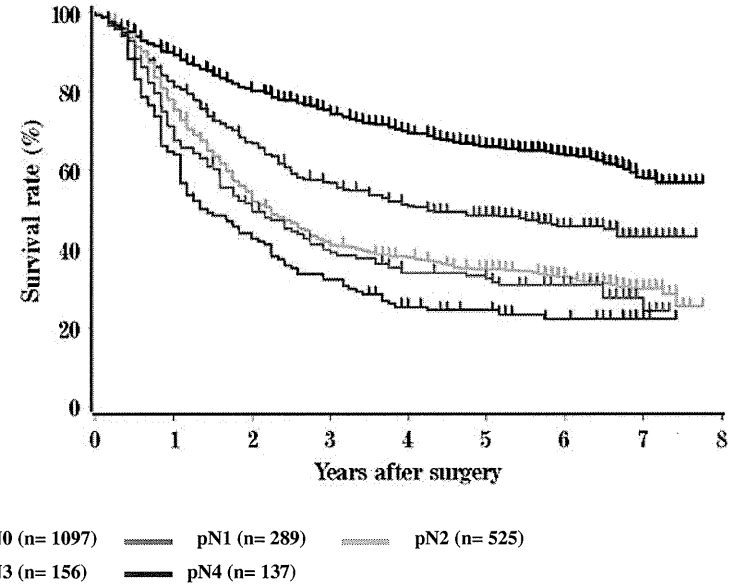

Fig. 13 Survival of patients treated by esophagectomy in relation to lymph node metastasis (JSED-pTNM 9th: pN)

	Years after surgery							
	1	2	3	4	5	6	7	8
pN0	89.2%	80.1%	74.3%	69.5%	65.9%	63.9%	57.8%	56.6%
pN1	81.5%	67.2%	56.6%	50.9%	48.6%	45.6%	43.0%	43.0%
pN2	75.2%	52.5%	41.0%	37.7%	34.8%	33.0%	29.9%	25.3%
pN3	68.3%	50.8%	38.9%	33.9%	32.3%	30.7%	24.1%	24.1%
pN4	64.0%	42.5%	32.1%	25.2%	24.3%	22.2%	22.2%	22.2%

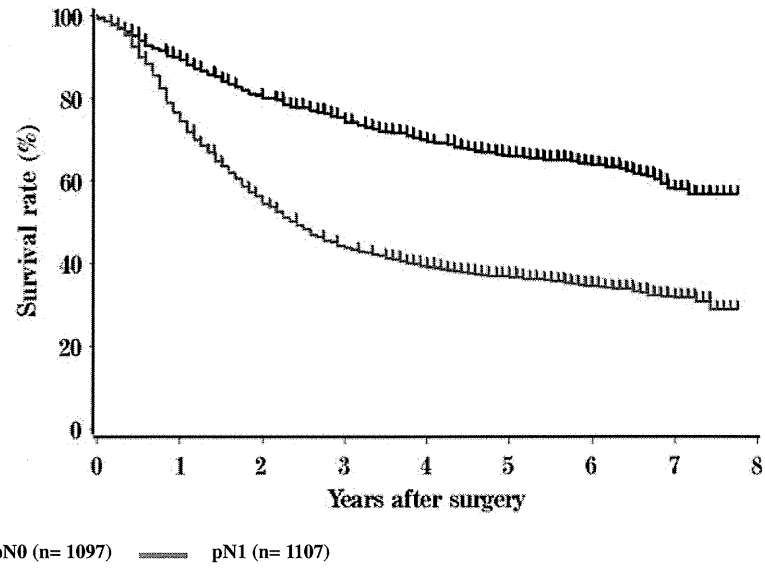

Fig. 14 Survival of patients treated by esophagectomy in relation to lymph node metastasis (UICC-pTNM 5th: pN)

	Years after surgery							
	1	2	3	4	5	6	7	8
pN0	89.2%	80.1%	74.3%	69.5%	65.9%	63.9%	57.8%	56.6%
pN1	74.5%	54.8%	43.6%	39.1%	36.7%	34.6%	31.7%	28.8%

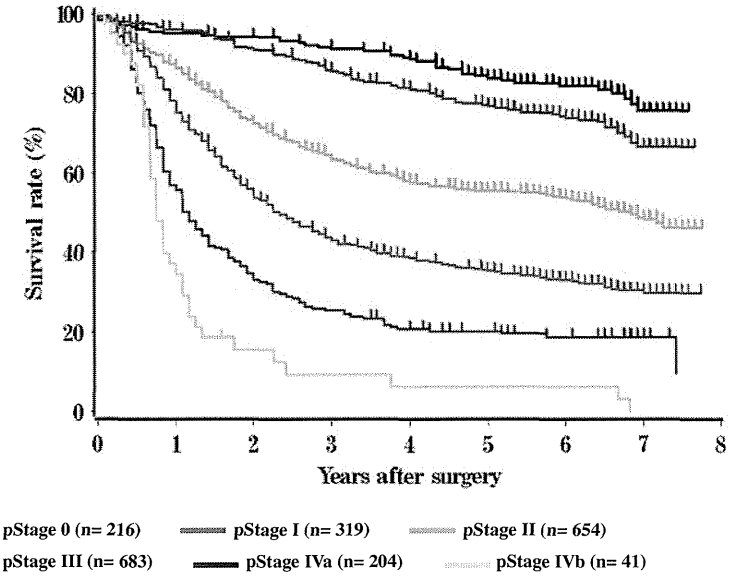

Fig. 15 Survival of patients treated by esophagectomy in relation to pathological stage (JSED-pTNM 9th)

	Years after surgery							
	1	2	3	4	5	6	7	8
pStage 0	95.2%	94.2%	91.2%	88.7%	83.9%	82.0%	75.7%	75.7%
pStage I	96.1%	91.1%	85.7%	81.2%	76.8%	73.9%	66.6%	66.6%
pStage II	86.5%	72.4%	63.5%	57.7%	55.6%	53.9%	48.4%	46.4%
pStage III	75.6%	54.3%	43.0%	38.5%	35.4%	33.1%	29.9%	29.9%
pStage IVa	55.9%	33.6%	25.5%	20.8%	20.2%	18.8%	18.8%	9.4%
pStage IVb	34.6%	15.5%	9.3%	6.2%	6.2%	6.2%	0.0%	-

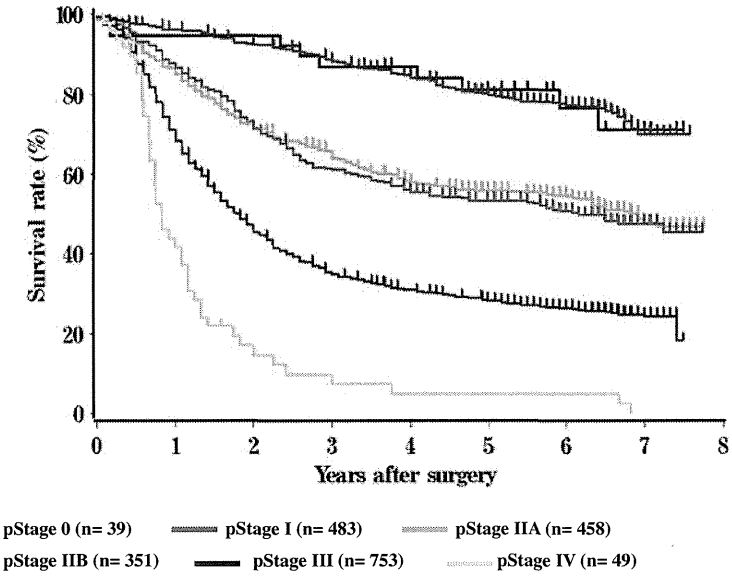

Fig. 16 Survival of patients treated by esophagectomy in relation to pathological stage (UICC-pTNM 5th)

	Years after surgery							
	1	2	3	4	5	6	7	8
pStage 0	94.8%	94.8%	86.9%	86.9%	81.0%	76.5%	71.0%	71.0%
pStage I	96.1%	92.4%	88.3%	84.2%	79.6%	77.2%	70.0%	70.0%
pStage IIA	85.2%	71.6%	64.1%	57.9%	55.9%	54.6%	48.0%	46.8%
pStage IIB	86.7%	71.4%	61.1%	55.4%	53.2%	50.6%	47.5%	45.4%
pStage III	68.6%	46.0%	34.9%	31.0%	28.3%	26.4%	24.3%	18.2%
pStage IV	41.6%	17.0%	9.7%	4.9%	4.9%	4.9%	0.0%	-

