Table 4 Radiotherapy ICR summary: JGOG1066

Items	Evaluation		
	Per protocol	Deviation	Violation
QA-1: EBRT beam energy	69	0	–
QA-2: EBRT method	69	0	0
QA-3: EBRT daily fraction dose (prescribed)	69	0	0
QA-4: EBRT total dose (prescribed)	69	0	0
QA-5: MB set-up timing	68	1	0
QA-6: EBRT treatment portals	63	6	0
QA-7: EBRT boosts	37	32	0
QA-8: EBRT dose homogeneity within PTV	69	0	–
QA-9: Divergence between simulation and verification	66	3	–
QA-10: Timing of the first HDR-ICBT	65	2	2
QA-11: EBRT and HDR-ICBT on same day	68	–	1
QA-12: HDR-ICBT planning for each fraction	68	–	1
QA-13: HDR-ICBT fraction dose (prescribed)	66	3	0
QA-14: HDR-ICBT total dose of (prescribed)	65	4	0
QA-15: Determination of point A	64	5	–
QA-16: Dose calculation of OARs (ICRU38)	66	3	–
QA-17: Total EBRT and HDR-ICBT dose (prescribed)	67	2	0
QA-18: Overall treatment time	66	3	0

ICR individual case review, *EBRT* external beam radiotherapy, *MB* midline block, *PTV* planning target volume, *HDR-ICBT* high-dose-rate intracavitary brachytherapy, *OAR* organ at risk

were 2 patients who received their first HDR-ICBT before 30 Gy of EBRT had been administered, which was judged as a violation.

QA-11 Prohibition against same-day delivery of EBRT and HDR-ICBT: There was 1 patient who received both EBRT and HDR-ICBT on the same day, which was judged as a violation.

QA-12 HDR-ICBT planning for each fraction: The protocol stated that dose calculations should be performed for every HDR-ICBT session. There was 1 patient who received her second and third HDR-ICBT based on planning data from her first application. This was judged as a violation.

QA-13 HDR-ICBT fraction dose: There were 2 patients who received HDR-ICBT with an incorrectly prescribed point A dose, which was judged as a deviation. Another patient received HDR-ICBT using an inappropriate reference point instead of point A, which was also judged as a deviation.

QA-14 HDR-ICBT total dose: The 3 patients with QA-13 deviations and 1 patient who did not receive the last HDR-ICBT because of acute toxicity were judged as deviations.

QA-15 Determination of point A: There were 5 patients who received HDR-ICBT at an incorrectly defined point A. These were judged as deviations. One of those patients also had deviations for QA-13 and -14. In 4 of these patients, the external os was selected as the geometrical origin for point A instead of the vaginal vault level (which was the correct definition), although the external os was located caudally to the cranial ovoid applicator surface.

Table 5 Numbers of cases and quality assurance items with deviations or violations

Number of deviations	Number of cases[a]
0	24
1	36 (2)
2	6 (1)
3	0
4	1 (1)
5	1
6	0
7	1

[a] Parentheses include number of cases also having violations

QA-16 Organs at risk (OAR) dose calculation [10]: Bladder dose calculations were not performed in 3 patients, which were judged as deviations.

QA-17 Total EBRT and HDR-ICBT dose: Two of 3 patients who had deviations in QA-13 were also assessed with deviations for this.

QA-18 Overall treatment time (OTT): There were 3 deviations in OTT. The OTTs of these 3 patients were 56, 57, and 65 days. The longest OTT was

caused by a delayed starting time of the EBRT boost to the parametrium.

Discussion

This study determined that there was favorable radiotherapy compliance with the JGOG1066 protocol. Based on our findings, we expect the final results of this study on long-term outcomes and complications to be scientifically valid.

A credentialing process was used to select the participating institutions in this study. Our credentialing consisted of a review of questionnaires received from institutions and an assessment of radiotherapy QA, especially with regard to HDR-ICBT. The credentialing process has been adopted for some recent clinical trials performed by the Gynecologic Oncology Group (GOG). Lowenstein and colleagues reported that major protocol deviations were more frequently seen in non-certified institutions than in certified institutions [11]. We believe that the credentialing process in this study may be one of the reasons that favorable protocol compliance was achieved.

Favorable radiotherapy compliance was observed for EBRT, especially with regard to parameters defined by numerically prescribed values, such as beam energy and prescribed dose, which had 100% compliance. Regarding EBRT port arrangements, deviations were observed in 6 patients. These were all from a single institution and were based on CTV delineation-based treatment planning. Only 2-dimensional (2D) treatment planning was prescribed in the protocol. Some clinical study groups have published consensus guidelines for CTV delineation of the pelvic node region [12, 13], and the Radiation Therapy Oncology Group (RTOG) has also released a guideline for primary cervical cancer tumors [14]. For future clinical trials, it will be essential to include detailed descriptions of 3-dimensional (3D) treatment planning, including the definition of CTV contouring. In this study, frequent deviations were observed for EBRT boosts. Most deviations were omissions at the discretion of the treating physicians, despite indications for a boost. These physicians might have prioritized their clinical impressions and experiences over the protocol. We believe that there was a discrepancy between the protocol and current daily clinical practice. At present, there is no obvious evidence that an EBRT boost provides therapeutic value [15]. In ongoing Gynecology Oncology Group (GOG) and RTOG trials, EBRT boosts have been optional. Therefore, for trials in the near future, it is reasonable to keep the EBRT boost as an option.

Although protocol compliance was also favorable for HDR-ICBT administration, 4 violations were seen. Two were in patients who received their first HDR-ICBT application before they received 30 Gy of EBRT. Eligible patients in this study all had extensive cervical disease. It is thought that locoregionally advanced disease should receive adequate doses of EBRT before HDR-ICBT application, and it is essential to deliver an adequate HDR-ICBT dose to the entire cervical tumor [16]. There was 1 patient who received EBRT and HDR-ICBT on the same day, which was judged as a violation. In accordance with the ABS guidelines [6], concurrent delivery of EBRT and HDR-ICBT was strictly prohibited in the protocol. In 1 patient, treatment planning for the first HDR-ICBT was also applied during the subsequent HDR-ICBT sessions. We believe that these types of violations should be strictly avoided, because they could cause poor treatment outcomes and decrease safety [6].

Only 4 deviations were observed for the designation of point A. We adopted 2 alternative determination methods for point A from a previous prospective study (JAROG0401/JROSG04-2) [17]. In that study, 10 of 60 patients were assessed with deviations regarding the definition of point A [17]. We think that compliance with this definition has improved over the previous study. To further improve compliance with point A determination, a dummy run may be effective. This would also be effective for CTV delineation on EBRT treatment planning. While image-guided brachytherapy is becoming popular, especially in the United States [18], point A is still widely used for dose prescription along with DVH parameters [19]. We think that our system can provide consistent and clinically appropriate point A determinations [20].

The theoretical weakness of our present QA process is lack of physics QA, including an external dosimetry audit and independent dose calculation of HDR-ICBT. In the GOG and RTOG studies, an independent HDR-ICBT dose calculation was performed and revealed some variation of actual doses compared with prescribed doses [20]. We need to establish an effective QA system for physics by ensuring active participation of medical physicists in the CCRT studies of cervical cancer. Our QA assessments regarding deviations and violations may be considered subjective. We classified the cases into 3 QA categories based on previously decided criteria. Our QA criteria were developed with reference to those used in other clinical study groups, such as GOG [11]. Development of standard QA criteria, including those pertaining to physics which can be used globally, should be encouraged.

In conclusion, compliance with the radiotherapy protocol in JGOG1066 was favorable, except for indications for the EBRT boost. The results of this compliance study validate the quality of radiotherapy in JGOG1066 and indicate that the final analysis will provide meaningful results.

Acknowledgments This study was partly supported by Grants-in-Aid for Cancer Research (Nos. 16-12, 20S-5), Clinical Cancer Research (22100301), and H22-3rd Term Cancer Control-General-043 from the Ministry of Health, Labor and Welfare of Japan, and also by a Grants-in-Aid for Scientific Research from the Japan Society for the Promotion of Sciences (Nos. 18591387 and 21591614).

Conflict of interest No author has any conflict of interest.

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JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2011;41(9)1119–1126
doi:10.1093/jjco/hyr096

A Consensus-based Guideline Defining Clinical Target Volume for Primary Disease in External Beam Radiotherapy for Intact Uterine Cervical Cancer

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Received April 25, 2011; accepted June 9, 2011

Objective: To develop a consensus-based guideline to define clinical target volume for primary disease (clinical target volume primary) in external beam radiotherapy for intact uterine cervical cancer.

Methods: The working subgroup of the JCOG Radiation Therapy Study Group began developing a guideline for primary clinical target volume in November 2009. The group consisted of 10 radiation oncologists and 2 gynecologic oncologists. The process started with comparing the contouring on computed tomographic images of actual cervical cancer cases among the members. This was followed by a comprehensive literature review that included primary research articles and textbooks as well as information on surgical procedures. Extensive discussion occurred in face-to-face meetings (three occasions) and frequent e-mail communications until a consensus was reached.

Results: The working subgroup reached a consensus on the definition for the clinical target volume primary. The clinical target volume primary consists of the gross tumor volume, uterine cervix, uterine corpus, parametrium, vagina and ovaries. Definitions for these component structures were determined. Anatomical boundaries in all directions were defined for the parametrium. Examples delineating these boundaries were prepared for the posterior border of the parametrium for various clinical situations (i.e. central tumor bulk, degree of parametrial involvement).

