evaluated by a physician's inspection and palpation, which is the method recommended by FIGO for evaluating primary lesion size. However, we think that tumor size assessment by physical examination has the potential to estimate tumor size incorrectly. Especially in clinical trials, we should evaluate primary lesion size by MRI because of its accuracy. Pelvic lymph node status was not evaluated for a certain percentage of patients in both surveys. Although the evaluation of lymph node status is an important prognostic factor and is essential for radiation treatment planning, it is not included in the FIGO guidelines despite improvements in imaging techniques. We believe that physicians should evaluate the lymph node status at least in institutions with access to MRI/CT because cervical cancer has a poor prognosis in the presence of lymph node metastasis, and this is particularly evident in early stage disease [15]. We think that pelvic CT is unnecessary for the pretreatment assessment of a cervical cancer patient when her MRI covers the whole pelvis, but if not, pelvic CT is also necessary. In addition, abdominal CT is required for the assessment of para-aortic lymph node status in the case of positive pelvic lymph node or a locally-advanced stage.

PET was rarely performed for cervical cancer in the two survey periods in Japan, although it has dramatically increased in the evaluation of patients with malignant neoplasms since approximately 2000 in Japan. This was due to the Japanese health insurance plan which did not cover cervical cancer at that time. Several studies showed the accuracy of PET for the staging of cervical cancer [16]. The Japanese health insurance plan started to cover cervical cancer in 2006. Its application is expected to increase in Japan in the next Japanese PCS survey for cervical cancer.

The limitation of our study was that several cases reviewed in this survey had unknown or missing data. The tables for pretreatment diagnostic tests in this study probably do not provide an accurate estimate of overall usage. Nevertheless, our results demonstrate that the FIGO-recommended workup including cystoscopy and proctoscopy is steadily decreasing in Japan, and there is a large discrepancy between the FIGO-recommended workup with cystoscopy and proctoscopy, and the actual tests being used.

In summary, the Japanese PCS describes the changes over the years in pretreatment work-up from the 1999–2001 to 2003–2005 survey periods in Japan. This study revealed that the FIGO recommended workup is steadily decreasing in Japan, while CT and MRI have been routinely performed. Patterns of pretreatment workup should be continuously monitored in order to avoid staging migration, to properly treat individual patients, and to fairly compare treatment methods.

Conflict of interest statement
None.

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

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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.

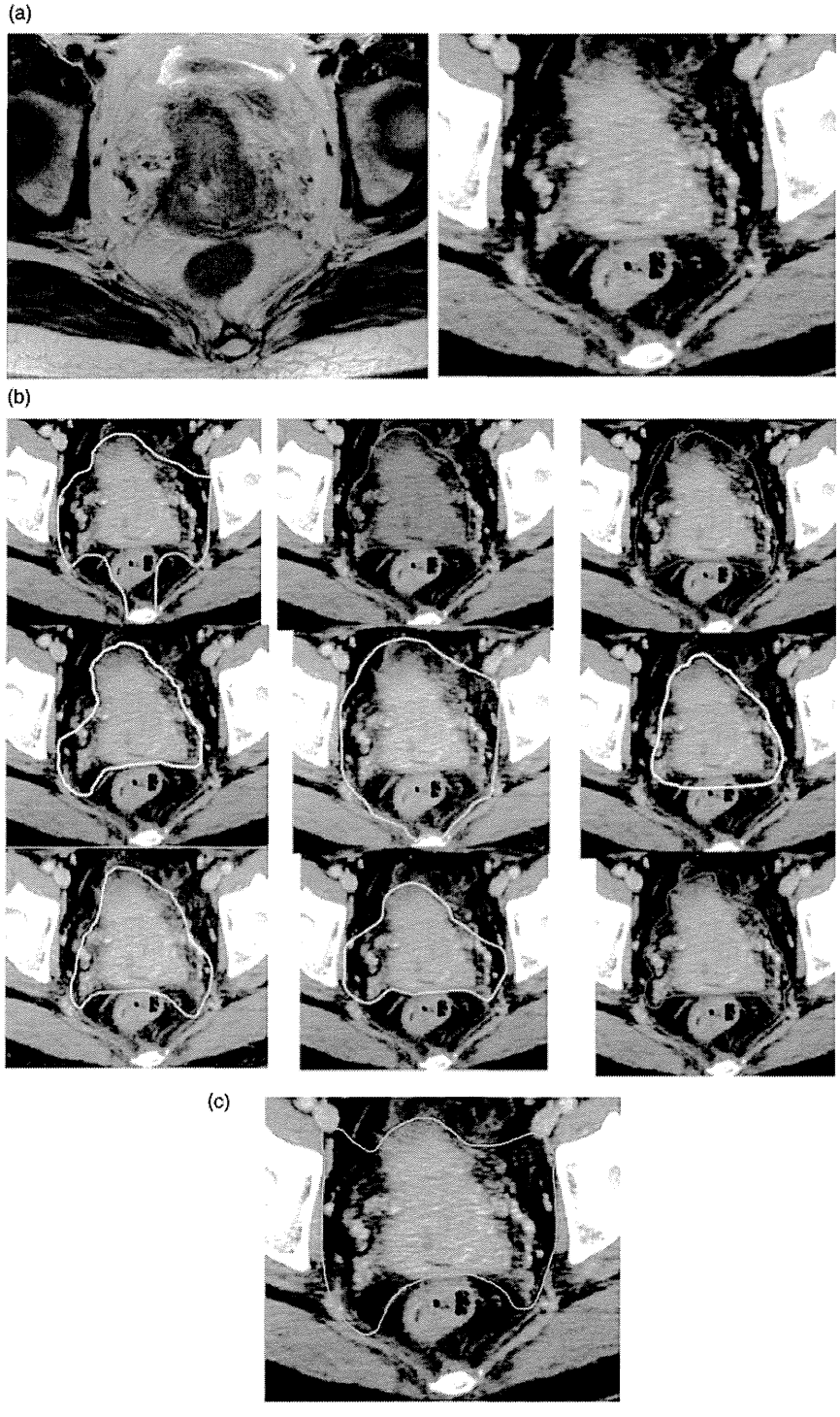

Figure 1. (a) Magnetic resonance imaging (MRI) and computed tomographic (CT) slices of a FIGO Stage IIIB cervical cancer patient who demonstrated bilateral parametrial invasion with nodular fixation to the right pelvic wall on pelvic exam. Clinical information for this patient was also distributed to 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

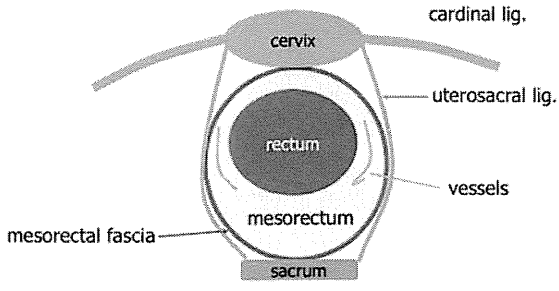

Figure 2. An illustration of the anatomical components around the cervix with reference to the parametrium.

