	Deviation	Acceptable
1) Time interval from patient entry to start of treatment	1	59
2) EBRT beam energy	0	60
3) Prescribed EBRT daily fraction dose	0	60
4) Prescribed EBRT total dose	0	60
5) Planned EBRT target volume	1	59
6) EBRT dose homogeneity in PTV[a]	1	59
7) Timing of MB set-up	0	60
8) MB set-up position and shape	1	59
9) All ports were treated each day	0	60
10) Divergence between simulation films and verification films	6	54
11) Interval between EBRT 20 Gy administration and HDR-ICBT start	1	59
12) Single point A dose of HDR-ICBT (prescribed)	1	59
13) Total point A dose of HDR-ICBT (prescribed)	1	59
14) Point A determination protocol compliance	10	50
15) Dose calculation of organs at risk (ICRU 38)	3	57
16) Overall treatment time	0	60

[a]Central axis plane.

(b) EBRT beam energy
No deviations were observed. A total of 41 cases received 10 MV X-rays, 2 received 15 MV, 16 received 18 MV and 1 received 20 MV.
(c) EBRT dose (daily fraction and total dose)
All cases were treated according to protocol and were thus determined to be acceptable.
(d) Planned EBRT target volume
One case was determined to be a deviation, as lateral field shaping was evaluated inappropriately because the external iliac node region was partially missed.
(e) EBRT dose homogeneity(central plane)
Two-dimensional (2D) dose homogeneity evaluation was performed on the axis of the field isocentre. One deviation occurred because 108% of the dose area was observed within the external iliac node region.
(f) Midline block (MB) (set-up position, shape and timing)
One case was classified as a deviation, because MB set-up did not follow the protocol (the MB was not properly positioned from the cranial to caudal border of the field). The width of the MB was confirmed to be 3 cm in 31 cases and 4 cm in 29 cases; these met protocol criteria. A custom block was used in 15 cases, and multi-leaf collimators were utilized in the remaining 45 cases. Timing of MB insertion was appropriate in all cases.
(g) EBRT treatment ports
Thirty-six cases were treated through antero-posterior portals, and a four-box field technique was used in the remaining 24 cases. All cases were treated all ports a day and were determined to be acceptable.
(h) Geographic divergence between simulation and verification films (linacgraphy or EPID)
Divergence $\geq$5 mm was observed in six cases, which were therefore judged to be deviations.
(i) Timing of the first HDR-ICBT
In one case, the first HDR-ICBT session was performed 11 days after delivery of EBRT 20 Gy; this case was therefore classified as a deviation. All other cases fulfilled the protocol criteria (median interval, 7 days).
(j) HDR-ICBT dose (fraction dose and total dose at point A)
One case received a reduced prescribed point A dose (5.85 Gy) during the first HDR-ICBT session, because the calculated rectal dose exceeded the dose constraint of the rectum (within 110% of the point A dose). Consequently, the resulting total HDR-ICBT dose at point A was 23.8 Gy. Although this case was counted as a deviation, it was considered to be a 'clinically reasonable deviation'.
(k) Point A determination for HDR-ICBT
Physicians were required to use one of the following rules for determining point A according to the geography between ovoid applicators and the external os (Fig. 1).
(i) Within two existing point A's (i.e. on the left and right sides), a point that indicates a lower dose is to be selected as the 'prescribed point A'.
(ii) Basically, a point at the external os (usually equivalent to the position of the tandem flange) would be selected as the geographic origin of point A. In cases in which the external os is located caudally to the cranial ovoid applicator

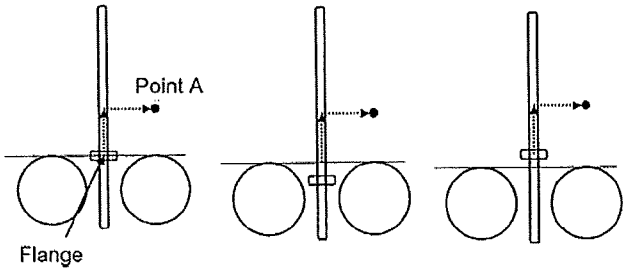

Figure 1. Point A definitions according to the geography between ovoid applicators and the external os.

surface, the vaginal vault level should be selected as the origin to the point A.

Treatment of 50 patients followed these rules for all four HDR-ICBT sessions. In eight cases (26 sessions), the first rule was violated: for six cases (21 sessions), the mean dose of the two point A's was applied as the 'prescribed point A' dose instead of the lower dose and for the other two cases (5 sessions), a point that indicated a higher dose was selected as the 'prescribed point A'. Treatment of three patients (7 sessions) violated the second rule described above.

(l) Dose calculation for organs at risk (ICRU 38)

Rectal and bladder doses were calculated appropriately according to the ICRU 38 method in all sessions in all cases. However, in three cases (7 sessions), the vaginal surface dose was not calculated.

(m) Overall treatment time

Overall treatment time ranged from 38 to 55 days (median, 43 days); no deviations were observed.