Conclusions: A consensus-based guideline defining the clinical target volume primary was developed for external beam radiotherapy for intact uterine cervical cancer. This guideline will serve as a template for radiotherapy protocols in future clinical trials. It may also be used in actual clinical practice in the setting of highly precise external beam radiotherapy, including intensity-modulated radiotherapy.

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

INTRODUCTION

Standard radiotherapy for cervical cancer patients consists of external beam whole pelvic radiotherapy (EBRT) and intracavitary brachytherapy (1). Recently, treatment planning for both modalities has been shifting away from conventional two-dimensional planning to volume-based three-dimensional (3D) planning (2,3). Three-dimensional planning should achieve appropriate target coverage within sufficient doses and effective sparing of organs at risk (OARs). Intensity-modulated radiation therapy (IMRT) is the most promising 3D EBRT method, and its use has been increasing in actual clinical practice in the USA (4) and other countries. Several investigators reported promising treatment results in terms of reduced toxicity for patients with uterine cervical cancer (5–7). In Japan, IMRT has been covered by the public insurance system since April 2010 for all cancer patients. Therefore, as is now the case for other solid malignancies, the use of IMRT should be promoted for cervical cancer patients. To correctly deliver IMRT, an accurate and reproducible contouring of the clinical target volume (CTV) is primarily important and essential. There is, however, a degree of uncertainty in the delineation of the CTV (8). To achieve consistent CTV delineations, which minimize unexpected variation, consensus guidelines have been published for the pelvic lymph node CTV (9–11). A working subgroup for developing a consensus-based guideline on the CTV for cervical cancer was organized within the Radiation Therapy Study Group (RTSG) of the Japan Clinical Oncology Group (JCOG) in July 2008. The subgroup has already published a guideline on pelvic node CTV (12). More recently, the Radiation Therapy Oncology Group (RTOG) in the USA published guidelines regarding primary tumor CTV (CTV primary) for intact uterine cervical cancer (13). We have also conducted a study to establish a CTV primary guideline to perform appropriate contouring of the CTV primary in actual clinical practice as well as in the setting of clinical trials with IMRT. This paper describes the process used to develop the guideline, as well as examples of CTV delineation schemes.

PATIENTS AND METHODS

The working subgroup, which was formed to establish a consensus-based guideline on the CTV for EBRT in cervical cancer, started working on the CTV for primary lesions (CTV primary) in November 2009. In addition to the original seven members, five members consisting of three radiation oncologists and two gynecologic oncologists joined the committee. The members had three face-to-face meetings and extensive discussions via e-mail throughout the working process.

In the first meeting, a brainstorming discussion was held with review of the CTV definitions of image-guided intracavitary brachytherapy (IGBT) for cervical cancer (14–16), and the CTV primaries of other disease sites, e.g. head and neck, and prostate (17). After this meeting, electronic copies of computed tomographic (CT) and magnetic resonance imaging (MRI) images of two actual patients were distributed to the members. Each member then independently made his or her own CTV primary delineations on the CT images. The contoured images were then reviewed in the second meeting. Some areas of discrepancy were observed in the CTV primary delineations (Fig. 1a and b). Following extensive discussion to reach consensus, drafts of the definitions of structures composing the CTV primary and actual figures were prepared by a principal investigator (T.T.) referring to the RTOG guidelines (13). These were presented and reviewed at the JCOG RTSG meeting in November 2010. These were then refined further through additional e-mail discussions. A consensus among the working group members was nearly reached in the third meeting. Any remaining discrepancies were addressed through subsequent e-mail discussions. A final version of the consensus-based guideline on the CTV primary was established in February 2011.

RESULTS

Components for the CTV Primary

The CTV primary consists of the gross tumor volume of the primary tumor (GTV primary), uterine cervix, uterine corpus, parametrium, vagina and ovaries.

Definitions for Each Component Structure of the CTV Primary

GTV Primary

The GTV primary includes gross disease visible on an MRI T2-weighted image (T2WI) and lesions detected by clinical examinations.

Uterine Cervix

The entire cervix, if not already included within the GTV contour, is to be contoured (13). The cranial margin is defined at the level at which the uterine arteries enter the uterus (same level of the superior border of the parametrium CTV).

Uterine Corpus

No CTV margin should be added to the visualized corpus on CT images, even for cases in which the tumor has significant corpus invasion. This decision was based on the fact that the majority of the uterine corpus is suspended within the pelvic cavity without surrounding the connective tissue.

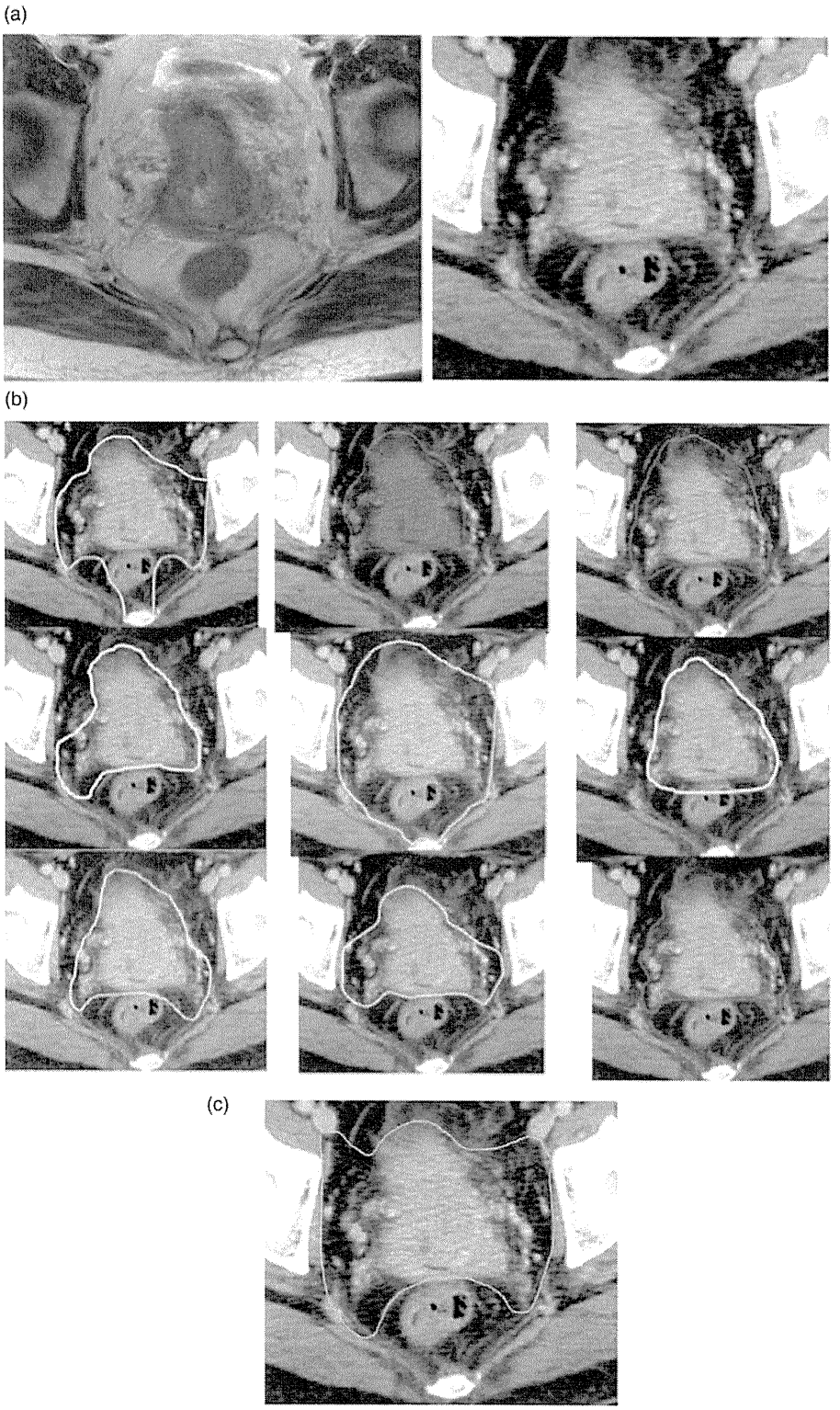

Figure 1. (a) Magnetic resonance imaging (MRI) and computed tomographic (CT) slices of a FIGO Stage IIIB cervical cancer patient who demonstrated bilateral parametrial invasion with nodular fixation to the right pelvic wall on pelvic exam. Clinical information for this patient was also distributed to the nine working group members along with the CT and MRI images. (b) CT images with the primary clinical target volume (CTV) contouring drawn by the working group members, which reveal substantial contouring variations among the members. (c) The same CT image with the primary CTV contouring following the present guideline.