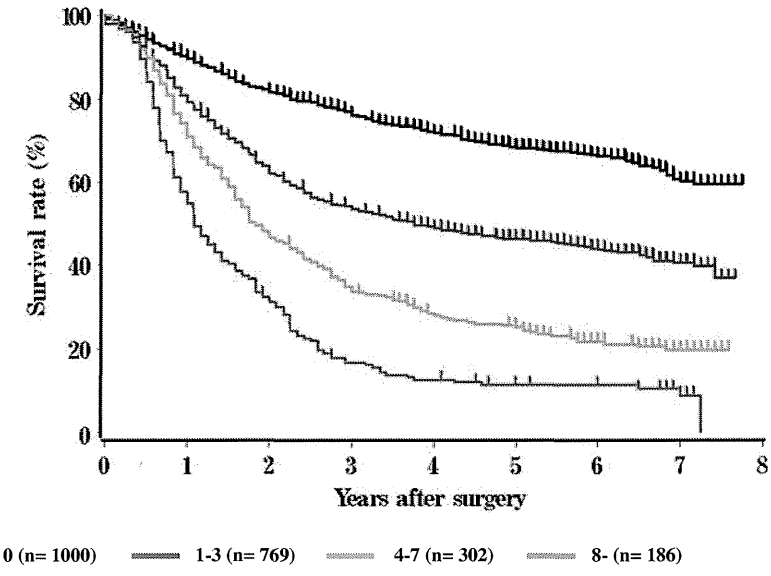

Fig. 17 Survival of patients treated by esophagectomy in relation to number of metastatic node

	Years after surgery							
	1	2	3	4	5	6	7	8
0	89.7%	81.5%	75.9%	71.7%	68.2%	66.3%	60.3%	59.5%
1-3	79.4%	62.3%	53.6%	48.8%	46.4%	44.0%	40.6%	36.9%
4-7	71.3%	47.1%	33.9%	28.0%	25.2%	21.7%	19.7%	19.7%
8-	54.9%	31.8%	16.7%	12.5%	11.2%	11.2%	8.8%	0.0%

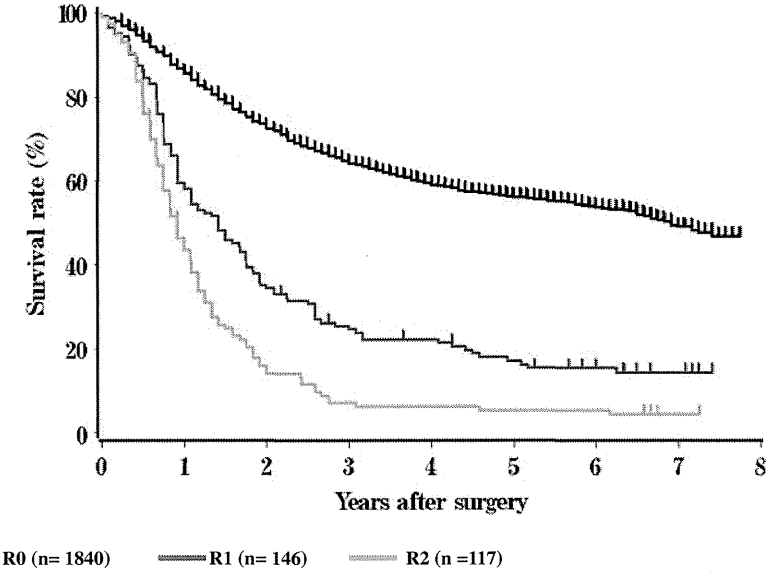

Fig. 18 Survival of patients treated by esophagectomy in relation to residual tumor (R)

	Years after surgery							
	1	2	3	4	5	6	7	8
R0	85.8%	72.7%	64.2%	59.1%	56.1%	53.8%	49.0%	46.8%
R1	58.1%	34.4%	24.6%	22.3%	17.2%	15.4%	14.3%	14.3%
R2	43.5%	14.2%	7.1%	6.2%	5.3%	5.3%	4.4%	-

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Homogeneity of GAFCHROMIC EBT2 film among different lot numbers

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EBT2 film is widely used for quality assurance in radiation therapy. The purpose of this study was to investigate the homogeneity of EBT2 film among various lots, and the dose dependence of heterogeneity. EBT2 film was positioned in the center of a flatbed scanner and scanned in transmission mode at 75 dpi. Homogeneity was investigated by evaluating gray value and net optical density (netOD) with the red color channel. The dose dependence of heterogeneity in a single sheet from five lots was investigated at 0.5, 2, and 3 Gy. Maximum coefficient of variation as evaluated by netOD in a single film was 3.0% in one lot, but no higher than 0.5% in other lots. Dose dependence of heterogeneity was observed on evaluation by gray value but not on evaluation by netOD. These results suggest that EBT2 should be examined in each lot number before clinical use, and that the dose calibration curve should be constructed using netOD.

PACS number: 87

Key words: homogeneity, EBT2, lot, gray value, netOD

I. INTRODUCTION

GAFCHROMIC EBT film (ISP Corporation, Wayne, NJ) has high spatial resolution and can be handled without processing in a darkroom, allowing artifacts associated with the chemical processing of radiographic films to be eliminated.(1) Recently, GAFCHROMIC EBT film has been replaced by a newer version, EBT2, which incorporates a yellow marker dye in the active layer to protect this layer from ambient light exposure. EBT2 was designed for intensity-modulated radiotherapy (IMRT) quality assurance (QA) applications(1-4) and has been widely used in clinical practice because of its advantage of weak energy dependence with regard to both radiation energy and type including photon, electron, and proton beams.(5,6) However, many studies have demonstrated the need for particular attention in the use of EBT2 film due to uncertainties regarding the influence of scanning orientation, nonuniformity of scanners, film development time, and film uniformity.(7,8) In particular, several papers have demonstrated significant effects on film uniformity in earlier batches of this film.(7,9) Among these, Hartmann et al.(9) reported that EBT2 film had local heterogeneity with dose differences of up to ± 6% at 1 Gy, while Aland et al.(7) reported uncertainty of 3.8% arising from film heterogeneity in an earlier batch of EBT2 film. Although planar dose distributions are often assessed using gamma criteria of 3%/3 mm,(10) film heterogeneity might require larger gamma criteria. To solve the problem of film heterogeneity, Kairn et al.(11) demonstrated that EBT2 film should be scanned

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before and after irradiation without the use of blue channel correction to reduce the effect of local heterogeneity on dose measurements. To our knowledge, however, neither variation in local heterogeneity among several lot numbers, nor the effect of the dose dependence of film heterogeneity, has been reported.

In this study, we investigated film heterogeneity in five lots of GAFCHROMIC EBT2 film. We also investigated the dose dependency of heterogeneity.

II. MATERIALS AND METHODS

A. GAFCHROMIC EBT2 film preparation

EBT2 film from lots F12170902A, A052810-02AA, A08161005A, A09171002, and A05131001B was defined as lots A, B, C, D, and E, respectively (Table 1). Three sheets from each lot were used to investigate film homogeneity, and two were used to determine the dose dependency of heterogeneity. The sheets were cut into 12 pieces (6.4 × 6.8 cm) each and numbered according to the schema shown in Fig. 1.

TABLE 1. Lot number list of EBT2 films used in this study.

	Lot Number	*Expiration Date*
Lot A	F12170902A	2011.12
Lot B	A052810-02AA	2012.5
Lot C	A08161005A	2012.5
Lot D	A09171002	2012.8
Lot E	A05131001B	2012.9

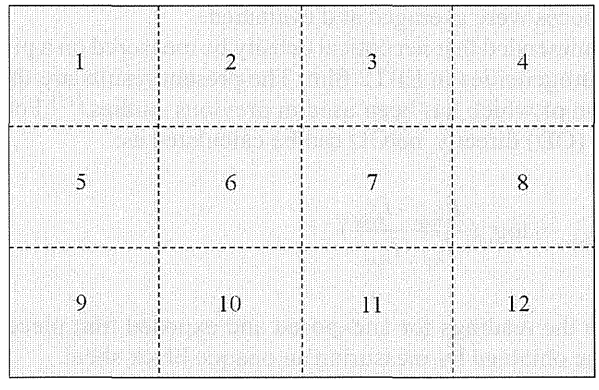

FIG. 1. Numbering schema for section of film sheets. The small cut marking is at the upper right side in this schema.