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,

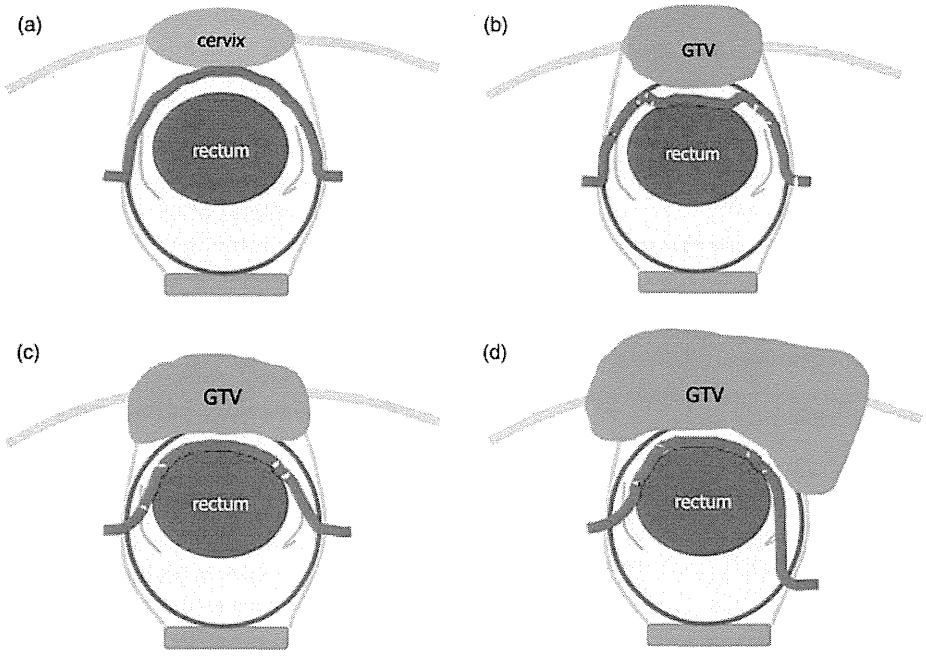

Figure 3. Stage-specific delineation schemes for the posterior border of the parametrium (solid red line). (a) Non-bulky early-stage (IB1 or IIA1) disease. (b) Bulky early-stage (IB2 or IIA2) disease. (c) Stage IIB disease (slight parametrial involvement). (d) Stage IIIB disease (massive parametrial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

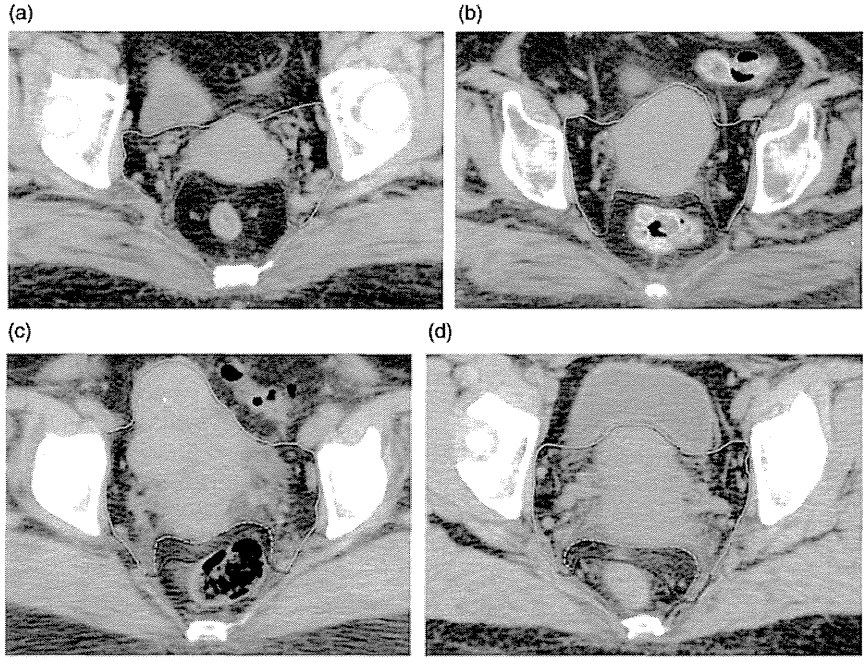

Figure 4. Actual delineations of the primary CTV (solid orange line) and posterior border of the parametrium (solid red line) according to disease status Dotted orange lines indicate the anterior border of the perirectum. (a) A case with non-bulky Stage IB1 disease. (b) A case with bulky Stage IB2 disease. (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

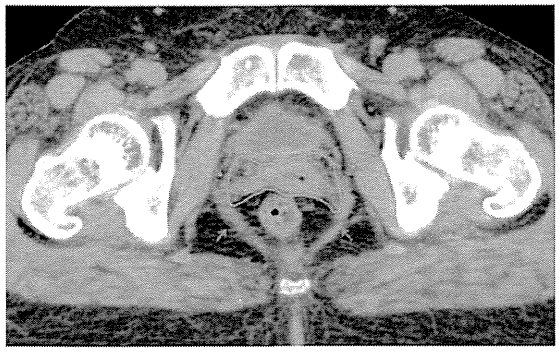

Figure 5. An actual delineation of the primary CTV (solid orange line) at the level of the levator ani (blue arrows).

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.

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Conflict of interest statement

None declared.

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Appendix

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CLINICAL INVESTIGATION **Lung**

STEREOTACTIC BODY RADIOTHERAPY (SBRT) FOR OPERABLE STAGE I NON–SMALL-CELL LUNG CANCER: CAN SBRT BE COMPARABLE TO SURGERY?

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Purpose: To review treatment outcomes for stereotactic body radiotherapy (SBRT) in medically operable patients with Stage I non–small-cell lung cancer (NSCLC), using a Japanese multi-institutional database.

Patients and Methods: Between 1995 and 2004, a total of 87 patients with Stage I NSCLC (median age, 74 years; T1N0M0, *n* = 65; T2N0M0, *n* = 22) who were medically operable but refused surgery were treated using SBRT alone in 14 institutions. Stereotactic three-dimensional treatment was performed using noncoplanar dynamic arcs or multiple static ports. Total dose was 45–72.5 Gy at the isocenter, administered in 3–10 fractions. Median calculated biological effective dose was 116 Gy (range, 100–141 Gy). Data were collected and analyzed retrospectively.

Results: During follow-up (median, 55 months), cumulative local control rates for T1 and T2 tumors at 5 years after SBRT were 92% and 73%, respectively. Pulmonary complications above Grade 2 arose in 1 patient (1.1%). Five-year overall survival rates for Stage IA and IB subgroups were 72% and 62%, respectively. One patient who developed local recurrences safely underwent salvage surgery.

Conclusion: Stereotactic body radiotherapy is safe and promising as a radical treatment for operable Stage I NSCLC. The survival rate for SBRT is potentially comparable to that for surgery. © **2011 Elsevier Inc.**

Stereotactic body radiotherapy, Lung cancer, Non–small-cell, Operable, Stage I.