Table 1. Anatomical boundaries of clinical target volume for parametrium

Margin	Structures
Cranial	Isthmus of uterus (=level where uterine artery drains into)
	*Contouring would stop at the level where bowel loops are seen
Caudal	Medial boarder of levator ani (Fig. 5)
Anterior	Posterior boarder of bladder or posterior boarder of external iliac vessels
Posterior	Anterior part (semicircular) of mesorectal fascia
	*In case with bulky central tumor or significant parametrial invasion, some modification would be considered (Figs 3 and 4)
Lateral	Medial edge of internal obturator muscle, piriformis muscle, coccygeus muscle and ischial ramus

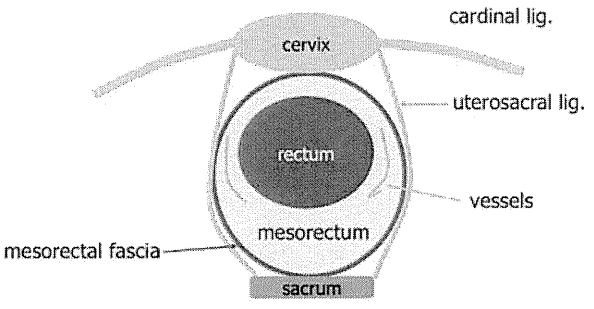

Figure 2. An illustration of the anatomical components around the cervix with reference to the parametrium.

The broad ligaments, round ligaments and ovarian ligaments do not need to be included.

Consensus was not reached regarding feasibility of excluding some portions of the uterine corpus (e.g. fundus) from the CTV primary in selected cases (i.e. non-bulky Stage I or II cases who may be candidates for radical trachelectomy).

Parametrium

Adipose tissues between the cervix and pelvic wall are included as well as visible linear structures that run laterally (e.g. vessels, nerves and fibrous structures).

Overlapping between the nodal CTV and the parametrium CTV is feasible (13).

Boundary structures of the parametrium CTV for each direction are listed in Table 1. Figure 2 shows a scheme of anatomical components around the cervix with reference to the parametrium. Figures 3a and 4a show a scheme and actual delineation for the posterior border of the parametrium, respectively. Some variations are prepared as determined by the central tumor bulk or parametrial involvement status for the posterior boundary of the parametrium CTV (Figs 3 and 4). The CTV margin could be increased in the posterior direction into the perirectum (Figs 3b and 4b) and/or along the uterosacral ligaments (Figs 3c and d, and 4c and d). Figure 5 shows the primary CTV contouring at the level of the levator ani.

Vagina

Paravaginal tissue would be included as well as the vaginal wall. The caudal level should be individually determined based on the findings of both the MRI and clinical examinations. Arrangements of the caudal level according to the status of vaginal invasion are stated as per the RTOG guidelines (13):

Minimal or no vaginal extension: upper half of the vagina
Upper vaginal involvement: upper two-thirds of the vagina
Extensive vaginal involvement: entire vagina

Ovary

Ovaries visible on the CT/MRI would be included.

A consensus was not reached regarding the possibility of excluding the ovaries in selected cases (i.e. non-bulky Stage I or II cases with squamous cell carcinoma).

An Example of the CTV Primary Delineation (Fig. 1c)

Figure 1c shows an example of the CTV primary delineation in accordance with the definition developed (on the same slice used in the previous comparison test).

DISCUSSION

The working subgroup developed a consensus-based guideline for the delineation of the CTV primary for EBRT in patients with intact uterine cervical cancer. The guideline describes the anatomical components to be included in the CTV primary, as well as the definitions for each component. Examples of CTV delineation are also included.

The guideline states that the CTV primary consists of the GTV primary, uterine cervix, uterine corpus, parametrium, vagina and ovaries. This concept seems to be almost the same with surgical treatment: radical hysterectomy, which is a standard surgical procedure for invasive cervical cancer, also includes resection of these structures.

Anatomically, the uterine corpus is concealed within the broad ligament and suspended in the pelvis. This means that no surrounding connective tissues are visible around the corpus on CT or MRI. Therefore, the guideline states that no margin should be added to the visualized corpus for the CTV. We also reached a consensus that the fallopian tubes and round ligaments would not be included in the CTV, in agreement with the RTOG guidelines (13).

The most challenging issue was delineating the parametrium and defining its anatomical boundaries on CT. This difficulty was caused by the limited information of diagnostic radiology to illustrate the relationship between transverse images and the actual parametrial anatomy. In our preliminary comparison of each member's CTV contouring,

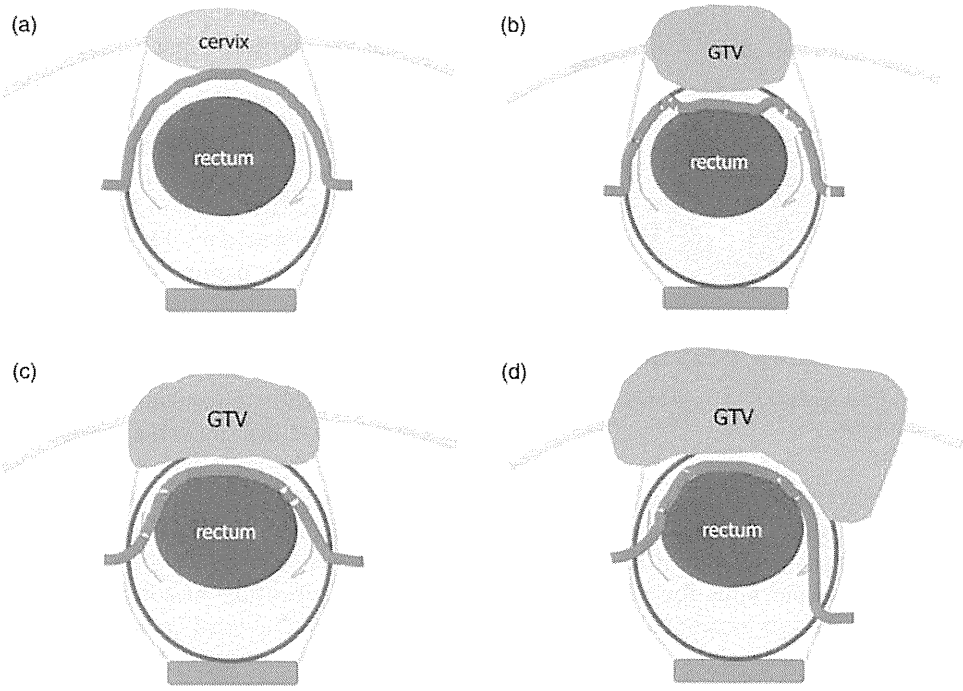

Figure 3. Stage-specific delineation schemes for the posterior border of the parametrium (solid red line). (a) Non-bulky early-stage (IB1 or IIA1) disease. (b) Bulky early-stage (IB2 or IIA2) disease. (c) Stage IIB disease (slight parametrial involvement). (d) Stage IIIB disease (massive parametrial involvement).

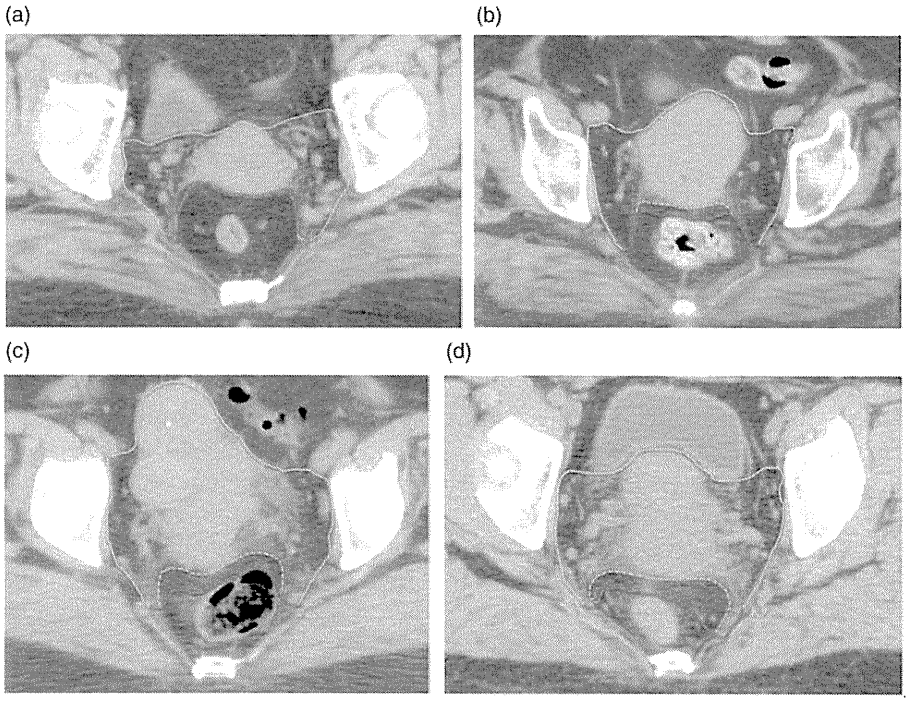

Figure 4. Actual delineations of the primary CTV (solid orange line) and posterior border of the parametrium (solid red line) according to disease status Dotted orange lines indicate the anterior border of the perirectum. (a) A case with non-bulky Stage IB1 disease. (b) A case with bulky Stage IB2 disease. (c) A case with Stage IIB disease (bilateral parametrial involvement on pelvic exam). (d) A case with Stage IIIB disease (massive parametrial involvement with fixation to the left pelvic wall on pelvic exam).

significant variations were observed for the parametrium. Lim et al. (13) reported a similar wide range of variation among the WG members in the RTOG. The present discrepancies were resolved through reviewing the anatomical (18–20) and surgical (21) literatures. In the present work, two gynecologic oncologists participated in addition

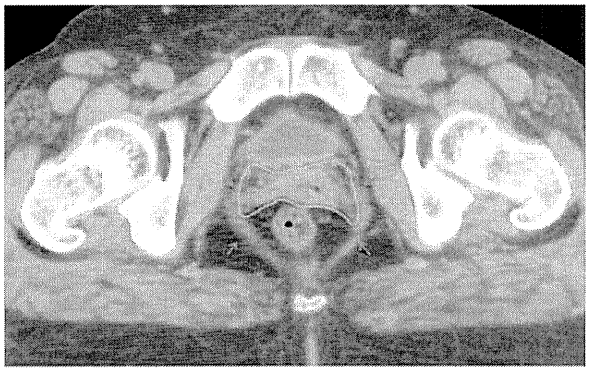

Figure 5. An actual delineation of the primary CTV (solid orange line) at the level of the levator ani (blue arrows).

to the radiation oncologists. They contributed valuable information regarding surgical findings, which was instrumental for developing anatomically appropriate definitions of the boundaries. We believe that the participation of surgical oncologists is essential for the design of clinically reliable CTV definitions and contouring atlases.