B. Irradiation

Each piece of film was placed between solid water slabs at a depth of 10 cm and an SSD of 90 cm. Irradiation was performed using a 10 × 10 cm field with a 10 MV beam with a Varian Clinac 21C/D (Varian, Palo Alto, CA). To investigate intra- and intersheet uniformity, three sheets from five lots were exposed to 2 Gy. To investigate the dose dependency of heterogeneity, a single sheet from each of five lots was irradiated at 0.5 Gy and 3 Gy, in addition to 2 Gy. All irradiated films were digitized 24 hr after exposure.[12] The irradiated and nonirradiated films were stored at room temperature in a lightproof box.

C. Film analysis

Digitization was done using an Epson GT-X970 flatbed scanner (Seiko Epson Corp., Nagano, Japan). Saur and Frengen[13] reported that the central area of the scanner bed should be used to achieve the most uniform response. In addition, scanner uniformity has been reported to be dependent on the orientation of the film, due to the different light scatter conditions created by the structure of film's active component.[13] To minimize possible confounding by these factors, all pieces were positioned in the center of the scanner bed and scanned in the same side and landscape (original long axis of film parallel to short axis of scan bed) orientation.[14] A scan resolution of 72 dots per inch (dpi) and color depth of 48-bit RGB were used.

Warm-up effects arising from the warming up of the scanner lamp and subsequent heating of the scanner bed which, in turn, result in an initial decrease in optical density with repeated scanning, have been observed with some flatbed scanners operating in transmission mode.[15,16] Five warm-up scans were accordingly done prior to each batch of scans to stabilize the lamp and scanner bed temperature.

Previous investigations of EBT film have indicated that the measured optical density increases with repeated scanning of the same film.[14] This effect is dependent on the initial level of irradiation, and has been attributed to the increase in temperature of the scan bed and film. To reduce or correct for the sensitivity of the measured dose to the properties of the film scanner, films were scanned with a minimal number of consecutive scans.

The manufacturer recommends that measurement be conducted with consideration to both red and blue channel data. However, Aland et al. and Kairn et al.[7,11] recently suggested that the conversion of film optical density to measured dose should utilize red channel data only, without application of blue channel correction. In the present study, images were saved in TIFF format, and the red channel of the scan images was extracted and processed using ImageJ (NIH: National Institute of Health, Bethesda, MD). The row reading values were obtained as gray values, which corresponded to ADC values. Gray values over a 3 × 3 cm region of interest in the middle of the film pieces were averaged and evaluated.

Kairn et al.[11,17] recommended that net optical density be measured on a pixel-by-pixel basis to account for local heterogeneities in EBT2 film. The present results are therefore presented in netOD, the calculation of which has been used in previous studies.[15] For scanners that do not read optical density (OD) directly, netOD can be calculated as:

$$\text{netOD} = \text{OD}_{\text{exp}} - \text{OD}_{\text{unexp}} = \log_{10}\left(\frac{I_{unexp} - I_{bckg}}{I_{exp} - I_{bckg}}\right) \quad (1)$$

where I_{unexp} and I_{exp} are the readings for unexposed and exposed film pieces, and I_{bckg} is the zero-light intensity value obtained by measuring an opaque black sheet.

D. Dose calibration curve

To obtain dose calibration curves for the five lots, 1 sheet from each lot was cut into 3 × 3 cm pieces, and 16 pieces of film were irradiated from 25 cGy to 400 cGy. Sixteen pieces of film from a similar area of the sheet were used to reduce the effect of local heterogeneity on the calibration curve. To reduce spatial variation in the measured dose, dose calibration curves were created by converting netOD values rather than gray values to the dose.[13] Differences among dose calibration curves of the five lots were evaluated from 25 cGy to 400 cGy in 25 cGy increments.

E. Intrasheet uniformity

To investigate intrasheet uniformity, 12 pieces of film from the same sheet were exposed to 2 Gy. Three sheets from each lot were used. Intrasheet uniformity was evaluated by the coefficient of variation of homogeneity for all pieces of a single sheet, and assessed in terms of gray value

and netOD. Variations in irradiated film evaluated by gray value were compared to those in nonirradiated film to determine the correlation between irradiated and nonirradiated film.

F. Intersheet uniformity

To evaluate intersheet uniformity, three sheets of the same lot number were irradiated at 2 Gy. Intersheet uniformity was evaluated by the coefficient of variation of homogeneity among the same piece numbers in the three sheets and assessed in terms of gray value and netOD.

The distribution of gray values and netOD obtained were analyzed. Intersheet uniformity was evaluated in terms of gray value and netOD.

G. Dose evaluation

The netOD values of film pieces irradiated with 2 Gy were translated into dose values using the dose response curve. The obtained doses were compared to the applied dose of 2 Gy, and the differences in each lot number were evaluated.

H. Dose dependence of heterogeneity

To investigate the dose dependence of heterogeneity, overall pieces in a single sheet of each lot were irradiated at 0.5 Gy, 2 Gy, and 3 Gy. The dose dependence of heterogeneity was evaluated by comparison of the intrasheet uniformity of nonirradiated films with that of irradiated films at 0.5 Gy, 2 Gy, and 3 Gy.

III. RESULTS

A. Dose calibration curve

Dose calibration curves of five lots were created in the dose range of 25 cGy to 400 cGy with 25 cGy increment, as shown in Fig. 2. Differences between lots A and B, A and C, A and D, and A and E were 6.5% ± 2.7%, 3.1% ± 2.4%, 8.2% ± 1.9%, and 3.1% ± 2.6%, respectively; differences between lot B and C, B and D, and B and E were 3.3% ± 1.4%, 1.7% ± 4.0%, and 3.2% ± 1.4%, respectively; between lot C and D, and C and E, differences were 5.1% ± 3.9%, and 0.1% ± 2.2%, respectively; and between lot D and E they were 4.6% ± 3.6%.

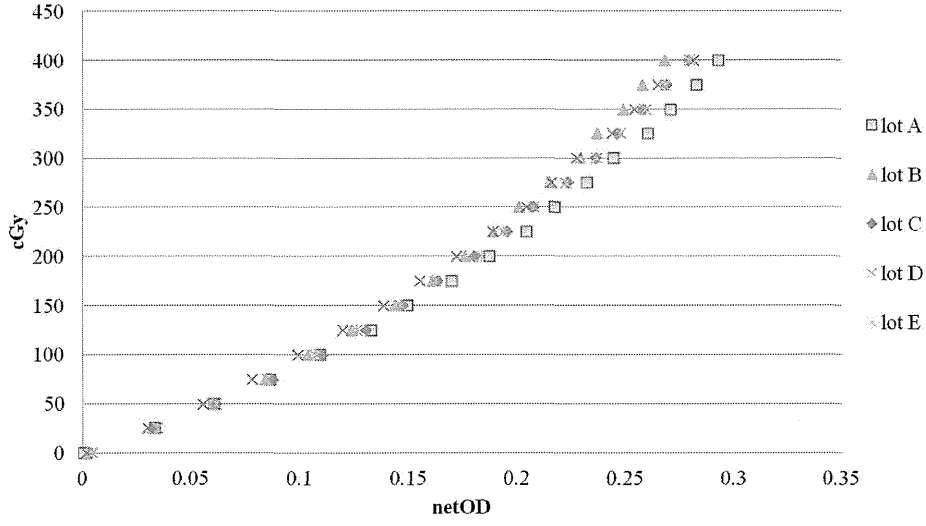

FIG. 2. Dose-response curve of the EBT2 film Lot Nos.F12170902A (lot A), A052810-02A (lot B), A08161005A (lot C), A09171002 (lot D), and A05131001B (lot E). This is a sensitometric curve for conversion of netOD value to dose.

B. Intrasheet uniformity

Figure 3 shows the gray value variations before and after irradiation at 2 Gy. These data show average gray values of three sheets, and error bars indicate the coefficient of variation which represents intersheet uniformity. Regarding lots A and B, heterogeneity was increased by irradiation. Although intrasheet uniformity before irradiation was less than 0.4% in all lots, intrasheet uniformity after irradiation in lots A, B, C, D, and E was 1.5%, 1.3%, 0.4%, 0.2%, and 0.4%, respectively.