INTRODUCTION

With the popularization of computed tomography (CT) screening, lung cancers are increasingly detected at an early stage. For patients with Stage I (T1 or 2, N0, M0) non–small-cell lung cancer (NSCLC), resection of the set of full lobar and systemic lymph nodes represents standard treatment. Five-year overall survival rates for clinical Stage IA and IB treated surgically are approximately 60–75% and 40–60%, respectively (1–3). However, a proportion of patients who meet the criteria for surgery refuse such intervention for various reasons. Radiotherapy offers a therapeutic alternative in such cases, but the effects of conventional radiotherapy in patients with Stage I NSCLC are unsatisfactory, with local control rates of approximately 50% during a short 5-year survival period in 15–30% of patients (4–7). Survival rates for conventional radiotherapy for a statistically sufficient number of cases of operable Stage I NSCLC have not been reported, because most

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patients receiving radiotherapy are inoperable. The poor local control rates with conventional radiotherapy have been attributed to doses of conventional radiotherapy that are too low to control the tumor. Mehta *et al.* (8) provided a detailed theoretical analysis of NSCLC responses to radiotherapy and a rationale for dose escalation. They concluded that higher biologically effective doses (BED) irradiated during a short period must be administered to achieve successful local control of lung cancer. To provide a higher dose to the tumor without increasing adverse effects, three-dimensional conformal radiotherapy techniques have been used, and better local control and survival have recently been reported (9–11). Over the last decade, hypofractionated high-dose stereotactic body radiotherapy (SBRT) has been actively performed for early-stage lung cancer, particularly in Japan (12–17). We have previously reported preliminary results for a Japanese multi-institutional review of 257 patients with Stage I NSCLC treated with SBRT (18). The results showed that local control and survival rates were better with BED $\geq$100 Gy than with <100 Gy, and survival rates were much better for medically operable patients than for medically inoperable patients. These results were encouraging, but the duration of follow-up for the study was somewhat short (median, 38 months), and we have not presented a detailed analysis of medically operable patients as a distinct subgroup. Although the standard therapy for operable Stage I NSCLC remains surgery, the effect of SBRT on medically operable patients is an issue of great concern. We provide herein detailed and matured results of SBRT (BED $\geq$100 Gy) for medically operable patients with Stage I NSCLC, using a retrospectively collected Japanese multi-institutional database.

PATIENTS AND METHODS

Eligibility criteria

All patients who satisfied the following eligibility criteria were retrospectively collected from 14 major Japanese institutions in which SBRT for lung cancer was actively performed: (*1*) identification of T1N0M0 or T2N0M0 primary lung cancer on chest and abdominal CT, bronchoscopy, bone scintigraphy, or brain magnetic resonance imaging; (*2*) histopathologic confirmation of NSCLC; (*3*) medically operable cancer but selection of SBRT after refusal to undergo surgery. Medical operability was discussed within the multidisciplinary tumor board of each institution according to respiratory function, age, and complicating diseases. Basic cutoff values for medical operability were World Health Organization performance status $\leq$2, pressure of arterial oxygen $\geq$65 mm Hg, predicted postoperative forced expiratory volume in 1 s $\geq$800 mL, no heart failure requiring pharmacotherapy, no diabetes requiring insulin, no severe arrhythmia, and no history of cardiac infarction. Positron emission tomography was not essential in the staging procedures.

Patients were informed of the concept, methodology, and rationale of this treatment, which was performed in accordance with the 1983 revision of the Declaration of Helsinki.

Table 1. Patient characteristics

Number (14 institutions)	87
Male	63
Female	24
Age (y), median (range)	74 (43–87)
ECOG performance status	
0	51
1	30
2	6
Histology	
Adenocarcinoma	54
Squamous cell carcinoma	25
Other	8
Stage	
IA	64
IB	23
Tumor diameter (mm), median (range)	25 (7–50)
IA	21
IB	39
Chronic lung disease	
Positive	38
Negative	49

Abbreviation: ECOG = Eastern Cooperative Oncology Group. Values are number unless otherwise noted.

Patient characteristics

A summary of patient pretreatment characteristics is given in Table 1. From April 1995 to March 2004, a total of 87 medically operable patients with primary NSCLC were treated using hypofractionated high-dose SBRT in 14 major Japanese institutions. Each of these 87 cases was judged medically operable, and surgery was initially recommended, but the patients declined surgery and selected SBRT as a radical treatment. Pathology of all tumors was confirmed as NSCLC by transbronchial or CT-guided percutaneous biopsy. The 14 participating institutions were these: Hokkaido University; Kyoto University; Cancer Institute Hospital; Tokyo Metropolitan Komagome Hospital; Kitasato University; Tohoku University; Hiroshima University; Tokyo Metropolitan Hiroo Hospital; Sapporo Medical University; Institute of Biomedical Research and Innovation; International Medical Center of Japan; Tenri Hospital; Kitami Red Cross Hospital; and Yamanashi University.

Treatment methods

Although the techniques to accomplish stereotactic methods differed among these institutions, all "stereotactic radiotherapy techniques" fulfilled the following five requirements: (*1*) reproducibility of the isocenter (setup error $\leq$5 mm), as confirmed by image guidance for every fraction; (*2*) respiratory motion (internal margin) suppressed using as much as possible, to <5 mm; (*3*) slice thickness on CT $\leq$3 mm for three-dimensional treatment planning; (*4*) irradiation with multiple noncoplanar static ports or dynamic arcs; and (*5*) single high dose $\geq$5 Gy.

Gross target volume (GTV) was delineated on CT images displayed with a lung window level. Clinical target volume (CTV) marginally exceeded GTV by 0–5 mm as judged by the individual radiation oncologist. Internal margin was

calculated and set around the CTV by 2–5 mm according to the individual measurements for respiratory motion of each institution. Internal margin caused by respiratory motion was reduced by gating, tracking, breath-hold technique, or abdominal compression. Planning target volume (PTV) comprised the CTV, a proper internal margin measured in each patient, and a 5-mm safety margin. The total margin between PTV and GTV was thus 7–15 mm. The irradiated port marginally exceeded PTV by 3–5 mm to secure the surface dose of PTV. Dose calculation was performed using the Clarkson algorithm and heterogeneity correction. A total dose of 45–72.5 Gy (mean, 58.7 Gy) at the isocenter in 3–10 fractions with single doses of 6.25–15 Gy was administered with 6-MV X-rays within 20% heterogeneity in the PTV dose. Minimum dose in the PTV corresponded to 85–95% of the prescribed dose in most cases. Typical dose/fractionation schedules were 75 Gy in 10 fractions for 42 patients and 48 Gy in 4 fractions for 38 patients. In principal, patients were treated on consecutive days, but some patients were treated every other day. No chemotherapies were administered before or during radiotherapy.