The anterior and lateral boundaries are virtually identical to those specified by the RTOG guidelines (13). Minor adjustments were made to the lateral definition in the present guideline. The medial edges of the piriformis and coccygeus muscles were added to the lateral boundary. The RTOG guidelines state that the caudal margin of the parametrium is the urogenital diaphragm (13). However, the term 'urogenital diaphragm' usually indicates the inferior surface of the pelvic diaphragm. Therefore, we consider the superior surface of the pelvic diaphragm, which corresponds to the medial edge of the levator ani, a more appropriate term for the definition.

To determine the cranial boundary of the parametrium, we also reviewed the anatomy of the uterus and surrounding structures including the parametrium. The broad ligaments are formed by the peritoneum covering the uterine body and the parametrium (18,20). Instead of using the top of the fallopian tube/broad ligament for the cranial parametrial margin, as specified in the RTOG guidelines (13), we elected to use the cranial margin of the cervix. In an anatomical view, this margin corresponds to the isthmus of the uterus (18); however, the margin is not recognized on CT images. Therefore, the junction of the uterine artery with the uterus was proposed to be the cranial margin of the cervix. This parameter must be evaluated further clinically to ascertain the degree of variability associated with this definition.

There was extensive discussion concerning the posterior boundary of the parametrium. The RTOG guidelines use the uterosacral ligament as one of the boundaries (13). The uterosacral ligaments, however, are not always identifiable on CT images. In contrast, the mesorectal fascia is visible on the CT images in most cases. Chen et al. (22) have demonstrated that 95 and 97.5% of the CT and MRI studies, respectively, show the fascia encircling the rectum and perirectal adipose tissue as either a continuous or interrupted line. They have also shown in a cadaveric space perfusion study that the perirectal space is completely separated from the pararectal space (outside the mesorectum) by the mesorectal fascia (22). Therefore, we selected the semicircular, anterior portion of the mesorectal fascia as the posterior boundary. The RTOG guidelines include an optional definition for Stage IIIB cases (13). We also include additional areas in the parametrium CTV in cases with a bulky cervical tumor or extensive parametrial involvement. Furthermore, we developed protocol variations to address specific situations. Chao et al. (23) stressed the importance of delivering an adequate dose to the uterosacral space for patients with uterosacral space involvement. In contrast, the RTOG guidelines recommend that the entire mesorectal space be included for patients with Stage IIIB or higher disease. We consider this to be excessive. Kato et al. (24) reported clinical outcomes for locally advanced cervical cancer patients (Stage IIB–IVA) treated with carbon ion radiotherapy. Although the posterior part of the mesorectum was not included within the CTVs, favorable local control was reported in their series (24). These results appear to support our opinion. Careful evaluation is warranted to determine whether the entire mesorectal space should be included in the CTV for patients with massive parametrial involvement, and additional discussion is still required to achieve a consensus.

Another challenge in the development of the guideline is the subdefinition of the CTV primary according to the disease status of each patient. Three-dimensional EBRT, notably IMRT, has the ability to precisely exclude structures not intended to be irradiated. There are at least two potential areas for individualization of the CTV primary in uterine cervical cancer. The first is to permit the exclusion of the ovaries. If the ovaries were excluded from the CTV primary, the planning target volume (PTV) would be smaller. The small PTV may result in lower doses and volumes delivered to the surrounding OARs. This option is feasible as several surgical studies have demonstrated that patients with early-stage cervical squamous cell cancer rarely have ovarian metastases (25,26). The second issue pertains to whether a portion of the uterine corpus may be excluded from the CTV primary. Uterine corpus exclusion may also achieve a significant decrease in the doses to the surrounding OARs. As mentioned in the previous RTOG guidelines (13), excluding a portion of the corpus would be an option for selected cases when sufficient data are available regarding the incidence and exact location of uterine recurrence after conservative surgical procedures (e.g. radical trachelectomy) (27). Although we were not able to reach a consensus on these issues, the discussion continues. For these situations, subdivision of the CTV based on risk estimation of disease (i.e. high-, intermediate- and low-risk CTV) may be considered. The CTV primary definitions on IGBT may serve as a reference for this concept (14,15).

Although the CTV delineation for 3D EBRT planning is performed primarily based on CT/MRI findings, some small or superficial lesions may only be detected by a clinical

examination. These small/superficial lesions should also be included in the GTV. This has been addressed in the present guideline. Generally, the CTV delineation is performed on CT images. It is, however, sometimes difficult to accurately contour the CTV due to low soft tissue resolution of CT. The working subgroup recommends the use of MRI T2WI as a reference. Even with MRI, it is sometimes difficult to perform CTV contouring in thin women who have little adipose tissue in the pelvis. Solving this problem remains a challenge.

In conclusion, we propose that the present consensus-based guideline be used as a reference to perform appropriate contouring of the CTV primary in actual clinical practice as well as in the setting of clinical trials with IMRT for intact cervical cancer patients. The use of the present guideline in combination with the previously published guideline for the node (12) will minimize variation in the CTV contouring process. Additional discussion is still required to achieve a consensus regarding how much individualization will be permissible within the guideline. To perform appropriate IMRT, as well as accurate CTV contouring, consensus on the delineation of the OARs is important. Management of organ movement and tumor shrinkage over the treatment course represent additional challenges (28). Further substantial discussions are warranted to define the PTV margins for each CTV primary substructure. The working group needs to continue to develop additional consensus-based guidelines for the precise delivery of IMRT for patients with intact uterine cervical cancer.

Acknowledgements

The authors thank all of the gynecologic oncologists of the JCOG Gynecologic Cancer Study Group (GCSG), Dr Yoshinori Ito and Dr Shin Fujita for their advice and expertise.

Funding

This study was supported in part by the Grant-in-Aid for Cancer Research (20S-5) and Clinical Cancer Research (10103757) from the Ministry of Health, Labor and Welfare, Japan, and the Japan Society for the Promotion of Sciences (no. 21591614).

Conflict of interest statement

None declared.

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Appendix

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Risk Factors for Treatment-Related Death Associated with Chemotherapy and Thoracic Radiotherapy for Lung Cancer

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Introduction: The aim of the study is to evaluate the current status of treatment-related death (TRD) in lung cancer patients.

Methods: We retrospectively analyzed the incidence and risk factors of TRD in lung cancer patients who received chemotherapy and/or thoracic radiotherapy using logistic regression analyses.

Results: Between January 2001 and December 2005, 1225 (222 small cell and 1003 non-small cell lung cancers) patients received chemotherapy and/or thoracic radiotherapy as the initial treatment. Of these, 43 patients receiving chemotherapy followed by thoracic radiotherapy were included into both the chemotherapy-alone and radiotherapy-alone groups. There were a total of 23 (1.9%) TRDs. Chemotherapy-related deaths occurred in 7 of 927 (0.8%) patients, including 4 from drug-induced lung injury, 2 from pneumonia, and 1 from unknown cause. Concurrent chemoradiotherapy-related deaths occurred in 12 of 245 (4.9%) patients, including 11 from radiation pneumonitis and 1 from pneumonia. Thoracic radiotherapy-related deaths occurred in 4 of 96 (4.2%) patients. The incidence of chemotherapy-related death was correlated with poor performance status (odds ratio [OR]: 11.4, 95% confidence interval [CI]: 3.53–37.1), the presence of hypoxia (OR: 19.3, CI: 6.06–61.7), hyponatremia (OR: 45.5, CI: 13.4–154), and treatment with epidermal growth factor receptor-tyrosine kinase inhibitors (OR: 8.56, CI: 2.48–29.5), whereas the incidence of concurrent chemoradiotherapy-related death was correlated with pulmonary fibrosis (OR: 22.2, CI: 5.61–87.8). Radiotherapy results were not analyzed because there were too few patients.

Conclusions: TRD occurred in 1.9% of the patients as a result of treatment-related lung injury in the majority of the cases.

Key Words: Lung cancer, Treatment-related death, Risk factor, Chemotherapy, Thoracic radiotherapy.