Figure 4 shows netOD distribution. Intrasheet uniformity of lots A, B, C, D, and E was 3.0%, 2.7%, 0.8%, 0.5%, and 0.6% respectively. NetODs of lots A and B were high at areas 1, 5, and 9, whereas those of lots C, D, and E were low at areas 4, 8, and 12.

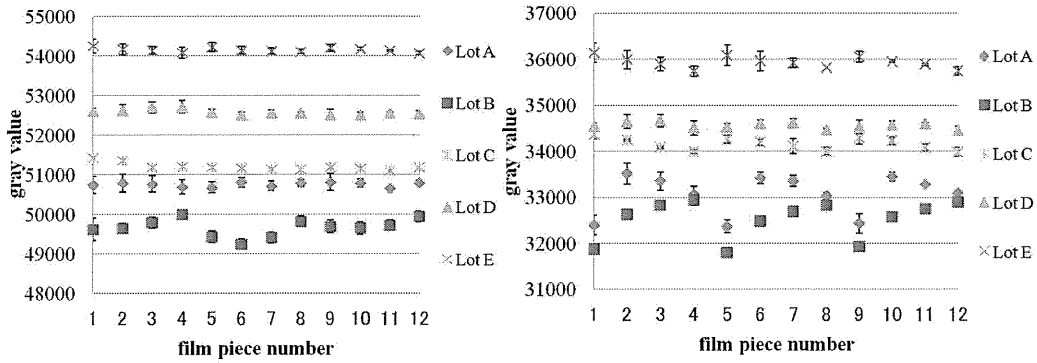

FIG. 3. Gray value distribution of film pieces from lots A, B, C, D, and E before (a) and after (b) irradiation at 2 Gy.

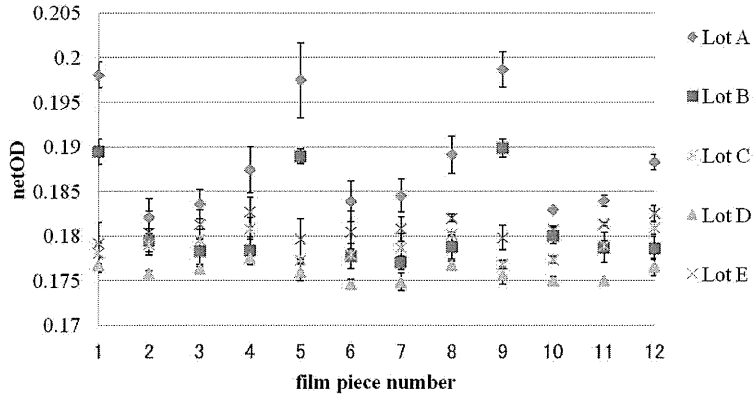

FIG. 4. NetOD distribution of film pieces from lots A, B, C, D, and E after irradiation at 2 Gy.

C. Intersheet uniformity

Intersheet uniformity of all lots evaluated by gray value showed less than 0.6% before and after irradiation, and intersheet uniformity of all lots evaluated by netOD was less than 1.0% (Table 2). Intersheet uniformity evaluated by both gray value and netOD showed no significant difference.

TABLE 2. Intrasheet uniformity and intersheet uniformity obtained by netOD value.

	Lot A	*Lot B*	*Lot C*	*Lot D*	*Lot E*
Intrasheet Uniformity	3.0%	2.7%	0.8%	0.5%	0.6%
Intersheet Uniformity	1.0%	0.7%	0.4%	0.3%	0.8%

D. Dose evaluation

Figure 5 shows dose variations of film pieces irradiated at 2 Gy in lots A, B, C, D, and E. NetOD values were converted into the corresponding dose using the dose calibration curve shown in Fig. 2. The positions of bars in the graph correspond to the film sheet position in the Fig. 1 schema. Each lot showed a specific trend in dose distribution. Lots A and B showed the highest value at area 9. These lots had maximum differences of up to 7.8%, and 11.9% in comparison with 2 Gy. In contrast, lots C, D, and E showed the highest value at area 4. These lots had maximum differences of up to 3.1%, 3.6%, and 4.1% in comparison with 2 Gy. Intrasheet uniformity of lots A, B, C, D, and E were 4.8%, 4.3%, 1.1%, 0.7%, and 0.9%, respectively. In contrast, intrasheet uniformity evaluated by gray value was 4.6%, 5.5%, 1.4%, 0.6%, and 1.0%, respectively (data not shown). Intersheet uniformity of lots A, B, C, D, and E was 1.3%, 1.2%, 0.5%, 0.4%, and 1.2%, respectively (Table 3).

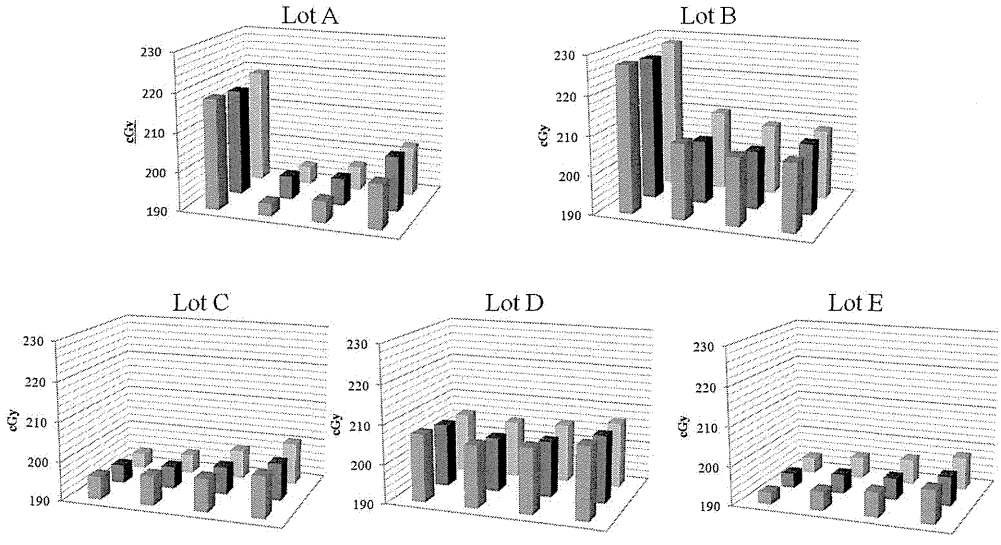

FIG. 5. Dose distribution of lots A, B, C, D and E at 2 Gy. NetOD values of film pieces irradiated at 2 Gy were translated into dose values using the dose response curve. Film sheet position is displayed as in the schema in Fig. 1.

TABLE 3. Intrasheet uniformity and intersheet uniformity obtained by dose.

	Lot A	*Lot B*	*Lot C*	*Lot D*	*Lot E*
Intrasheet Uniformity	4.8%	4.3%	1.1%	0.7%	0.9%
Intersheet Uniformity	1.3%	1.2%	0.5%	0.4%	1.2%

E. Dose dependence of heterogeneity

Figure 6 shows the intrasheet uniformity of lots A, B, C, D, and E on irradiation at 0.5, 2, and 3 Gy. Lots were evaluated by both gray value and netOD. Dose dependence of film heterogeneity was observed in the gray value in all lots, but this was not observed in netOD in any

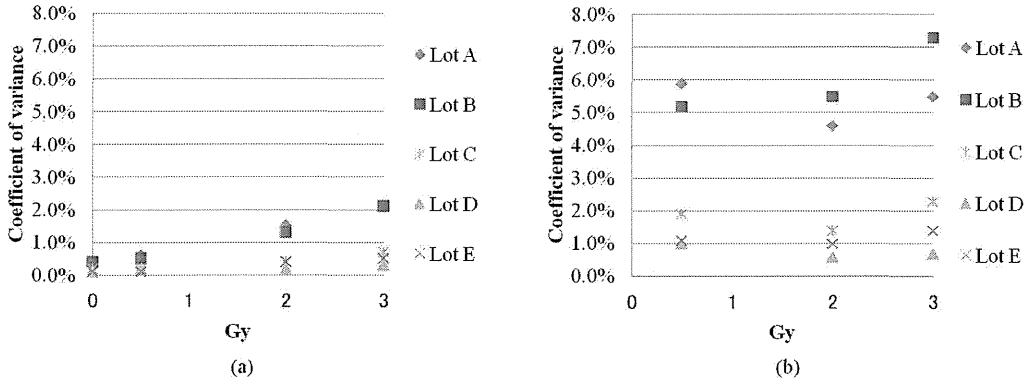

FIG. 6. Intrasheet uniformity of lots A, B, C, D, and E after irradiation at 0.5, 2, and 3 Gy. Films were evaluated by gray value (a) and netOD (b).

lot. Intrasheet uniformity of lots A and B was greater than that of lots C, D, and E in both gray value and netOD evaluations.