To compare the effects of various treatment protocols with different fraction sizes and total doses, BED was utilized in a linear-quadratic model (19). Biologically effective dose was here defined as $nd(1 + d/\alpha/\beta)$, with units of Gy, where n is fractionation number, d is daily dose, and α/β is assumed to be 10 for tumors. Biologically effective dose was not corrected with values for tumor doubling time or treatment term. Biologically effective dose was calculated at the isocenter in this study. Median calculated BED was 116 Gy (range, 100–141 Gy).

No restriction was placed on whether the tumor was located peripherally or centrally in the lung, but dose for the spinal cord was limited. Biologically effective dose limitation for spinal cord was 80 Gy (α/β was assumed to be 2 Gy for chronic spinal cord toxicity). Doses for other organs were not restricted.

Evaluation

The objectives of this study were to retrospectively evaluate toxicity, local control rate, and survival rate. Follow-up examinations were performed 4 weeks after treatment first, then patients were seen every 1–3 months. Tumor response was evaluated using the Response Evaluation Criteria in Solid Tumors by CT (20). Chest CT (slice thickness, 2–5 mm) was usually obtained every 2 to 3 months for the first year and repeated every 4–6 months thereafter. Complete response indicated that the tumor had completely disappeared or was judged to have been replaced by fibrotic tissue. Partial response was defined as a ≥30% reduction in maximum cross-sectional diameter. Distinguishing between residual tumor tissue and radiation fibrosis was difficult. Any suspicious residual confusing density after radiotherapy was considered evidence of partial response, so actual complete response rate may have been higher than presented herein. Distinguishing between local recurrence and inflammatory change was also difficult. Here, local recurrence was considered to have occurred only when enlargement of the local tumor continued for >6 months on follow-up CT, obviously positive findings were identified on positron emission tomography, or histologic confirmation was acquired. Findings on CT were interpreted by two radiation oncologists in each case. Absence of local recurrence was defined as locally controlled disease. Lung, esophagus, bone marrow, and skin were evaluated using version 2 of the National Cancer Institute–Common Toxicity Criteria.

Statistical analysis

Cumulative rates of progression-free status at local, regional lymph node, and distant sites and survival were calculated and drawn using Kaplan-Meier algorithms, with day of treatment as the starting point. Subgroups were compared using log–rank statistics. Values of $p < 0.05$ were considered statistically significant. Statistical calculations were conducted using StatView version 5.0 software (SAS Institute, Cary, NC).

RESULTS

All patients completed treatment without obvious complaints. Median durations of observation for all patients and survivors as of final follow-up were 55 and 63 months, respectively.

Local tumor response

Complete response was achieved in 28 patients (32.2%), and partial response was seen in 43 patients (49.4%).

Toxicity

Radiation-induced pulmonary complications of National Cancer Institute–Common Toxicity Criteria (version 2.0) Grade 0, 1, 2, and 3 were noted in 21 (24.1%), 61 (70.1%), 4 (4.6%), and 1 patient (1.1%), respectively. Rib fracture and Grade 3 dermatitis were observed in 4 (4.6%) and 3 patients (3.4%), respectively. All tumors bordered the chest wall. Grade 3 radiation-induced esophagitis was produced in 1 patient, in whom the tumor slightly bordered the esophagus. Maximum esophageal dose in this case was 30 Gy in 5 fractions. No vascular, cardiac, or bone marrow complications had been encountered as of last follow-up. In total, Grade 3 toxicities were identified in 8 patients (9.2%).

No definite second malignancies were found during follow-up, but 1 patient died of acute myelogenous leukemia 3.7 years after completing SBRT.

Recurrence

Local recurrence, lymph node metastases, and distant metastases occurred in 8 (9.2%), 13 (14.9%), and 19 cases (21.8%), respectively.

Cumulative local progression–free rate curves according to stage are shown in Fig. 1. Cumulative local progression–free rate after 5 years was 86.7% (95% confidence interval [CI], 78.3–94.9%) for total cases. Cumulative local progression–free rate at 5 years was 92.0% (95% CI, 83.8–99.6%)

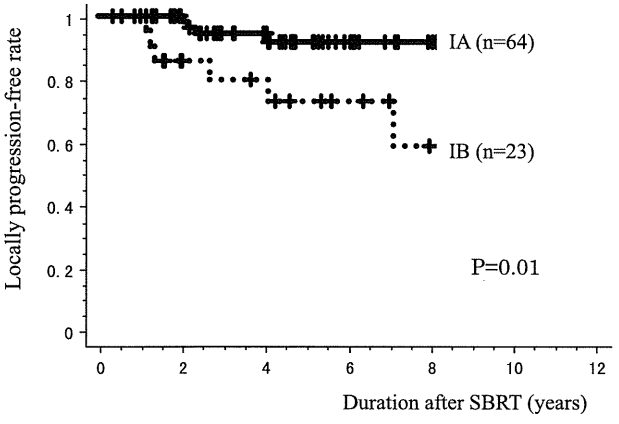

Fig. 1. Cumulative local progression–free rate curves, according to stage. SBRT = stereotactic body radiotherapy.

for the Stage IA subgroup, significantly superior ($p = 0.01$) to that for the Stage IB subgroup (73.0%; 95% CI, 52.2–93.7%). Five-year local progression–free rates were not significantly different between adenocarcinoma (80.9%; 95% CI, 68.7–93.1%) and squamous cell carcinoma (95.5%; 95% CI, 86.7–100.0%). One patient who developed local recurrence underwent surgery and has remained healthy for more than 3 years after operatively. The operation method was upper lobectomy and mediastinal lymphadenectomy, and they were performed safely without any trouble.

Cumulative curves of regional lymph node and distant metastases–free rates according to stage are shown in Figs. 2 and 3, respectively. The 5-year lymph node metastasis–free rate and distant metastasis–free rate for total cases was 85.3% (95% CI, 77.6–93.0%) and 75.1% (95% CI, 64.8–85.4%], respectively. No significant difference was identified between Stage IA and IB subgroups.

In patterns of regional nodal recurrence, 8 patients (61.5%) showed nodal failure alone, 2 patients (15.4%) had nodal failure combined with local failure, and 3 patients (23.1%) showed nodal failure combined with distant metastases.

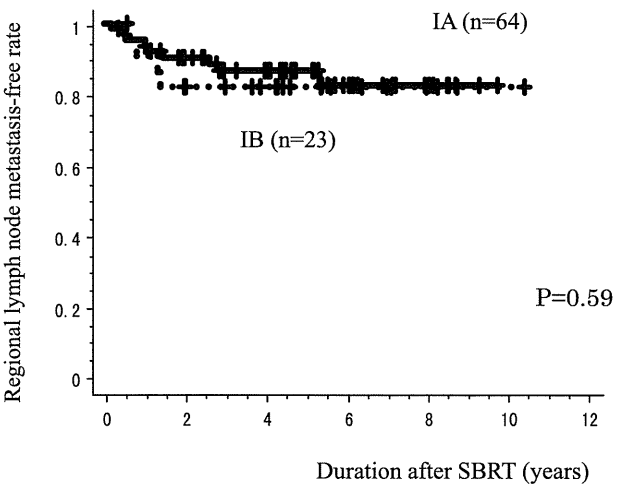

Fig. 2. Cumulative regional lymph node metastasis–free rate curves, according to stage. SBRT = stereotactic body radiotherapy.