(3) HDR-ICBT parameters other than 16 QA items evaluated

Other important parameters on HDR-ICBT are shown in Table 5.

Table 5. Additional important HDR-ICBT parameters

Parameters	No. of patients
Machines	
MicroSelectron-HDR	45
Buchlar Fact	12
VariSource	3
Applicators	
Selectron standard	45
Henschke	14
Other[a]	1
Vaginal cylinder	0
Dwell pattern	
Manchester	53
Other	7

[a]Gann-ken type (domestic non-rigid applicator).

DISCUSSION

We performed an ICR of radiotherapy compliance in our first prospective clinical trial of definitive radiotherapy using HDR-ICBT for early-stage uterine cervical cancer (JAROG0401/JROSG04-2). The ICR discussed herein revealed the favorable radiotherapy protocol compliance.

Dose is one of the most important parameters for successful radiotherapy. In the present ICR, we evaluated doses as prescribed values at the reference points that were recorded on treatment charts. As a result, no deviations were observed with respect to EBRT, and deviation occurred in one case on HDR-ICBT. This suggests that protocol compliance was excellent with respect to prescribed doses. In their report, on radiotherapy compliance in the RCT GOG165, which compared the outcome of protracted venous infusion of fluorouracil with standard weekly cisplatin and concurrent radiotherapy for locally advanced uterine cervical cancer, Lanciano et al. (14) demonstrated that major variation (if the dose was $\pm$11–20% than the prescribed protocol dose) was observed in 5% of the cases treated with HDR-ICBT. In the GOG165 study, credentialing of both institutions and treating physicians in HDR-ICBT was encouraged prior to trial participation. In reporting the frequency of protocol deviations in certified versus non-certified institutions, Lowenstein et al. (15) demonstrated that deviation occurred less frequently in institutions with credentialing compared with those that did not. Their credentialing procedure required administration of QA method descriptions on source strength and positioning verification. Ibbott et al. (16) reported QA results for a Phase I/II study in which breast cancer patients received adjuvant HDR interstitial brachytherapy. Prior to study participation, appropriate questionnaire responses and data administration of benchmark cases were required. They concluded that this QA procedure led to the achievement of high-quality brachytherapy (16). The number of deviations consecutively decreased during our QA process. We consider that this may have been a positive consequence of feedback to study participants. Poortmans et al. (17) reported a similar observation in a multi-institutional randomized EORTC breast cancer. We are planning implementation of additional QA procedures, such as credentialing and benchmark case administration, to further enhance the quality of HDR-ICBT in future trials.

Use of HDR-ICBT for cervical cancer is associated with potential dose variation to central tumor due to the methods used for point A determination. In patients with deep vaginal vaults, the external os may be located caudally to the cranial surface of the ovoid applicators. In this situation, a central cervical tumor would receive a lower dose than intended when the external os is adopted as an origin of point A determination. Previous and current RTOG and GOG studies have adopted a single method for determining point A, for which the origin is the external os. In our study (JAROG0401/JROSG04-2), two

methods were used for point A determination based on the relative positions of the ovoid applicators and the external os (which is usually in the same position as the flange of the tandem applicator). This concept is based on a combination of the original Manchester system and the arrangement proposed by Tod and Meredith (18,19). We believe that this method enables sufficient dose delivery for every case, including cases with deep vaginal vaults. The present ICR indicated that treatment of 17% of the cases involved protocol deviation with respect to point A determination. However, we believe that most cases received constant dose delivery from HDR-ICBT, allowing dose–response analysis to be performed properly in our prospective study.

A methodological limitation of our present ICR on HDR-ICBT doses was the lack of recalculation performed independently by the QA committee. The GOG165 QA process included not only a review of patient records and films but also an independent recalculation of dose for all HDR-ICBT sessions performed at the Radiological Physics Center (RPC) (15).

In our ICR, the planning target volume of EBRT was evaluated just visually based on the 2D position relative to bony structures, since the description for field arrangement in the protocol was based on the bony structures. One case in whom the clinical target volume (CTV) was determined by the 3D CT-based contouring was determined to be a deviation. In light of the current status of EBRT planning, the QA process applied in the present ICR appears to be outdated. Recently, the use of 3D treatment planning based on target delineation on multiple cross-sectional images has increased in clinical practice. In the QA process prescribed here, dose distribution evaluation was performed only on a single slice of the target volume at the level of isocentre. 3D dose volume analysis should also be encouraged. We are now preparing a consensus-based CTV delineation guideline for both future clinical trials and routine clinical practice in cervical cancer (20).

In conclusion, our first ICR demonstrated favorable compliance to the radiotherapy protocol in a multi-institutional prospective study (JAROG0401/JROSG04-2). On the basis of these results, we expect that the clinical results of this study can be evaluated scientifically. In future trials, we must implement additional QA processes, such as credentialing that includes benchmark case evaluation and independent dose recalculation for HDR-ICBT. Furthermore, an updated protocol description about certain radiotherapy parameters that could be used to meet 3D treatment era standards is highly encouraged.

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Conflict of interest statement

None declared.

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