IV. DISCUSSION

In this study, we investigated the local heterogeneity of EBT2 films among various lots, as well as the dose dependency of heterogeneity in these lots. Results showed that the degree of heterogeneity in gray values differed in a dose-dependent manner and varied among the lots.

Several studies have described local heterogeneity in EBT2 film. Kairn et al.[17] reported that EBT2 suffered from some inconsistency in an early batch. Hartmann et al.[9] reported significant heterogeneity, with intrasheet uniformity of 4.5% and a difference in dose determination due to heterogeneity of up to 6%. In the present study, two lots (A and B) showed significant local heterogeneity, and indicated large netOD values at the left side (areas 1, 5, and 9), which was compatible with the Hartmann study. The dose difference of lot B was biased toward the plus value (ranging from 0.5% to 11.9%) according to the film position of the calibration curve. Other film positions in calibration curve construction may lead to smaller differences in dose.

Richley et al.[8] reported that intra- and intersheet uniformities were 1.2% and 0.6%, respectively. Three lots (C, D, and E) showed homogeneity, which was consistent with Aland et al.[7] Their study reported that the degree of heterogeneity was smaller than that reported by Hartmann et al., noting intra- and intersheet uniformity of 0.7%, and 1.5%, respectively. Aland et al.[7] also demonstrated that the effect of uniformity on gray value to dose conversion was up to 1.9%. To date, however, little data has appeared about homogeneity among several lots evaluated at the same time. We found that homogeneity tended to be associated with lot number.

In dose measurement, lots A and B showed higher values on left side of a film (areas 1, 5, and 9) than the other regions. In contrast, lots C, D, and E showed higher values on the right side. If the side with the highest value was excluded and the whole of the remaining side was used in dose measurement, intrasheet uniformity improved to 1.9%, 0.8%, 0.7%, 0.6%, and 0.5% in lots A, B, C, D, and E, respectively. Most importantly, maximum dose differences for lots A and B compared at 2 Gy significantly improved to 4.2% and 3.2%, respectively, which were similar to those for other lots. These results suggest that the use the middle region of the film improves dose verification accuracy with EBT2 film.

Although lots B and C had the same expiration date, they differed in their degree of intrasheet uniformity. This finding suggests that film homogeneity was independent of expiration date, but dependent on lot number, and that film homogeneity continues to be variable, despite improvements in lot uniformity overtime.

The manufacturer recommends that EBT2 film scans be corrected using red and blue channels. However, Kairn et al.[11] reported that blue channel correction increased noise in the resulting dose images, leading to an increase in dose uncertainty of ± 7.5% or ± 1.2% with or without blue channel correction, respectively. These authors recommended that the films be analyzed using netOD without blue channel correction to ensure the production of dose images with minimal film heterogeneity effects. In the present study, dose variation was greater by gray value than by netOD analysis in lot B, but not significantly different in other lots. On the other hand, intrasheet uniformity evaluated by gray value indicated dose dependence, whereas that by netOD value indicated dose independence. These results suggested that evaluation by netOD was the appropriate analysis method for almost all lots of EBT2.

V. CONCLUSIONS

EBT2 should be examined for uniformity by sheet position in each lot number before clinical use. Close attention to the sheet location which shows the least uniformity will likely provide sufficient film homogeneity for clinical use independent of lot.

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Clinical Investigation: Gynecologic Cancer

Insufficiency Fractures After Pelvic Radiation Therapy for Uterine Cervical Cancer: An Analysis of Subjects in a Prospective Multi-institutional Trial, and Cooperative Study of the Japan Radiation Oncology Group (JAROG) and Japanese Radiation Oncology Study Group (JROSG)

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Summary

We analyzed subjects of a prospective multi-institutional study to investigate pelvic insufficiency fractures (IF) after definitive pelvic radiation therapy for early-stage uterine cervical cancer. The 2-year overall cumulative incidence of both symptomatic and asymptomatic IF was 36.9%, and the cumulative incidence of symptomatic IF was 16.1%. Higher age (>70 years) and low body weight (<50 kg) were thought to be risk factors for pelvic IF.

Purpose: To investigate pelvic insufficiency fractures (IF) after definitive pelvic radiation therapy for early-stage uterine cervical cancer, by analyzing subjects of a prospective, multi-institutional study.

Materials and Methods: Between September 2004 and July 2007, 59 eligible patients were analyzed. The median age was 73 years (range, 37-84 years). The International Federation of Gynecologic Oncology and Obstetrics stages were Ib1 in 35, IIa in 12, and IIb in 12 patients. Patients were treated with the constant method, which consisted of whole-pelvic external-beam radiation therapy of 50 Gy/25 fractions and high-dose-rate intracavitary brachytherapy of 24 Gy/4 fractions without chemotherapy. After radiation therapy the patients were evaluated by both pelvic CT and pelvic MRI at 3, 6, 12, 18, and 24 months. Diagnosis of IF was made when the patients had both CT and MRI findings, neither recurrent tumor lesions nor traumatic histories. The CT findings of IF were defined as fracture lines or sclerotic linear changes in the bones, and MRI findings of IF were defined as signal intensity changes in the bones, both on T1- and T2-weighted images.

Results: The median follow-up was 24 months. The 2-year pelvic IF cumulative occurrence rate was 36.9% (21 patients). Using Common Terminology Criteria for Adverse Events version 3.0, grade 1, 2, and 3 IF were seen in 12 (21%), 6 (10%), and 3 patients (5%), respectively. Sixteen patients had multiple fractures, so IF were identified at 44 sites. The pelvic IF were frequently seen at the sacroileal joints (32 sites, 72%). Nine patients complained of pain. All patients' pains were palliated by rest or non-narcotic analgesic drugs. Higher age (>70 years) and low body weight (<50 kg) were thought to be risk factors for pelvic IF ($P=.007$ and $P=.013$, Cox hazard test).

Conclusions: Cervical cancer patients with higher age and low body weight may be at some risk for the development of pelvic IF after pelvic radiation therapy.

Introduction

Insufficiency fractures (IF) are a type of stress fracture, occurring after normal or physiologic stress on bone with decreased mineralization and elastic resistance (1). Insufficiency fractures of the pelvic bones are thought to be associated with postmenopausal or corticosteroid-induced osteoporosis (1, 2). Pelvic radiation therapy (RT) also can affect the development of pelvic IF, although the precise pathogenesis is as yet unclear (1, 2). Although some investigators (3-5) have reported that pelvic IF are an uncommon adverse event in irradiated patients with gynecologic cancer, others (6-10) have reported that radiation-induced pelvic IF were frequently observed in women after RT. It seems that the precise incidence of IF is unclear. The findings on conventional radiographs are usually subtle (2, 10) and may be misleading. The fractures usually show increased uptake on radionuclide bone scans. A pattern of increased uptake in the body of the sacrum and in one or both sacrum alae (1, 2, 11) is indicative of a fracture, but increased uptake may also be present in metastases and sacroiliac joint osteoarthritis (12). The importance of understanding a pelvic IF lies in the potential for its misdiagnosis as bony metastases. Computed tomography (CT) is capable of displaying fracture lines and/or sclerotic changes associated with IF (8, 9, 11), whereas magnetic resonance imaging (MRI) is highly sensitive for revealing the reactive bone marrow changes associated with IF (9, 13).

Not only for unresectable locally advanced stages, RT has played an important role in the treatment of early-stage cervical cancer. Originally, to determine the efficacy of definitive RT using high-dose-rate intracavitary brachytherapy (HDR-ICBT) with a low cumulative dose schedule in nonbulky early-stage cervical cancer patients, we conducted a prospective multi-institutional study (JAROG0401/JROSG04-2) (14). Two-year pelvic disease progression-free rate was the primary endpoint, and late complication including IF was one of the secondary endpoints in the study (14). At first, IF was evaluated by only symptomatic features. However, we noticed that some follow-up imaging features after RT had shown IF of pelvic bones in several asymptomatic patients. Therefore, we planned this additional study to assess pelvic IF by adding a minute imaging evaluation prospectively, without changing the schedule and methods of the follow-up CT and MRI in the protocol.