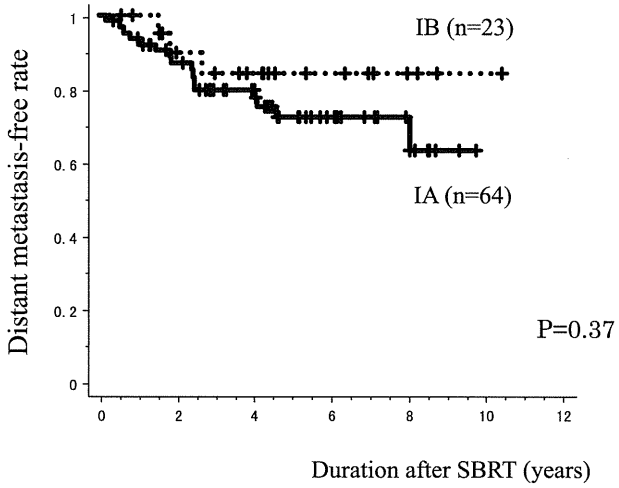

Fig. 3. Cumulative distant metastasis–free rate curves, according to stage. SBRT = stereotactic body radiotherapy.

Survival

Overall and cause-specific 5-year survival rates for total cases were 69.5% (95% CI, 58.8–80.1%) and 76.1% (95% CI, 65.9–86.3%), respectively. Overall and cause-specific survival curves according to stage are shown in Figs. 4 and 5, respectively. Five-year overall survival rate was 72.0% (95% CI, 59.6–84.4%) in Stage IA patients and 63.2% (95% CI, 42.7–83.6%) in Stage IB patients. A marginal but nonsignificant ($p = 0.14$) difference was found between overall survival rates of Stage IA and IB groups. In terms of histology, overall 5-year survival rate was 72.2% (95% CI, 59.2–85.2%) in the adenocarcinoma subgroup and 60.8% (95% CI, 38.4–83.2%) in the squamous cell carcinoma subgroup.

DISCUSSION

Exposing a tumor to a higher dose of radiation without increasing adverse effects can be achieved using stereotactic techniques. Stereotactic irradiation is an approach using

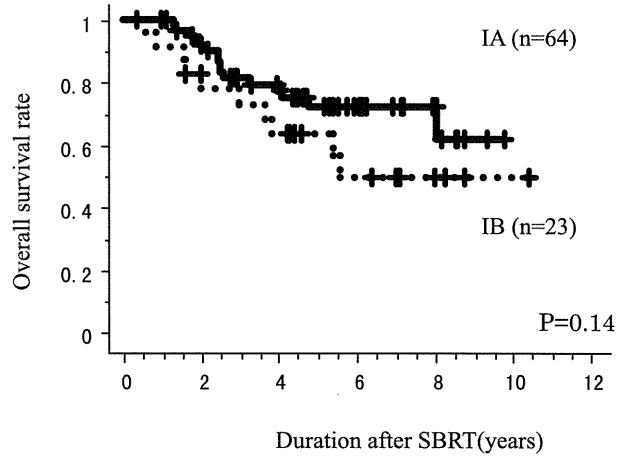

Fig. 4. Cumulative overall survival rate curves, according to stage. SBRT = stereotactic body radiotherapy.

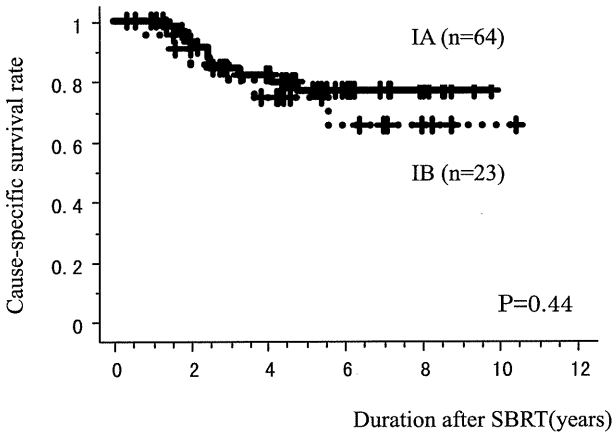

Fig. 5. Cumulative cause-specific survival rate curves, according to stage. SBRT = stereotactic body radiotherapy.

multiple noncoplanar convergent beams, precise localization with a stereotactic coordinate system, rigid immobilization, and single high-dose treatment, maximizing delivery to the tumor and minimizing the exposure of normal tissue. This approach can also substantially reduce overall treatment time from several weeks of conventional radiotherapy schedule to a few days, offering an important advantage to the patient. Stereotactic irradiation techniques are well established for the treatment of intracranial malignancies, but use in extracranial malignancies has been considered problematic because of the issues of fixation and internal motion. In 1994, Blomgren *et al.* (21) described a technique of SBRT using a custom-made body cast and stereotactic coordinates. In 1996, Uematsu *et al.* (22) reported a CT–linear accelerator unit sharing a common couch, enabling image-guided fractionated SBRT without rigid immobilization. Since verification of the effects and safety of SBRT for lung cancer (12), this treatment method has rapidly been adopted in many institutions (Table 2) (12–17, 23, 24). Although various fractionation schedules are undergoing evaluation around the world, a frequently used BED prescribed for tumors with SBRT for Stage I NSCLC in Japan has been set at a little over 100 Gy, as recommended in our previous study (18). However, concerning determination of the truly optimal dose of SBRT for Stage I NSCLC, many problems and controversies remain, such as dose-calculation algorithms (16), inhomogeneity corrections, essential dose for tumor control (24), and dose constraints for organs at risk (25, 26).

Although a number of articles on SBRT for Stage I NSCLC have been published, duration of follow-up in most cases has not been sufficiently long, and almost all treated patients were medically inoperable. The present study thus provides data on two important areas.

One was cumulative local recurrence and metastatic rates with a long duration of follow-up after SBRT. Rates of local control and metastases depend largely on the duration of follow-up and generally deteriorate as the duration of follow-up increases. Furthermore, recurrence rates have been reported in numerous articles, but most of them were crudely calculated rate. We have presented 5-year cumulative local control, regional lymph node recurrence–free and distant metastasis–free rates, calculated using Kaplan-Meier methods. The local progression–free rate in our results was unsatisfactory, particularly for the T2 tumor subgroup. The Japanese Clinical Oncology Group (JCOG) has thus started a multi-institutional dose-escalation study for Stage IB NSCLC patients (JCOG 0702).