(*J Thorac Oncol.* 2012;7: 177–182)

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ISSN: 1556-0864/12/0701-0177

Before any medical interventions are undertaken in patients with lung cancer, they must be clearly informed about the risks and benefits of the intervention(s) and about alternative treatment options. Careful delivery of this is particularly important if the planned treatment may not only result in cure but may also be harmful. Provision of accurate information to help patients make the most appropriate decision is therefore crucial. However, the risks of death from drug toxicity and the incidences of such events tend to be uncertain[1–4] and also constantly change with the wide use of newer agents, such as third-generation chemotherapy agents, and molecular-targeted agents. In addition, the incidence of treatment-related deaths (TRDs) has not been thoroughly examined in clinical settings outside of clinical trials. Prospective clinical trials for poor-risk patients are often difficult to perform because of poor accrual, reflecting the reluctance of physicians to subject patients with underlying comorbid illness to the toxic effects of chemotherapy and radiation.

Our ultimate goal is to prospectively identify individuals who are at a high risk of TRD so as to provide the most precise estimation of the possible risks to each patient. In this study, we retrospectively examined the data of patients with locally advanced or metastatic lung cancer who were treated at the National Cancer Center Hospital, Tokyo, Japan, focusing on the risks and incidences of TRD associated with chemotherapy and radiotherapy.

PATIENTS AND METHODS

Patients

Between January 2001 and December 2005, a total of 1623 lung cancer patients were admitted to the thoracic oncology ward at the National Cancer Center Hospital. All patients were admitted in this period to be treated as part of standard practice in Japan. Patients who received chemotherapy alone usually stayed in the hospital for 7 to 10 days for one cycle of chemotherapy, and those who received concurrent chemoradiotherapy stayed for 6 weeks. Among these, a total of 1225 patients who had received first-line chemotherapy and/or radiotherapy on an inpatient basis were extracted from the institutional database. Additional details about the patients, including the diagnostic imaging findings, were then reviewed from the patients' medical records. The data of patients receiving chemotherapy and/or thoracic radiotherapy

as the initial treatment were evaluated. They included patients with stage III to IV disease and postoperative recurrent disease who received chemotherapy; those with stage III disease who received chemoradiotherapy or radiotherapy alone; and those with stage III disease who received preoperative induction therapy or postoperative adjuvant therapy. All the patients had been followed for at least 4 weeks after the completion of treatment.

Treatment Selection

After a thorough evaluation of the operability and/or curability, the eligibility of each patient for enrollment in an open clinical trial was determined. Although patient recruitment for protocol treatments is a priority of ours, patients were free to refuse treatment. If no appropriate clinical trials were scheduled or under way, the known best standard treatments were administered.

Best Standard Treatments

For first-line treatment, patients with non-small cell lung cancer (NSCLC) who were deemed inoperable but curable with good local control with chemoradiotherapy received three to four cycles of cisplatin (CDDP) 80 mg/m^2 on day 1 + vinorelbine (VNR) 20 mg/m^2 on days 1 and 8, every 4 weeks, along with early concurrent thoracic radiotherapy, usually at a total dose of 60 Gy/30 fractions.[5] Sequential chemoradiotherapy, rather than concurrent chemoradiotherapy, was offered if the calculated percentage of the total lung volume receiving radiation in excess of 20 Gy (V_{20}) was more than 40%.[6] Thoracic radiotherapy alone was selected if chemotherapy could not be given due to comorbidity. If the radiation field involved the contralateral hilum or if the patients had malignant effusion and/or distant metastasis, platinum doublet therapy was administered; the most common combination was four cycles of carboplatin (CBDCA) area under the curve = 6 on day 1 + paclitaxel (PTX) 200 mg/m^2 on day 1, every 3 weeks.[7] For limited-disease SCLC, four cycles of a combination of CDDP 80 mg/m^2 on day 1 + etoposide 100 mg/m^2 on days 1 to 3, every 4 weeks, were administered concurrently with hyperfractionated thoracic radiotherapy at a total radiation dose of 45 Gy in fractional doses of 1.5 Gy, administered twice a day.[8] In patients with extensive-disease SCLC, four cycles of a combination of CDDP 60 mg/m^2 on day 1 and irinotecan (CPT) 60 mg/m^2 on days 1, 8, and 15, every 4 weeks, were usually administered.[9] Radiotherapy was given using megavoltage photons (6–15 MV). The routine radiation schedule without chemotherapy for locally advanced NSCLC was a total radiation dose of 60 to 66 Gy, or as high as 70 Gy, administered in fractional doses of 2.0 Gy once a day.

Definition of TRD

Chemotherapy-related death was defined as death occurring within 4 weeks of the completion of treatment, without clear evidence of any other cause of death, or death obviously caused by treatment toxicity. Radiotherapy-related death was defined as death secondary to hypoxia or to complications of corticosteroid administration after the diagnosis of radiation pneumonitis. Steroid therapy was administered based on the attending physician's discretion, without a standardized treatment dose or duration, for the management of radiation-induced lung injury.[10]

Definition of Treatment-Induced Lung Injury

The criteria of drug-induced lung injury in this study were as follows: (1) appearance of new symptoms and radiological abnormalities in the course of chemotherapy with the onset within a few months of the start of the therapy; (2) diffuse or multifocal ground-glass opacities and intralobular interstitial thickening without segmental distribution in computed tomography (CT) scans of the chest; and (3) no evidence of underlying heart disease, infection, or lymphangitic carcinomatosis. Lung biopsy was not routinely performed in our hospital because patients were frequently too frail to undergo biopsy. The criteria of radiation-induced lung injury were (1) appearance of new symptoms and radiological abnormalities with the onset within 6 months of the end of thoracic radiotherapy; (2) opacification, diffuse haziness, infiltrates, or consolidation conforming to the outline of the sharply demarcated irradiated area in CT scans; and (3) a reduction in lung volume within the irradiated area and linear, ground-glass opacities or reticular shadows beyond the irradiated area developing during clinical course. In contrast, the criteria of bacterial pneumonia were (1) clinical suspicion of pneumonia including rapidly developing fever and/or productive cough; and (2) consolidation spreading through anatomical structure of the lung in CT scans.

Statistical Analysis

We investigated the associations between chemotherapy-related or concurrent chemoradiotherapy-related death and the potential risk factors at the time of diagnosis. The following potential risk factors were investigated: sex, age ($\geq$70 years versus $<$70 years), performance status (Eastern Cooperative Oncology Group criteria; 2–4 versus 0–1), smoking history (presence versus absence), partial pressure of oxygen (70 mmHg $\leq PO_2$ versus $>$70 mmHg), hemoglobin (Hgb $<$ 13.7 g/dl versus $\geq$ 13.7 g/dl), platelet (Plt $>$ 367 $\times$ 10^9/L versus $\leq$367 $\times$ 10^9/L), albumin (Alb $<$ 3.7 g/dl versus $\geq$3.7 g/dl), sodium (Na $<$ 138 mEq/L versus $\geq$138 mEq/L), clinical trial (in versus out), and chemotherapy regimen (The cutoff values of hemoglobin, platelet, albumin, and sodium are the institutional normal limits [above or below]). For concurrent chemoradiotherapy-related factors, the presence of coincidental diseases such as emphysema (with versus without) or pulmonary fibrosis (with versus without) and the location of the primary tumor (lower lobe versus other lobes) were also included in the analyses. The diagnostic criteria of pulmonary fibrosis were a linear, ground-glass attenuation or reticular shadows on chest radiographs and CT scans before treatment that were predominant in the lower zone of the lung. Also, the influence of the chemotherapy regimens was evaluated.

In the univariate preliminary analysis, the relation between previously defined variables at the time of presentation and the occurrence of the outcome variable (toxic death) was assessed using the χ^2 test. To adjust for each factor, multivariate logistic regression analyses were planned. When the number of observed events was less than 10, multivariate

analysis was not performed. When the number of patients for each factor was small, the factor was excluded from the model, even when it appeared to be statistically significant. All the analyses were performed using the STATISTICA 4.1J program (StatSoft, Inc., Tulsa, OK).

RESULTS

Patient Characteristics

The patient characteristics before treatment are listed in Table 1. Of the 1225 patients (SCLC: 222; adenocarcinoma: 652; squamous cell carcinoma: 194; NSCLC not otherwise specified: 111; large cell carcinoma: 7; others: 39), chemotherapy alone was administered in 884 patients, concurrent chemoradiotherapy in 245, sequential chemoradiotherapy in 43, and thoracic radiotherapy alone in 53 patients. To evaluate the incidence of TRD among the patients who received chemotherapy, radiotherapy, or a combination of these modalities, we included the 43 patients who received sequential chemoradiotherapy into both the chemotherapy-alone group and the thoracic radiotherapy-alone group. Therefore, the patients who received sequential chemoradiotherapy were regarded as having been exposed to the risks of treatment twice. The groups were therefore analyzed as chemotherapy alone in 927 patients, concurrent chemotherapy in 245 patients, and thoracic radiotherapy alone in 96 patients. In these groupings, the percentages of patients enrolled in clinical trials were 62, 53, and 23%, respectively.

Cumulative Incidence and Causes of TRD

The cumulative incidence and causes of TRD are listed in Table 2. Of the 1225 patients, a total of 23 (1.9%) TRDs occurred. Chemotherapy-related deaths occurred in 7 of 927 (0.8%) patients, including 4 (0.4%) from drug-induced lung injury (gefitinib, $n = 3$ and CBDCA + gemcitabine, $n = 1$), 2 (0.2%) from pneumonia (CBDCA + PTX, $n = 2$), and 1 (0.1%) from unknown cause. The patient who died of unknown cause experienced hemodynamic instability (shock) of unknown etiology within 24 hours of ingestion of the first dose of gefitinib (250 mg). No TRDs from sepsis occurred in this series.