The purpose of this study was to investigate the incidence of radiation-induced pelvic IF using CT and MRI and to investigate the risk factors and radiation doses associated with IF, as well as the distribution of IF sites among patients with this complication. In our study, patients were treated with the constant RT method described in the protocol and followed with CT and MRI regularly. To our knowledge, this is the first multi-institutional prospective analysis on IF.

Methods and Materials

Patient eligibility criteria

The women enrolled in these analyses were a group of patients with cervical carcinoma who were treated with a protocol JAROG0401/JROSG04-2) (14). Eligible patients had histologically proven squamous cell carcinoma of the intact uterine cervix with International Federation of Gynecologic Oncology and Obstetrics (FIGO) stage Ib1/IIa/IIb disease and were aged 20-80 years. A complete physical examination, pelvic examination performed without anesthesia, and chest X-ray were required to determine the clinical stage. Patients were required to have cervical tumors <40 mm in diameter as assessed by T2-weighted MRI and negative pelvic and paraortic lymph nodes (<10 mm in shortest diameter) as

determined by CT. All patients were required to give their written informed consent.

Treatment

The treatment protocol has been described in detail previously (14). The treatment protocol consists of a combination of external-beam radiation therapy (EBRT) and HDR-ICBT. Interstitial brachytherapy and chemotherapy were not allowed. External-beam radiation therapy was delivered to a total dose of 50 Gy in 25 fractions over 5-6 weeks. The early part with 20 Gy was delivered to the whole pelvis. After that, 30 Gy was administered through the same whole-pelvic field with a midline block (MB) of 3- to 4-cm width. The MB was formed with multileaf collimators or custom cerrobend block. The first HDR-ICBT was performed within 10 days after the initial 20 Gy of EBRT. Treatment was to be completed within 56 days.

All patients were treated with a photon beam of 10 MV or greater. Both anteroposterior/posteroanterior (AP/PA) and a 4-field technique were allowed. In cases in which the 4-field technique was used, the portal arrangement was changed to the AP/PA technique after the insertion of the MB. Tissue heterogeneity correction was not used in the dose calculation. The upper border of the pelvic field was L4/5, and the lower border was a transverse line below the obturator foramen. The lateral borders of the AP/PA fields were 1-2 cm beyond the lateral margins of the bony pelvis. For the lateral fields, the anterior border was placed at a horizontal line drawn 1 cm anterior to the symphysis pubis anteriorly and a vertical line at the posterior border of the sacrum posteriorly. The upper and lower borders were the same as the AP/PA fields. The fields were shaped to shield normal tissues using a custom block or multileaf collimators. Prophylactic paraortic RT was not allowed.

High-dose-rate intracavitary brachytherapy using a tandem and 2 ovoids was performed once per week giving 24 Gy to point A in 4 fractions with ^{192}Ir afterloading machines.

Evaluation

After RT the patients were evaluated by both pelvic CT and pelvic MRI at 3, 6, 12, 18, and 24 months. Diagnosis of IF was made when the patients had positive findings on both CT and MRI, without recurrent tumor lesions or traumatic histories. Computed tomography findings of IF were defined as fracture lines or sclerotic linear changes in the bones, and MRI findings of IF were defined as signal intensity changes in the bones of >5 mm both on T1 and T2-weighted images (Fig. 1). All CT and MR images were evaluated together by 4 investigators. The cumulative occurrence rate of IF was calculated by the Kaplan-Meier method. Risk factors that could affect the incidence of IF (age, stage, body weight, simulation, beam technique, energy of X-ray, and location of facilities) were assessed by log-rank test and Cox hazard test. Statistical analyses were performed with SPSS 16.0 (SPSS, Chicago, IL).

The patients were also evaluated by CTCAE (Common Terminology Criteria for Adverse Events) version 3.0 every 3 months from 3-30 months. Clinical characteristics, including sites of IF and doses administered to IF lesions, were identified by a review of the medical records and imaging studies of the participating facilities, including isodose curves of pelvic RT.

The study was approved by the Protocol Review Committee of our study group and the local institutional review board of participating institutions.

Results

Patients

Between September 2004 and July 2007, 60 patients were enrolled from 13 institutions. One patient was considered ineligible, leaving 59 patients in the final patient cohort.

The median age was 73 years (range, 37-84 years). The eligible patients had squamous cell carcinoma of the uterine cervix, and the FIGO stages were Ib1 in 35, IIa in 12, and IIb in 12 patients. No patients had pelvic/paraortic lymphadenopathy. The median follow-up was 24 months.

Incidents and clinical characteristics of IF

A total of 21 patients were diagnosed with IF after RT. The 2-year overall cumulative incidence of both symptomatic and asymptomatic IF was 36.9% (Fig. 2). On CTCAE version 3.0, grade 1, 2, and 3 were seen in 12 (21.4%), 6 (10.2%), and 3 patients (5.3%), respectively.

On univariate analysis by log-rank test, age >70 years ($P=.004$) and body weight <50 kg ($P=.007$) were thought to be risk factors of pelvic IF. Multivariate analysis by Cox hazard test showed that age >70 years ($P=.007$) and body weight <50 kg ($P=.013$) were significant predisposing factors for developing IF (Table).

The cumulative incidence of symptomatic IF at 2 years was 16.1% (9 patients) in all patients (Fig. 2). Nine patients complained of pelvic or back pain. The pain was palliated by rest or non-narcotic analgesic drugs in all 9 cases, and no patients required surgical intervention. Sixteen patients had multiple fractures, so the pelvic IF was identified at 44 sites. The symptomatic patients had from 1-4 IF sites (mean 2.7 sites), and the asymptomatic patients had 1 or 2 IF sites (mean 1.7 sites). The pelvic IF was seen at the sacroileal (SI) joints (32 sites, 72%), pubis (9 sites, 20%), acetabula (2 sites, 4%), and lumbar spine (1 site, 2%) (Fig. 3).

The external-beam doses of all 44 IF sites were calculated from the isodose curves. It was estimated that the median dose was 49 Gy and the mean dose was 46 Gy (range, 23-50 Gy). The doses of 38 IF sites (86%) were estimated at >45 Gy.

Discussion

Insufficiency fractures occur most often in elderly women with postmenopausal osteoporosis (2). Other predisposing factors include rheumatoid arthritis, corticosteroid therapy, heparin use, diabetes mellitus, low body weight, current smoking, and RT (15). Fu et al (16) reported that the incidence of IF increased when the dose was above the threshold of 45 Gy. However, there have been no tolerance dose data for IF. In conventional pelvic RT, the irradiated dose of the pelvic bone is usually 45-50 Gy, and the development of IF after pelvic RT at this level has been considered a rare complication (3-5).

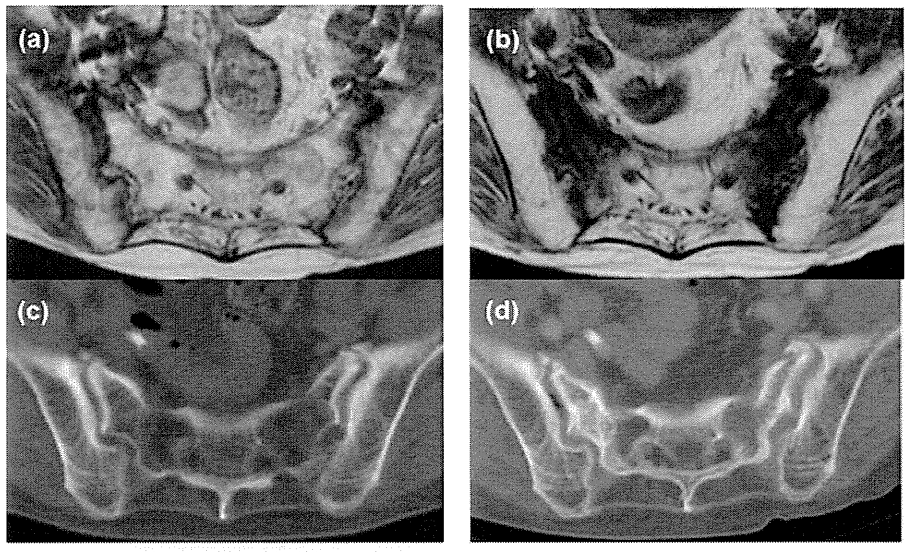

Fig. 1. Pelvic MRI shows low signal intensity in both sacroiliac joints (b) after radiotherapy (RT). Pelvic bone window CT shows (d) cortical fractures and sclerotic changes in the bilateral sacroiliac joints. M = month.