Another meaningful result was the overall survival rate with a longer follow-up duration, allowing comparison between SBRT and surgery. Although the survival rate in this study was less than in our previous reports, we consider this information worth reporting, because median duration of follow-up was almost 5 years. Uematsu *et al.* (12) reported a 3-year overall survival rate of 86% in 29 medically operable patients with Stage I NSCLC, but the number of patients was small, and follow-up duration was relatively short. Because the number of medically operable patients treated with SBRT was very small in individual institutions, the present study collated the data of operable patients from multiple institutions. Whether the survival rate of SBRT was lower than that of surgery could not be clarified from our results. Representative 5-year overall survival rates of surgery for clinical

Table 2. Reports of SBRT for Stage I NSCLC

First author (reference)	*N*	Total dose (Gy)	Single dose (Gy)	BED (Gy)	Median follow-up (mo)	Local recurrence (%)	3-y overall survival (%)
Uematsu (12)	50	72	7.2	124	60	6*	6
Nagata (13)	42	48	12	106	52	3*	82
Onimaru (14)	28	48	12	106	27	36†	82 (Stage IA) 32 (Stage IB)
Onishi (15)	26	72	7.2	124	24	8*	75
Takeda (16)	63	50	10	100	31	5†	90 (Stage IA) 63 (Stage IB)
Koto (17)	31	45–60	7.5–15	105–113	32	29*	72
Hof (23)	10	19–26	19–26	55–94	15	40*	37
Fakiris (24)	47	60–66	20–22	180–211	50	12†	43

Abbreviations: SBRT = stereotactic body radiotherapy; NSCLC = non–small-cell lung cancer; BED = biologically effective dose ($\alpha/\beta = 10$).
* Crude data.
† Cumulative data calculated with Kaplan-Meier method.

Table 3. Comparison of 5-y overall survival rate between surgical series and SBRT

Clinical stage	United States (1)	Japanese National Cancer Center (2)	Japanese National Survey (3)	SBRT
IA	61	71	77	76
IB	40	44	60	64

Abbreviation: SBRT = stereotactic body radiotherapy. Values are percentages.

Stage IA and IB NSCLC are listed in Table 3 (1–3), ranging approximately 60–75% for Stage IA and 40–60% for Stage IB. We cannot conclude that the survival rate for SBRT is equivalent to that for surgery, because the present data for SBRT are based on a retrospective study and small sample size. However, the background of patients treated by SBRT in this study seems likely to have included worse prognostic factors than those in patients treated surgically. Concerning the size and characteristics of tumors, good prognostic factors such as smaller tumor size (27) or lower-density mass (so-called ground-glass opacities) (28) might be more frequently included in patients treated with surgery, because the determination of histological malignancy before SBRT was difficult for such tumors. In addition, median age of patients treated by surgery was approximately 10 years younger in the surgical series (median, 60–65 years) than in the SBRT series (median, 75 years). We therefore believe that survival rates for SBRT in medically operable patients are potentially comparable to those for surgery.

Regarding treatment-related toxicity, the rate of severe (Grade ≥3) acute and short-term chronic complications after SBRT was very low and acceptable, despite the high age of those patients (median, 74 years) in our experience. In results for pulmonary lobectomy, Deslauriers *et al.* (29) reported much higher mortality and morbidity rates that increased with aging. In other reports, mortality rates for patients aged >70 years old after pulmonary lobectomy were 7.6% (30). Even though improvements of mortality and morbidity of surgery may have recently been achieved (31), in particular under a technique of video-assisted thoracoscopic lobectomy (32), we consider SBRT as a safer and less invasive treatment modality than surgery, at least for peripherally located lung tumor up to 5 years after treatment. However, reports of SBRT for centrally located lung tumor have shown a comparably high risk (25, 26), and long-term chronic toxicity remains unclear. A longer and larger follow-up of SBRT is needed.

We thus consider that SBRT may offer a useful option for initial radical treatment of at least peripheral Stage IA NSCLC, not only for medically inoperable patients but also for operable patients. However, regarding centrally located or large T2 tumors, surgery must still be recommended as the first choice of treatment until further data can be accumulated. Although we encountered only 1 case in the present study, pulmonary lobectomy and mediastinal lymph node resection were performed without difficulty for a locally recurring tumor after SBRT. Surgery might be an option as salvage therapy for locally recurrent cases after radical SBRT for Stage I NSCLC.

In Japan, the number of patients treated with SBRT has exploded, especially since SBRT for lung cancer has been covered by the national health insurance since 2004. A Phase II multi-institutional study of JCOG researching the efficacy and toxicity of SBRT for both medically operable and inoperable Stage IA NSCLC patients (JCOG 0403) started in 2004, and patient entry was completed in October 2008. A total of 90 medically inoperable and 65 operable patients have been enrolled. In the United States, a Phase II multi-institutional study of SBRT for only medically inoperable Stage I NSCLC patients (Radiation Therapy Oncology Group 0236) has been ongoing.

Even multi-institutional Phase II studies of SBRT for Stage I NSCLC may have inevitable selection bias compared with surgical series. A prospective randomized trial is essential to conclude whether outcomes of SBRT for medically operable patients are truly comparable to those of surgery. A protocol for randomized studies comparing SBRT with surgery for Stage I NSCLC has been initiated (33) but has not progressed. Such a randomized study is likely to prove very difficult to perform, because most patients may hope for more minimally invasive therapy, such as SBRT. Many more experiences for more patients with a longer follow-up duration are thus needed to confirm the safety and effects of SBRT as a radical treatment for operable Stage I NSCLC. If the experience of SBRT for medically operable Stage I NSCLC matures and produces no poor results in future, SBRT will have a marked impact on standard treatment procedures for lung cancer and provide good news for Stage I lung cancer patients, the prevalence of whom is likely to increase.

In conclusion, treatment results of SBRT reviewed from a Japanese multi-institutional database showed that SBRT is safe and promising as a radical treatment for operable Stage I NSCLC. The survival rate of SBRT is potentially comparable to that of surgery.

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特集 高精度治療および短期照射治療に伴う有害事象 ……臨床放射線 56：935-942，2011

頭頸部癌 IMRT 症例の唾液腺機能評価の検討

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はじめに

2010年11月18日～20日に舞浜にて日本放射線腫瘍学会第23回学術大会が開催され，要望演題として「高精度治療および短期照射治療に伴う有害事象」というテーマで当院の治療成績の発表の機会を頂いた。本邦のIMRTの需要は急速に拡大しているが，実地医療ではまだ一般化された治療技術という認識には到達していないと思われ，有効性のみならず安全性の臨床評価は重要なテーマである。本邦における高精度治療の診療実績は次第に蓄積されてきているが，臨床的評価はいまだ十分なレベルに到達していないのが現状である。比較的実地臨床への浸透が進んできている前立腺癌のIMRTに比較し，頭頸部領域は治療計画手技がより複雑で，対象疾患の専門性が高い点などからも臨床の浸透はいまだ十分ではないと考えられる。

本稿はJASTRO要望演題の企画で発表した当院の頭頸部癌IMRTの有害事象に関する後方視的検討をまとめたものだが，本稿が今後の本邦の頭頸部癌IMRTへの標準化の一助となれば幸いである。

❶ 背　景

IMRTは本邦においては2000年頃より数施設で臨床応用が開始され，先進医療の過程を経て実施可能施設が増加してきた。2008年からは頭頸部癌を含む3疾患で保険適応が可能となり，さらには2010年より限局性固形癌へ適応拡大が行われ現在に至っている。