Concurrent chemoradiotherapy-related deaths occurred in 12 of 245 (4.9%) patients, including 11 (4.5%) from radiation pneumonitis and 1 (0.4%) from pneumonia during the last planned cycle of CDDP + VNR. Radiotherapy-

TABLE 1. Patient Characteristics

Characteristics	Chemotherapy Alone[a] ($n = 927$)	Concurrent Chemoradiotherapy ($n = 245$)	Radiotherapy Alone[a] ($n = 96$)
Sex			
Male	639	201	43
Female	288	44	53
Age			
Median (range)	64 (27–86)	59 (18–77)	67 (35–81)
Performance status			
0–1	871	245	88
2	140	0	8
3–4	16	0	0
Stage			
III	297	235	71
IV	454	2	17
Postoperative recurrence	176	8	8
Histology			
Non-small cell carcinoma	760	191	88
Small cell carcinoma	167	54	8
Coincidental lung disease			
Pulmonary fibrosis	34	1	4
Pulmonary emphysema	69	30	1
Chemotherapy regimen			
Platinum + taxane	368	21	—
Platinum + irinotecan	133	1	—
EGFR-TKI	125	0	—
Platinum + etoposide	95	54	—
Platinum + antimetabolite	85	0	—
Platinum + vinca alkaloid	37	168	—
Others	84	1	—

[a] Forty-three patients who received sequential chemotherapy followed by radiotherapy are included in the analysis of both the chemotherapy-alone group and radiotherapy-alone group, as described in the text.

EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor.

TABLE 2. Treatment-Related Death and Its Cumulative Incidence

Characteristics	Chemotherapy Alone[a] (n = 927)	Concurrent Chemoradiotherapy (n = 245)	Radiotherapy Alone[a] (n = 96)
No. of treatment-related deaths	7	12	4
Cumulative incidence (%)	0.8	4.9	4.2
Sex			
Male	5	11	4
Female	2	1	0
Age of patients who died of treatment (yr)			
Median (range)	69 (46–77)	68 (50–77)	75 (65–77)
Causes			
Treatment-induced lung injury	4	11	4
Infectious pneumonia	2	1	0
Unknown	1	0	0
Chemotherapy regimen			
Platinum + taxane	2	2	—
EGFR-TKI	4	—	—
Platinum + antimetabolite	1	—	—
Platinum + etoposide	0	1	—
Platinum + vinca alkaloid	0	8	—
Others	0	1	—

[a] Forty-three patients who received sequential chemotherapy followed by radiotherapy are included in the analysis of both the chemotherapy-alone group and radiotherapy-alone group, as described in the text.
EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor.

related deaths occurred in 4 of 96 (4.2%) patients: all 4 (4.2%) patients died of radiation pneumonitis.

Risk Factors for TRD from Chemotherapy

Statistically significant factors identified by the univariate analysis were a performance status of 2 to 4, hypoxia, hypoalbuminemia, hyponatremia, out of clinical trials, and treatment with epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) (Table 3). Although statistically significant, the degrees of hyponatremia in the events were neither clinically significant nor symptomatic for the range of 133 to 137 mEq/L. Pulmonary fibrosis and emphysema were noted in 34 and 69 patients, respectively, among the 927 patients. None of these patients with lung disease died of treatment in this study. Multivariate analysis was not performed because the number of observed events was too small (n = 7).

Risk Factors for TRD from Concurrent Chemoradiotherapy

None of the factors, except for pulmonary fibrosis, were found to be statistically significant in the univariate analysis, although a trend toward increase in the risk of TRD was observed in patients of advanced age (>70 years) and with lower lobe as the primary tumor site (Table 4). Pulmonary fibrosis appeared to be a statistically significant risk factor for TRD; however, it was excluded from the multivariate analysis because of its limited incidence. Thus, we did not perform multivariate analysis for chemoradiotherapy group, and an analysis of the risk of TRD associated with thoracic radiotherapy alone was not conducted because of the limited number of cases.

DISCUSSION

We identified a total of 23 TRDs out of the 1225 patients (1.9%) enrolled in this study, which is lower than the rate (2.7%) indicated in a previous report, particularly in relation to the number of TRDs from infections, including pneumonia and sepsis.[1] The reason for the decrease in the incidence of infection-related deaths is likely explained by the infrequent use of triplet regimens when compared with previous studies. Especially, mitomycin-C-containing regimens are regarded as effective regimens in the treatment of lung cancer; however, prolonged neutropenia has been observed with these regimens. Ohe et al.[1] reported that combined mitomycin-C + vindesine + CDDP (MVP regimen) therapy is a risk factor for chemotherapy-related TRD (toxic deaths occurred in 9 of 301 patients; odds ratio [OR] = 9.36, 95% confidence interval [CI] = 1.29–68.0, p = 0.027). In this study, only 35 patients, the majority (89%) of whom were enrolled in a clinical trial, received the MVP regimen. In the past, however, the MVP regimen was widely used as part of practice-based regimens (only 28% recorded under clinical trials). In most cases, patients who were not eligible for clinical trials ended up receiving the MVP regimen. Another reason is the relatively frequent use of EGFR-TKI (in 13.5% of the patients in this study) at present, which does not induce myelosuppression. The reduction in the frequency of TRD might also be explained by a progress in supportive care in the treatments given for cancer treatment toxicities.

This study revealed that drug-induced lung injury was the most frequent cause of TRD in the era of molecular-targeted therapy. Three (75%) of four TRDs from drug-induced lung injury were associated with gefitinib. The re-

TABLE 3. Risk Factors for Treatment-Related Death from Chemotherapy

Factors	No. of Patients	Cumulative Incidence (%)	Univariate Analysis OR (95% CI)	*p*
Sex				
Female	288	0.8	1	
Male	639	0.7	1.13 (0.22–5.76)	0.89
Age				
<70	689	0.6	1	
≥70	238	1.3	2.17 (0.51–9.30)	0.30
PS				
0–1	870	0.5	1	
2–4	57	5.2	11.4 (3.53–37.1)	<0.001
Smoking history				
No	271	0.4	1	
Yes	656	0.9	2.49 (0.30–20.8)	0.40
PaO_2 (Torr)				
≥70	812	0.2	1	
<70	105	4.8	19.3 (6.06–61.7)	<0.001
Hemoglobin (g/dl)				
≥13.7	371	0.5	1	
<13.7	556	0.9	1.67 (0.33–8.39)	0.54
Albumin (g/dl)				
≥3.7	663	0.3	1	
<3.7	264	1.9	6.28 (1.51–26.1)	0.012
AST (IU/L)				
≤33	831	0.6	1	
>33	96	2.1	3.46 (0.75–16.0)	0.11
Na (mEq/L)				
≥138	819	0.1	1	
<138	108	5.6	45.5 (13.4–154)	<0.001
Clinical trial				
No	355	1.7	1	
Yes	572	0.2	0.10 (0.58–0.019)	0.001
Platinum + taxane				
No	559	0.9	1	
Yes	368	0.5	0.61 (0.12–3.14)	0.55
EGFR-TKIs				
No	802	0.4	1	
Yes	125	3.2	8.56 (2.48–29.5)	0.001
Platinum + antimetabolite				
No	842	0.7	1	
Yes	85	1.1	1.66 (0.20–13.9)	0.64

Multivariate analysis was not performed because the number of observed events was too small ($n = 7$).

OR, odds ratio; CI, confidence interval; PS, performance status; AST, aspartate transaminase; EGFR-TKIs, epidermal growth factor receptor-tyrosine kinase inhibitors.

TABLE 4. Risk Factors for Treatment-Related Death from Concurrent Chemoradiotherapy

Factors	No. of Patients	Cumulative Incidence (%)	Univariate Analysis OR (95% CI)	*p*
Sex				
Female	44	2.3	1	
Male	201	5.2	2.41 (0.35–16.6)	0.37
Age (yr)				
<70	221	4.1	1	
≥70	24	12.5	3.07 (0.92–10.3)	0.069
PS				
0	114	5.3	1	
1	131	4.6	0.87 (0.29–2.62)	0.81
Smoking history				
No	32	3.2	1	
Yes	213	5.2	1.65 (0.23–11.9)	0.24
Fibrosis				
No	244	4.5	1	
Yes	1	100	22.2 (5.61–87.8)	<0.001
Emphysema				
No	215	4.7	1	
Yes	30	6.7	1.43 (0.33–6.25)	0.63
Location of the tumor				
Other lobes	189	3.7	1	
Lower lobe	56	8.9	2.41 (0.82–7.13)	0.11
Histology				
SCLC	54	1.9	1	
NSCLC	191	5.8	3.11 (0.47–20.6)	0.24
Hemoglobin (g/dl)				
≥13.7	146	4.1	1	
<13.7	99	6.1	1.48 (0.49–4.42)	0.48
Albumin (g/dl)				
≥3.7	198	4.5	1	
<3.7	47	6.4	1.40 (0.40–4.99)	0.6
Na (mEq/L)				
≥138	219	5.0	1	
<138	26	3.8	0.77 (0.11–5.60)	0.79
Clinical trial				
No	114	5.3	1	
Yes	131	4.6	0.87 (0.29–2.62)	0.81
Platinum + taxane				
No	224	4.5	1	
Yes	21	9.5	2.25 (0.46–11.0)	0.32
Platinum + vinca alkaloid				
No	77	5.2	1	
Yes	168	4.8	0.91 (0.27–3.13)	0.88

Multivariate analysis was not performed because only fibrosis was significant in univariate analysis.