However, several recent studies (6-10) showed that the incidence of IF after pelvic RT might have been underestimated in gynecologic patients. Among these studies, the cumulative incidence of symptomatic IF at 2 years was 11.1%-14.9%, and that at 5 years was 8.2%-17.9%. In our series the cumulative incidence of IF was 36.9% at 2 years in all patients and 16.1% in symptomatic patients. The results of this study showed a relatively higher incidence of IF compared with previously reported data (2-10); however, the rate of occurrence of symptomatic IF was in accordance with other recent studies (6-10). In their prospective MRI study, Blomlie et al (13) reported that 89% of patients (16 of 18) had findings compatible with IF after pelvic RT. They showed that signal changes of MRI in pelvic bones were seen until 24 months after the end of RT, and 56% of patients (10 of 18) complained of pelvic pain. Abe et al (11) showed a 34% incidence of IF after pelvic RT using bone scintigraphy. We performed CT and MRI during the follow-up at least 2 times per year, so as to detect asymptomatic patients (12 of 21, 57.1%) with IF.

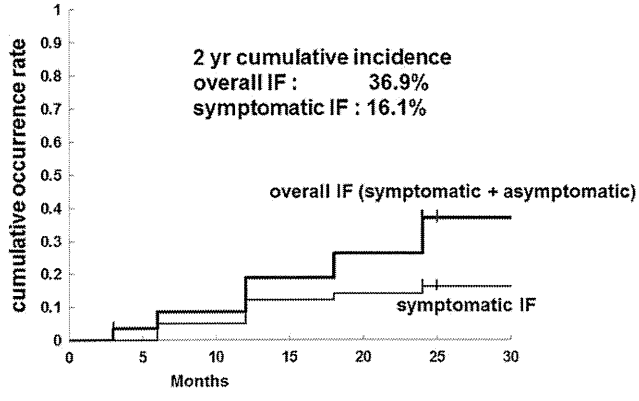

Fig. 2. Graph shows the overall incidence of both symptomatic and asymptomatic insufficiency fractures (IF) (thick line) and the incidence of symptomatic insufficiency fractures (thin line) after pelvic radiotherapy for cervical cancer.

The characteristics of irradiated patients can affect the incidence of IF. As revealed in our study, older patients receiving pelvic RT are more susceptible to the development of IF. In our study the incidence of IF at 2 years in patients aged >70 years was 52.8%, almost all the patients were elderly (the median age was 73 years), and all but 4 of the patients were postmenopausal. In the study by Ogino et al (6) all IF patients were postmenopausal, whereas in the study by Baxter et al (8) some of the patients were aged >65 years.

Our study showed that the SI joints are the most commonly involved site of pelvic IF, which agrees with the reports of several previous investigators (7, 9, 10). In our study most fractures were located at the SI joints; a solitary pubic bone fracture was seen in only 1 patient, and solitary acetabulum fracture was not seen. These findings indicated that initial mechanical failure of the sacrum causes other subsequent pelvic bone fracture (10, 13).

As has been reported by many investigators (2, 4, 6, 7, 13), our study showed that the symptoms of all patients were resolved after conservative management based on analgesics and rest. The extent of the lesions may correlate with the severity of symptoms. In the series reported by Blomlie et al (13), all patients without pain had smaller lesions (<1 cm^2) on MRI, and it was suggested that small fractures might not be painful. In our study symptomatic patients were more likely to have IF at multiple sites of pelvic bone (mean 2.7 sites) than asymptomatic patients (mean 1.7 sites).

The risk factors of osteoporosis are closely correlated with the development of IF (3, 6). Blomlie et al (13) showed that 95% of patients with IF reported in the literature were postmenopausal women. Ikushima et al (7) reported that the mean age of patients who developed IF was significantly higher than that of other patients (69 years vs 59 years, $P<.01$). Ogino et al (6) showed that low body weight (≤49 kg) and more than 3 deliveries were significant factors for the development of symptomatic IF. In our study, both low body weight (<50 kg) and older age (>70 years) were significant predisposing factors for IF in multivariate analysis. Many medical illnesses or medications, such as rheumatoid arthritis, hyperthyroidism, and corticosteroids, are also reported as risk factors for osteoporosis.

Table Risk factors associated with the development of IF

Variable	IF/n	*P* Univariate	*P* Multivariate
Age (y)		.004*	.007*
≤70	4/26		
>70	17/33		
Weight (kg)		.007*	.013*
<50	15/29		
≥50	6/30		
Stage		.347	.368
I	12/35		
II	9/24		
Simulation		.249	.271
X-ray	13/30		
CT	8/29		
Beam technique		.192	.211
AP/PA	15/35		
4-field	6/24		
Energy of X-ray		.928	.931
10 MV	14/40		
>10 MV	7/19		
Facilities		.932	.569
East	11/31		
West	10/28		

Abbreviations: AP/PA = anteroposterior/posteroanterior parallel opposing field; IF = insufficiency fracture.
* $P<.05$.

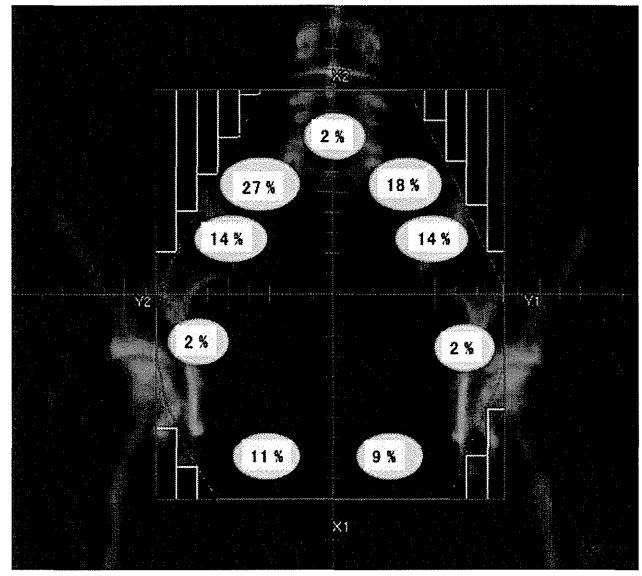

Fig. 3. Schematic shows the distribution of insufficiency fractures in our study population. Some patients had multiple fractures.

In our study, no patients had a history of either rheumatoid arthritis or hyperthyroidism.

It is well known that radiation toxicity is strongly correlated with irradiated volume and dose. In our study, both the 4-field box technique and the AP/PA parallel opposing technique were used. In the 4-field box technique, lateral portals could spare the irradiated volume of the small bowel and rectum and also spare the irradiated volume of the posterior portion of the sacrum and SI joints. Oh et al (9) reported that the incidence of IF was higher in patients receiving the AP/PA technique than in those receiving the 4-field box technique in univariate analysis. In our study there was no significant difference between the 2 techniques. However, in our study these techniques differed only until 20 Gy of EBRT, and the following 30 Gy of EBRT was administered through the same whole-pelvic field with MB.

Patients who received a higher irradiated dose to the pelvic bone had a greater risk of IF. In our study the external-beam doses of all 44 IF sites were estimated to have a median dose of 49 Gy, and the doses of 38 IF sites (86%) were estimated at >45 Gy. There might be a threshold dose for IF at approximately 45 Gy, as reported by Fu et al (16). Oh et al (9) reported that the risk factors of IF were receiving a higher dose (>50.4 Gy) and receiving curative RT. In our study all patients received 50 Gy by EBRT and received an additional dose of HDR-ICBT. Fu et al (16) calculated the contribution of the brachytherapy dose to the pelvic bone and estimated it to be approximately 10% of the central brachytherapy dose. It was uncertain whether this small additional dose of HDR-ICBT to the pelvic bones was one of the causes of the higher occurrence of IF in our study.

Concurrent chemoradiation therapy is used frequently in gynecologic cancer for increasing tumor control, but it is well known that it also increases radiation toxicity. Thus many investigators have thought that combination therapy with radiation and chemotherapy might increase the risk of IF, but there have been few studies to evaluate this (17). Jenkins et al (17) reported that combined treatment with radiation and chemotherapy might predispose to pelvic fracture in patients with cervical cancer.