本邦でのIMRTの浸透状況の調査目的で，日本高精度放射線外部照射研究会の企画によりアンケート調査が行われた。その報告によると2003年には10施設で169件，2005年は19施設427件，2007年は43施設1,347件のIMRTの治療実績の報告があり，この結果よりIMRTが近年急速に日常臨床に浸透してきている事が理解できる。一方で頭頸部癌に対してのIMRTの報告件数は2003年が49件，2005年は93件，2007年は192件と緩やかな増加にとどまっている。この結果から示されるように，頭頸部癌においては全体のIMRT治療件数の急速な増加に比べ増加割合は比較的緩やかで，臨床への浸透はいまだ十分ではない状況と推察される。

頭頸部癌の治療においては，放射線治療は手術療法に比べて機能・臓器温存を可能とする点で，臨床的有用性が優れていると考えられる。しかしながら，従来の放射線治療の問題点として，治療後に高率に起きる唾液腺障害，これに関連した齲歯，歯周病などの口腔衛生上の問題，さらに下顎骨放射線壊死などの晩期障害が臨床上の課題として重要視さ

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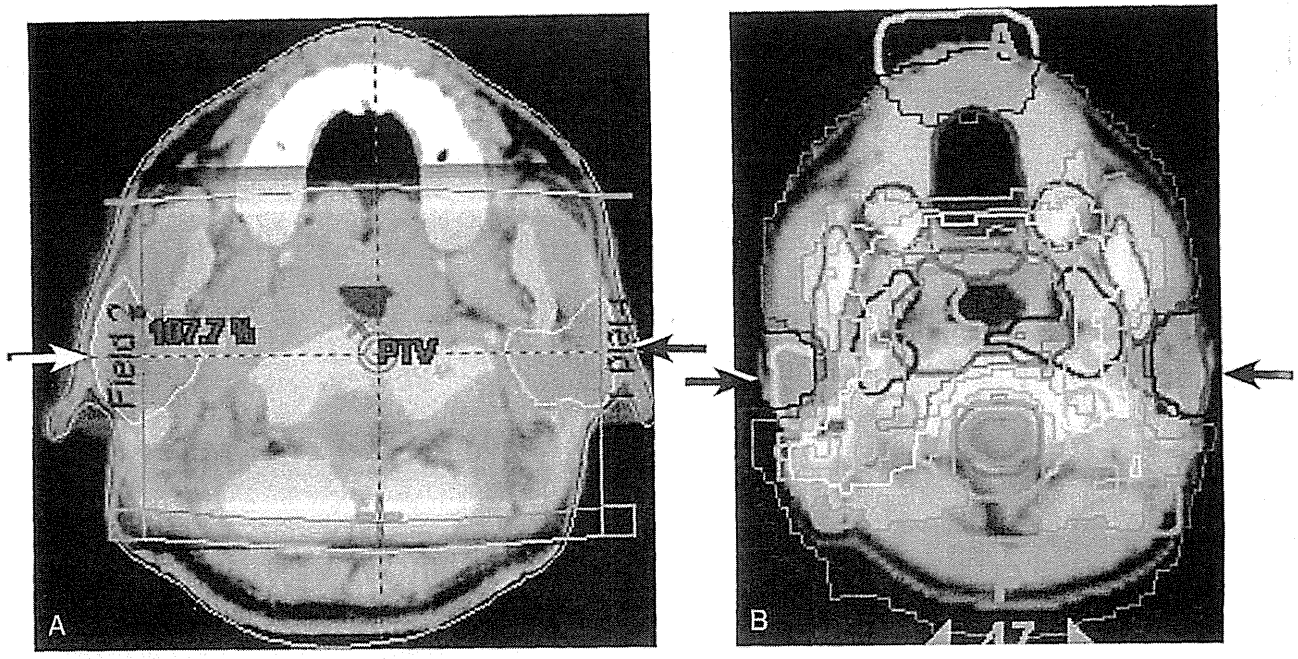

図1　通常照射法とIMRTの唾液腺への影響の比較
A　通常照射法　B　IMRT

れてきている（図1）。また化学療法の同時併用による生存率向上などの治療成績改善が実現された一方[1)2)]，相反して治療後に生じる誤嚥や嚥下機能障害に伴うQOLの低下が増えてきたことが重要な課題として注目されている[3)]。IMRTは正常臓器の投与線量を減らすことが可能で，そのため有害事象の軽減を達成でき，頭頸部癌の放射線治療に関する問題改善に有望であると期待されている。実際に欧米では頭頸部癌にたいしIMRTは実地臨床では本邦での実情より浸透している。

頭頸部癌に対するIMRTの特長として代表的なものとして唾液腺機能温存が挙げられる。唾液腺機能の客観的評価法として唾液分泌量測定がよく知られているが，手技が煩雑で検査に時間が掛かることなどより，一般臨床での実施には多くの課題がある。このほかには定量的評価法として，唾液腺シンチを用いた方法がよく知られている。この検査法では，静注したパーテクネテートが一定時間後に唾液腺に集積した後に，唾液腺刺激物の口腔内投与でアイソトープが唾液腺よりwash outされる状態を定量的に評価する。この検査法を用いることで，刺激による唾液腺分泌機能の定量的評価が可能になる。また唾液分泌量計測法に比し，より簡便で再現性が高いという利点がある。

当院では2006年6月にトモセラピー（TomoTherapy社 TomoTherapy Hi-Art System）が設置されて以来，臨床例のIMRTによる治療を開始してきた[4)]。我々は今回IMRTの臨床的評価の目的で咽頭癌および頭頸部リンパ腫症例に対し，治療前後での唾液腺機能評価の目的で唾液腺シンチグラフィを実施してきた。今回我々はIMRTの治療内容と定量的な唾液腺機能との相関関係を検討し当院での頭頸部IMRTの臨床的評価を試みる事で，臨床的有用性・妥当性の評価を行うことを目的とした。

② 対象と方法

1）対象疾患

2006年6月～2010年4月に頭頸部癌に対しヘリカルトモセラピーを用い220例の頭頸部癌へのIMRT治療の経験を得た。上咽頭および中咽頭はIMRTによる耳下腺の線量低減のメリットが大きいと考えられ，積極的にIMRTの適応を勧めてきたがこれらの治療症例の唾液腺機能の臨床的有用性の評価目的で，治療前・治療後3カ月・治療後1年に唾液腺シンチグラフィを施行した。今回の解析は，41症

表1　対象の背景

因子	項目	数
年齢	中央値（歳）	55（15～83）
性	男：女	27：14
PS	1：2	40：1
原発	上咽頭：中咽頭：ほか	24：15：2
T	1：2：3：4：X	8：19：4：6：4
N	0：1：2：3：X	4：11：19：3：4
M	0：1：X	39：1：1
Stage	Ⅱ：Ⅲ：Ⅳ：X	14：9：17：1