OR, odds ratio; CI, confidence interval; PS, performance status; NSCLC, non-small cell lung cancer.

ported risk factors for interstitial lung disease in NSCLC patients treated with gefitinib are male sex, history of smoking, and underlying interstitial pneumonitis.[11] In this study, however, none of these factors were associated with TRD from chemotherapy. Another TRD from drug-induced lung injury occurred in a patient who received gemcitabine, but this patient was also free from underlying pulmonary disease or concomitant use of taxanes, which are reported to be risk factors for gemcitabine-associated interstitial lung disease.[12]

For patients who receive concurrent chemoradiotherapy, we would like to emphasize the previous finding that the

presence of evidence of pulmonary fibrosis on a plain chest x-ray is an extremely strong risk factor for TRD (OR = 166, 95% CI = 8.79–3122, $p < 0.001$).[1] In this study, only one patient with pulmonary fibrosis was identified, and pulmonary fibrosis was not included in the multivariate analysis because of the small number of patients with this factor, because we generally exclude patients with evidence of pulmonary fibrosis on the chest x-ray from consideration of concurrent chemoradiotherapy. This study also suggested that advanced age may be a risk factor for TRD. This is consistent with the results of previous studies.[1,13–15] The association between advanced age and fatal radiation-induced lung injury may be explained by the increased likelihood of these patients developing comorbid lung disease, particularly among patients with a history of heavy tobacco exposure. A meta-analysis of chemoradiotherapy using individual data from 1764 patients with locally advanced NSCLC showed that the benefit of chemoradiotherapy was obtained in elderly patients (≥71 years) as well as in younger patients. However, it might be assumed that patients who are included in such trials are fit patients with minimal comorbidities. In addition, despite the increase in toxicity that accompanied chemoradiotherapy in elderly patients, it seemed that they had disease control and survival rates similar to those of younger patients.[16]

In conclusion, TRD occurred in a total of 1.9% of patients and was caused in the majority of the cases by treatment-related lung injury. This finding is in clear contrast with previous reports which suggested that the principal cause of TRD in lung cancer patients was septic shock.

ACKNOWLEDGMENTS

The authors thank Ms. Mika Nagai for her assistance in the preparation of this manuscript.

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Int. J. Radiation Oncology Biol. Phys., Vol. 82, No. 2, pp. 953–959, 2012

0360-3016/$ - see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2011.01.008

CLINICAL INVESTIGATION **Thoracic Cancer**

PHASE I STUDY OF CONCURRENT HIGH-DOSE THREE-DIMENSIONAL CONFORMAL RADIOTHERAPY WITH CHEMOTHERAPY USING CISPLATIN AND VINORELBINE FOR UNRESECTABLE STAGE III NON-SMALL-CELL LUNG CANCER

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Purpose: To determine the maximum tolerated dose in concurrent three-dimensional conformal radiotherapy (3D-CRT) with chemotherapy for unresectable Stage III non–small-cell lung cancer (NSCLC).

Patients and Methods: Eligible patients with unresectable Stage III NSCLC, age ≥20 years, performance status 0–1, percent of volume of normal lung receiving 20 GY or more (V_{20}) ≤30% received three to four cycles of cisplatin (80 mg/m^2 Day 1) and vinorelbine (20 mg/m^2 Days 1 and 8) repeated every 4 weeks. The doses of 3D-CRT were 66 Gy, 72 Gy, and 78 Gy at dose levels 1 to 3, respectively.

Results: Of the 17, 16, and 24 patients assessed for eligibility, 13 (76%), 12 (75%), and 6 (25%) were enrolled at dose levels 1 to 3, respectively. The main reasons for exclusion were V_{20} >30% (n = 10) and overdose to the esophagus (n = 8) and brachial plexus (n = 2). There were 26 men and 5 women, with a median age of 60 years (range, 41–75). The full planned dose of radiotherapy could be administered to all the patients. Grade 3–4 neutropenia and febrile neutropenia were noted in 24 (77%) and 5 (16%) of the 31 patients, respectively. Grade 4 infection, Grade 3 esophagitis, and Grade 3 pulmonary toxicity were noted in 1 patient, 2 patients, and 1 patient, respectively. The dose-limiting toxicity was noted in 17% of the patients at each dose level. The median survival and 3-year and 4-year survival rates were 41.9 months, 72.3%, and 49.2%, respectively.

Conclusions: 72 Gy was the maximum dose that could be achieved in most patients, given the predetermined normal tissue constraints. © **2012 Elsevier Inc.**

Lung cancer, Chemotherapy, Radiotherapy, High dose, Conformal.

INTRODUCTION

Approximately one third of patients with non–small-cell lung cancer (NSCLC) present with locally advanced Stage III disease at the initial diagnosis (1). Of this category, Stage IIIA disease with bulky N2 and Stage IIIB disease without pleural effusion are characterized by a large primary lesion and/or involvement of the mediastinal or supraclavicular lymph nodes. In addition, the majority of these patients have occult systemic micrometastases. Concurrent thoracic radiotherapy and chemotherapy has been the standard care for these patients with unresectable disease (2, 3). A platinum doublet with a third-generation anticancer agent combined with thoracic radiotherapy was reported to yield a median overall survival time (OS) of more than 2 years and long-term survivors (4–6), but the effect of platinum-based chemotherapy has reached a plateau.

The failure pattern in patients with Stage III NSCLC treated by concurrent chemoradiotherapy was roughly local recurrence alone in one third of the patients, both local and distant recurrence in another third of patients, and distant metastasis without local failure in the remaining third of patients (2, 5).

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Presented at the 45th Annual Meeting of the American Society of Clinical Oncology, May 29—June 2, 2006, Orlando, Florida.

Supported in part by Ministry of Health, Labour and Welfare, Health and Labour Science Research Grants, Research on Clinical Trials' Infrastructure Development, H21-RINKEN (Kikan)-IP-PAN-005.

Conflict of interest: none.

Acknowledgment—The authors thank Asako Sakamoto for her work as data manager and Mika Nagai for manuscript preparation.

Received June 7, 2010, and in revised form Dec 27, 2010. Accepted for publication Jan 10, 2011.

Thus, improvement of local control and suppression of distant metastasis are essential for prolongation of patient survival.

The conventional total dose of thoracic radiotherapy in patients with inoperable NSCLC has been 60 Gy administered in 30 fractions. This dose was established in 1987 by randomized Radiation Therapy Oncology Group trials that demonstrated better 3-year survival with a radiation dose of 60 Gy than with lower doses (7). In these trials, two-dimensional treatment planning was used, wherein the tumor volume was defined on kilovoltage radiographs (7). Thereafter, the standard initial target volume included the primary tumor, metastatic lymph nodes, and adjacent uninvolved ipsilateral hilar and mediastinal regions (elective nodal irradiation: ENI). Except for selected patients, excessive toxicity hampered an increase of the total dose to over 60 Gy in patients with locally advanced NSCLC.

It is, however, time now to reconsider the optimal dose of thoracic radiotherapy using new techniques in patients with locally advanced NSCLC, for the following reasons. First, positron emission tomography (PET) provides more accurate diagnosis of mediastinal lymph node metastases (8) and more accurate quantification of the tumor volumes, especially when atelectasis is present (9). Second, three-dimensional conformal radiation therapy (3D-CRT) enables radiation oncologists to delineate the tumor and adjacent normal tissue more sharply and to choose beam angles to maximize tumor coverage with minimum irradiation of normal tissues (10). Third, omission of the ENI resulted in improvement of radiation-associated toxicity without worsening the local control rate of the tumor (11, 12). Thus, by use of these new techniques, the optimal dose of thoracic radiation could exceed the conventional 60 Gy.

Two dose escalation studies in patients with locally advanced NSCLC showed that the total dose of thoracic radiotherapy could be increased up to 90 Gy in concurrent chemoradiotherapy using the 3D-CRT technique combined with weekly carboplatin and paclitaxel chemotherapy (13, 14). In these trials, chemoradiotherapy was administered after induction chemotherapy. However, it remained unclear whether these doses could be delivered safely to the majority of patients with locally advanced NSCLC, because it is not known how many patients were screened for the trials and how many of them were actually registered, and because some of the registered patients were excluded from the chemoradiotherapy phase after induction chemotherapy. The total number of patients evaluated in the two trials was also limited. Furthermore, chemotherapy other than weekly carboplatin and paclitaxel has not been evaluated in the setting of combined chemotherapy with high-dose thoracic radiotherapy, to our knowledge. The objectives of the current study were (1) to evaluate the toxicity of concurrent high-dose 3D-CRT without ENI with cisplatin and vinorelbine for unresectable Stage III NSCLC, (2) to determine the maximum tolerated dose (MTD) of thoracic radiotherapy, and (3) to observe the antitumor effects of this regimen.

PATIENTS AND METHODS

Study design

This study was designed as a Phase I study at the National Cancer Center Hospital. The protocol and consent form were approved by the Institutional Review Board of the National Cancer Center on July 28, 2005. We planned to treat 12 patients at a dose level and follow them up at least 6 months, and then escalate to the next level if 67% of the patients did not experience dose-limiting toxicity (DLT). We followed widely accepted normal tissue dose constraints. Patients with percent volume of the normal lung receiving 20 Gy or more (V_{20}) of greater than 30% were excluded and treated outside the study. Other dosimetric constraints were applied at the discretion of the treating radiation oncologist. Maximum doses exceeding 50 Gy to the spinal cord, 66 Gy to the esophagus, or 66 Gy to the brachial plexus were generally excluded.