例・82耳下腺を対象に，経過中少なくとも2回以上の唾液腺シンチグラフィを施行できた症例を対象とした。また臨床的評価の指標として，唾液腺シンチグラフィの検査結果の対比目的でCTCAE version 3を用いた口渇のgrade分類も評価し検討を行った。

今回検討を行った対象症例の内訳を表1に示す。年齢の中央値は55歳，男性27名，女性14名であった。Stage III-IVは全体の63%，N2以上は55%であった。

2）治療計画

IMRTの治療計画について概要を説明する。治療計画には熱可塑性マスクを用い頭部から肩までを覆う固定具を作成し，これを装着し計画CTを撮影した。CTは2.5mmスライス厚の条件で，頭蓋底から気管分岐部までの範囲を撮影した。原則として可能な限りMRI，CT-PETの撮影を行い，治療計画用ソフト（Pinnacle米国PHILIPS/ADAC社製）上でimage fusionを行い治療計画のガイドとして使用した。咽頭癌の症例は原発巣および臨床的に浸潤の疑われるリンパ節転移病巣をGross Tumor Volume（GTV1）とし，これに微小病変の広がりを加味した範囲をClinical Target Volume（CTV1）とした。またCT-PET陽性の病変は原則GTV1に含めた。CTV1に適切なmarginをつけたPlanning Treatment Volume（PTV1）を設定し，このPTVに対してD95を規準に70Gy/35回を投与した。リンパ節領域はlevel II-Vおよび咽頭後リンパ節領域を予防的リンパ節領域（CTV2）として設定し，これにset up marginを加えたものをPTV2とした。Level IVまでの浸潤を認める場合には鎖骨上窩リンパ節領域を，Level IIの浸潤を認める場合level IBを適宜CTV2に加えた。PTV2への照射はsimultaneous integrated boost（SIB）法により，PTV1への70Gy/7週と同じ期間にD95を規準に54Gyの投与を行った。リンパ腫の場合は治療前の浸潤領域をGTVとしてこの領域を含むinvolved fieldをCTVとしこれに適切なmarginを加えてPTVを設定したが，予防領域の設定は行わなかった。T cell lymphomaではPTVに50Gy/25fxを，B cell lymphomaは30-40Gy/15-20fxを投与した。B cellリンパ腫ではR-CHOP投与後にPETを撮影して治療効果を判定し，化学療法後にCRを達成した症例は線量を30Gyとした。治療計画は専用の計画装置のtomoproviderを使用して最適化計算を行った。PTVへの線量制約はDmax＜110%，D99＞93%，D95＝100%，D1＜107%を目標とし，平均線量は103%以下を目標とした。また正常臓器への線量制約はDmaxとして脊髄45Gy，脳幹54Gy，視神経・視交叉50Gy，眼球45Gyとし，PRV cord50Gy＜1%，PRV stem60Gy＜1%，PRV optic pathway＜54Gyと設定した。内耳は平均線量を55Gy以下（可能なら50Gy以下）とし，下顎骨は60Gy以上投与される容積を可能な限り最小化するようにした。腕神経叢の線量制約は最大線量66Gyを目標とした。耳下腺はどちらか少なくとも一側を平均線量30Gy以下（可能なら26Gy），中央値線量26Gy以下（可能なら20Gy以下），両側耳下腺の20Gy以下の容積が20cc以上になることを目標として最適化計算を行った。

表2　対象例の放射線治療内容

項目	中央値（幅）
テーブル移動（cm）	25.2（20.7～31.3）
照射時間（秒）	576.3（413.8～816.1）
PTV1 線量（Gy）	70　（30～70）
PTV1 1回線量（Gy）	2　（1.8～2.1）
PTV1 容積（cc）	223.9（44.9～783.6）
総治療期間（日）	59　（24～69）

3）解析と方法

唾液腺シンチは以下に述べる手法で行われた。$^{99m}TcO_4^-$を静注後30分経過したところで耳下腺，顎下腺にROIを設定しアイソトープのカウントを計測しこれを負荷前の最大値カウントとする。次に唾液分泌を刺激するためクエン酸を口腔内へ投与し，ROIのtime-activity curveを計測し30秒後のカウントを用いて以下の式に基づいてmaximum ejection rate（MER）を計算する。MERは1－（クエン酸投与30分後の最大値カウント）／（静注30分後のカウント）より計算した。この結果を用いて，治療計画時に計算された唾液腺投与線量と，MER値との相関関係を統計学的に検討した。2群間の割合の差はカイ2乗検定で，両群の平均の差はt-検定により検討し，統計学的有意差は$p < 0.05$とした。治療後のMER値と耳下腺の線量パラメータとの相関に関してはピアソンの相関係数を算定して検討した。生存期間の計算は治療開始日を起算日としてKaplan-Meier法により算定し，2群間の生存率の比較はlog-rank検定を用いた。

❸ 結　果

1）放射線治療結果

解析対象症例での放射線治療の内容を表2に示す。今回の解析対象症例の照射時間は中央値で10分弱であった。ちなみに，最近の症例では治療時間は治療計画の調整によりさらに短縮できており，2010年4月以降の集計では照射時間の中央値は396secである。また，照射範囲を示すテーブル移動距離は中央値で25.2cmであった。化学療法は38例で併用されており23例は交替療法，15例は導入化学療法または導入化学療法+同時併用法により治療が行われた。化学療法は白金製剤をベースにしたものが34例，R-CHOPが3例で行われた。1例の中咽頭原発の小細胞癌では照射中にCisplatinの同時併用が行われ，adjuvant chemotherapyとしてCPT-11とCisplatinの多剤併用療法を追加した。

治療後の経過観察期間の中央値は28.5カ月（12.6～46.5カ月）で，2010年11月の最終観察時点で無病生存は37例，担癌生存が4例であった。

2）唾液腺の線量とシンチグラフィの結果

表3にIMRTによる治療計画時の耳下腺線量結果につき示す。41症例の82唾液腺での解析結果では，耳下腺容積は中央値で27.7ccで，平均線量は29.1Gy，中央値線量が21.5Gyであった。両側耳下腺の容積が20Gy以下の線量であったのは22.1ccだった。半数以上の耳下腺に関し，治療計画時の線量制約が遵守可能だった。また，どちらか一側の耳下腺が平均線量30Gy未満を達成した症例は29例（70.7%），20Gy以下の耳下腺容積が20cc以上を遵守できた症例は24例（58.5%）であった。

治療後の撮影時期に実施した唾液腺シンチのMER値の結果を表4に示す。治療前の評価が行えた症例は約半数程度と十分でないが，治療後3カ月のMER値に比較し，治療後1年のMER値は有意に上昇していた（$p < 0.0001$）。図2に治療後の撮影時期により分類したMER値の箱ひげ図を示すが，治療前に対し治療後3カ月のMER値が，同じく治療後1年に対して治療後3カ月のMER値はそれぞれ有意に良好な結果だった（$p < 0.0001$）。

図3にCTCAE vesion3で評価した口渇の有害事象発生割合を示す。治療後3カ月時点の分布に比し，治療後1年のG2の割合は有意に減少してお