Patient selection

Previously untreated patients with locally advanced NSCLC without effusion were screened for entry into this study. The eligibility criteria were (1) histologically or cytologically proven NSCLC, (2) unresectable Stage IIIA or IIIB disease confirmed by both computed tomography (CT) and PET, (3) no previous treatment, (4) measurable disease, (5) $V_{20} \leq 30\%$, (6) age ≥ 20 years, (7) Eastern Cooperative Oncology Group performance status (PS) of 0 or 1, and (8) adequate bone marrow function (white blood cell [WBC] count $\geq 4.0 \times 10^9$/L, hemoglobin ≥ 9.5 g/dL, and platelet count $\geq 100 \times 10^9$/L), liver function (total bilirubin ≤ 1.5 mg/dL and transaminase ≤ 80 IU/L), renal function (serum creatinine ≤ 1.5 mg/dL), and pulmonary function ($PaO_2 \geq 70$ Torr under room air). Patients were excluded if (1) they had malignant pleural or pericardial effusion or (2) they had a concomitant serious illness such as uncontrolled angina pectoris, myocardial infarction in the previous 3 months, heart failure, uncontrolled diabetes mellitus, uncontrolled hypertension, interstitial pneumonitis or lung fibrosis identified by a chest x-ray, infection, or other diseases contraindicating chemotherapy or radiotherapy, or (3) they were pregnant or breast feeding. All patients gave their written informed consent.

Pretreatment evaluation

The pretreatment assessment included a complete blood cell count and differential count, routine chemistry determinations, creatinine clearance, blood gas analysis, electrocardiogram, lung function testing, chest x-rays, chest CT scan, brain CT scan or magnetic resonance imaging, abdominal CT, and PET.

Treatment schedule

Chemotherapy consisted of cisplatin 80 mg/m^2 on Day 1 and vinorelbine 20 mg/m^2 on Days 1 and 8, repeated every 4 weeks for three to four cycles. Cisplatin was administered by intravenous infusion for 60 minutes with 2,500 to 3,000 mL of intravenous fluid for hydration and prophylactic antiemetic therapy consisting of a 5-hydroxytriptamine-3 antagonist on Day 1 and a corticosteroid on Days 1 to 5. Vinorelbine, diluted in 50 mL of normal saline, was administered intravenously.

Radiation therapy started on Day 1 of the first cycle of chemotherapy and was delivered with megavoltage equipment (6–10 MV) once daily for 5 days a week. The total dose was 66 Gy in 33 fractions at level 1, 72 Gy in 36 fractions at level 2, and 78 Gy in 39 fractions at level 3. All patients underwent a 3D treatment planning CT 3 to 7 days before the start of the treatment, and the eligibility was finally confirmed based on evaluation using the

dose–volume histogram (DVH). The gross tumor volume (GTV) was defined as the primary tumor delineated on pulmonary windows of the chest CT or on the diagnostic PET scans. Atelectasis or secondary changes in the peripheral lung region of the primary tumor were not included. Metastatic lymph nodes defined as nodes of 1 cm or larger visualized on mediastinal windows of the CT images or PET-positive lymph nodes were also included in the GTV. The clinical target volume (CTV) was equivalent to the GTV. Uninvolved mediastinum or supraclavicular fossae were not included in the CTV. The planning target volume (PTV) was determined as the CTV plus 1.0 cm for the anterior, posterior, medial, and lateral margins and a 1.0 to 2.0 cm for the superior and inferior margins, taking account of setup variations and internal organ motion. The spinal cord dose was typically limited to 44 Gy, but a maximum of 50 Gy was allowed. The lung V_{20} was limited to 30% in all patients. The maximum dose to the brachial plexus and esophagus did not exceed 66 Gy. The 100% dose was prescribed to the reference point located in the central part of the PTV, and the entire PTV was covered with 95–107% of the prescribed dose principally, but variation of ±10% was allowed. Lung heterogeneity corrections using the equivalent path length algorithm were applied in all patients.

Toxicity assessment and treatment modification

Complete blood cell counts and differential counts, routine chemistry determinations, and a chest x-ray were performed once a week during the course of treatment. Toxicity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE v3.0). The lung toxicity grade was defined as the highest grade among cough, dyspnea, obstruction/stenosis of airways, pneumonitis/pulmonary infiltrates, and pulmonary fibrosis in the pulmonary/upper respiratory section (15).

Vinorelbine administration on Day 8 was omitted if any of the following were noted: WBC count $<3.0 \times 10^9$/L, neutrophil count $<1.5 \times 10^9$/L, platelet count $<100 \times 10^9$/L, Grade 2–3 elevation of the serum hepatic transaminase level or total serum bilirubin levels, Grade 2–3 infection, Grade 2–3 pneumonitis, other ≥Grade 3 nonhematologic toxicity, body temperature ≥38°C, or PS of 2–3. Subsequent cycles of cisplatin and vinorelbine chemotherapy were delayed if any of the following toxicities were noted on Day 1: WBC count $<3.0 \times 10^9$/L, neutrophil count $<1.5 \times 10^9$/L, platelet count $<100 \times 10^9$/L, serum creatinine level ≥1.6 mg/dL, Grade 2–3 elevation of the serum hepatic transaminase level or total serum bilirubin levels, Grade 2–3 infection, Grade 2–3 pneumonitis, other ≥Grade 3 nonhematologic toxicity, body temperature ≥38°C, or PS of 2–3. If these toxicities did not recover within 6 weeks from Day 1 of the previous cycle of chemotherapy, subsequent cycles of chemotherapy were stopped. The dose of cisplatin was reduced by 25% in all subsequent cycles if the serum creatinine level rose to 2.0 mg/dL or higher. The dose of vinorelbine was reduced by 25% in all subsequent cycles if any of the following toxicities were noted: WBC count $<1.0 \times 10^9$/L, platelet count $<25 \times 10^9$/L, or Grade 3 infection or liver dysfunction. Thoracic radiotherapy was suspended if any of the following were noted: body temperature ≥38°C, Grade 3 esophagitis, PS of 3, or suspected radiation pneumonitis. Thoracic radiotherapy was terminated if any of the following were noted: Grade 4 esophagitis, Grade 3 or 4 pneumonitis, PS of 4, or duration of radiotherapy of over 62 days (level 1), 67 days (level 2), or 70 days (level 3). Any protocol-defined treatments were terminated if Grade 4 nonhematologic toxicities other than transient electrolyte disturbances or a PS of 4 was noted.

Dose-limiting toxicity and maximum tolerated dose

The DLT was defined as the following toxicities observed during a 6-month period from the start of treatment: (1) Grade 3 esophagitis, lung toxicity, myelitis, dermatitis associated with radiation, and cardiac toxicity associated with radiation, (2) Grade 4 nonhematologic toxicity, or (3) treatment termination due to prolonged toxicity. Twelve patients were enrolled at each dose level. All patients were followed up for at least 6 months to evaluate DLT. During the period, if none to 4 of the 12 patients experienced DLT, the next cohort of patients was treated at the next higher dose level. If 5 or more of the 12 patients experienced DLT, that level was considered to be the MTD. The recommended dose for Phase II trials was defined as the dose preceding the MTD.

Response evaluation

Objective tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) ver. 1.0 (16).

Follow-up

Patients who completed the protocol therapy were followed up to monitor toxicity, response, and recurrence. CT of the chest was performed every 2 to 4 months for 1 year, every 6 months for 2 years, and then yearly for 2 years. The relapse pattern was categorized into (1) local alone, including relapse from the primary site or the hilar, mediastinal, or supraclavicular lymph nodes, (2) distant metastasis alone, including pleural dissemination, pleural and pericardial effusions, and distant metastases, and (3) local and distant.

Statistical analyses

Progression-free survival time (PFS) and OS were estimated by the Kaplan-Meier method. The PFS was measured from the date of registration to the date of disease progression or death resulting from any cause or date of last follow-up. The OS was measured from the date of registration to the date of death resulting from any cause or date of last follow-up. Patients who were lost to follow-up without events were censored at the date of their last known follow-up. A confidence interval (CI) for the response rate was calculated by the method used for exact binomial CIs. The Dr. SPSS II 11.0 software package for Windows (SPSS Japan Inc., Tokyo, Japan) was used for the statistical analyses.

RESULTS

Registration and characteristics of the patients

From August 2005 to September 2008, 57 patients were deemed to initially be eligible. Of these, 3 patients were excluded because idiopathic interstitial pneumonitis ($n = 1$) and anemia ($n = 2$) developed. Explanation of the study using the consent form was given to 54 patients, and informed consent was obtained in 51 patients. The 51 patients underwent 3D treatment planning, and eligibility was finally confirmed in 31 patients. Those 31 were enrolled into this study. A total of 20 patients were excluded as a result of the DVH evaluation: because of V_{20} higher than 30% in 10 patients, overdose to the esophagus in 8 patients, and overdose to the brachial plexus in 2 patients. Eventually, of 17 patients assessed as to their eligibility for dose level 1, 16 patients for dose level 2, and 24 patients to dose level 3, 13 (76%), 12 (75%), and 6 (25%) patients were actually enrolled into levels 1 to 3, respectively (Fig. 1).