Oh et al (9) suggested 2 approaches to reduce the risk of IF. The first approach is to improve the osseous environment by treatment of osteoporosis, and the second approach is to reduce radiation toxicity (9). Sambrook et al (18) reported that bisphosphonate has been used as an effective agent for treatment of osteoporosis, and Guise et al (19) reported that it has also been shown to be effective to reduce cancer-induced bone loss. Further study is required to determine whether it can reduce the risk of IF in patients with high-risk factors such as older age and lower body weight.

The irradiated volume and dose to the sacrum and SI joints might correlate with the risk of IF. Ogino et al (6) suggested that a multibeam arrangement by CT planning could shield the posterior portion of the sacrum and SI joints without inadequate coverage of the target volume. Intensity modulated radiation therapy (IMRT) can reduce the irradiated dose and volume of normal tissue (20). It may be difficult to achieve significant sparing to reduce the risk of IF because of its proximity to the target volume; however, bone-sparing IMRT may reduce the radiation dose to the pelvic bones and result in a decrease in the occurrence of IF.

There were some limitations to our study. First, we could not evaluate the presence and severity of osteoporosis in patients before treatment. This might have led to under- or overestimation of the true prevalence of pelvic IF.

Second, we did not obtain a short-time-inversion-recovery (STIR) sequence on MRI. Blomlie et al (13) reported that STIR imaging may be the best sequence for visualizing insufficiency fractures, but we did not use this technique because STIR imaging does not provide good contrast between gynecologic organs and the surrounding tissues.

Third, there is no histologic proof that a pelvic IF is indeed just that and not a pathologic fracture within a metastatic or other bone

lesion. However, many investigators (10-13) have emphasized that an appropriate reading of CT, MRI, and/or bone scan is able to definitively diagnose IF. And some investigators (10) have reported that biopsy of a lesion is not recommended because of the high probability of fracture and low diagnostic efficiency.

In conclusion, the development of IF is not a rare complication of standard pelvic RT for cervical cancer, especially in elderly women with low body weight. If patients complain of pelvic pain after pelvic RT for gynecologic malignancies, pelvic IF must be considered in the differential diagnosis. The symptoms of most patients are resolved after conservative management based on analgesics and rest. Knowledge of the IF is useful to rule out bone metastases and thus avoid inappropriate treatment. We plan to conduct a further prospective study in such patients to evaluate whether treatment of osteoporosis using bisphosphonate or sparing bones by using IMRT can decrease the risk of development of IF.

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Japanese structure survey of radiation oncology in 2009 based on institutional stratification of the Patterns of Care Study

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The ongoing structure of radiation oncology in Japan in terms of equipment, personnel, patient load and geographic distribution was evaluated in order to radiation identify and improve any deficiencies. A questionnaire-based national structure survey was conducted from March 2010 to January 2011 by the Japanese Society for Therapeutic Radiology and Oncology (JASTRO). These data were analyzed in terms of the institutional stratification of the Patterns of Care Study (PCS). The total numbers of new cancer patients and total of cancer patients (new and repeat) treated with radiation in 2009 were estimated at 201,000 and 240,000, respectively. The type and numbers of systems in actual use consisted of Linac (816), telecobalt (9), Gamma Knife (46), ^{60}Co remote afterloading system (RALS) (29) and ^{192}Ir RALS systems (130). The Linac systems used dual energy function for 586 (71.8%), 3DCRT for 663 (81.3%) and IMRT for 337 units (41.3%). There were 529 JASTRO-certified radiation oncologists (ROs), 939.4 full-time equivalent (FTE) ROs, 113.1 FTE medical physicists and 1836 FTE radiation therapists. The frequency of interstitial radiation therapy use for prostate and of intensity-modulated radiotherapy increased significantly. PCS stratification can clearly identify the maturity of structures based on their academic nature and caseload. Geographically, the more JASTRO-certified physicians there were in a given area, the more radiation therapy tended to be used for cancer patients. In conclusion, the Japanese structure has clearly improved during the past 19 years in terms of equipment and its use, although a shortage of manpower and variations in maturity disclosed by PCS stratification remained problematic in 2009.

Keywords: Structure survey; radiotherapy facility; radiotherapy personnel; radiotherapy equipment; caseload

INTRODUCTION

The medical care systems of the USA and Japan have very different backgrounds. In 1990, the Patterns of Care Study (PCS) conducted a survey of the structure of radiation oncology facilities in 1989 for the entire census of facilities in the USA [1]. In 1991, the Japanese Society for Therapeutic Radiation Oncology (JASTRO) conducted the first national survey of the structure of radiation therapy facilities in Japan based on their status in 1990, and the results were reported by Tsunemoto *et al.* [2]. The first comparison of these two national structure surveys to illustrate and identify similarities and differences in 1989–90 was conducted by the author and reported in 1996 [3]. The resultant international exchange of information proved especially valuable for Japan, where the structure of radiation oncology could be improved on the basis of those data.

The Japanese structure has gradually changed since a greater number of cancer patients are treated with radiation and public awareness of the importance of radiotherapy (RT) has grown. JASTRO has conducted national structure surveys every two years since 1990 [2] and every year since 2011. Furthermore, in 2006 the Cancer Control Act was approved in Japan, which strongly advocates the promotion of RT and an increase in the number of radiation oncologists (ROs) and medical physicists. The Japanese Ministry of Education, Sciences and Sports is supporting the education of these specialists at university medical hospitals. The findings of international comparisons and the consecutive structural data gathered and published by JASTRO have been useful for an understanding of our current position and future direction [4–7]. In this report, the recent structure of radiation oncology in Japan is analyzed and compared with the data of 2007 [6].

MATERIALS AND METHODS

From March 2010 to January 2011, JASTRO conducted a questionnaire based on the national structure survey of radiation oncology in 2009. The questionnaire dealt with the number of treatment systems by type, number of personnel by category and number of patients by type, site and treatment modality. To measure variables over a longer period of time, data for the calendar year 2009 were also requested. The response rate was 700 out of 770 (90.6%) of active facilities. The data from 241 institutions (31.3%) were also registered in the International Directory of Radiotherapy Centres (DIRAC) in Vienna, Austria in 2011.

The PCS was introduced in Japan in 1996 [8–17]. The Japanese PCS employed methods similar to those of the American version, which used structural stratification to analyze national averages for the data for each survey item by means of two-stage cluster sampling. For the regular structure survey, RT facilities throughout the country were stratified into four categories. This stratification was based on academic conditions and the annual number of patients treated with radiation at each institution, because academic institutions require and have access to more resources for education and training, while the annual caseload also constitutes essential information related to structure. For the study reported here, the following institutional stratification was used. A1: university hospitals/cancer centers treating 462 patients or more per year; A2: the same type of institutions treating 461 patients or fewer per year; B1: other national/public hospitals treating 158 patients or more per year; and B2: other national hospital/public hospitals treating 157 patients or fewer per year.

SAS 8.02 (SAS Institute Inc., Cary, NC, USA) [18] was used for statistical analyses and statistical significance was tested by means of the chi-squared test, Student's *t*-test or analysis of variance (ANOVA).

RESULTS

Current situation of radiation oncology in Japan

Table 1 shows that the numbers of new patients and total patients (new plus repeat) undergoing radiation in 2009 were estimated at 201 000 and 240 000, respectively, showing a 11.0% increase over 2007 [6], with 40% of the patients being treated at academic institutions (categories A1 and A2), even though these academic institutions constituted only 20% of the 700 radiotherapy facilities nationwide.

Cancer incidence in Japan in 2009 was estimated at 724 426 cases [19] with approximately 27.6% of all newly diagnosed patients treated with radiation. This number and corresponding rate have increased steadily over the last 19 years and is expected to increase further [14]. In 1990, the rate was estimated to be approximately 15% [3], and it was 16% in 1995, 17% in 1997, 20% in 1999, 22% in 2001, 23.3% in 2003 [4], 24.5% in 2005 [5], 26.1% in 2007 [6] and 27.6% in 2009.

Facility and equipment distribution patterns

Table 2 shows an overview of RT equipment and related functions. There were 816 Linac, 46 Gamma Knife, 29 ^{60}Co remote afterloading system (RALS), 130 ^{192}Ir and 1 ^{137}Cs RALS systems in actual use, as well as 9 of the 15 telecobalt systems installed. The Linac systems used dual energy function for 586 (71.8%), 3D conformal radiation therapy (3DCRT) for 663 (81.3%) and intensity-modulated radiation therapy (IMRT) for 337 units (41.3%). The IMRT function was employed more frequently for the equipment of academic institutions (A1: 73.4% and A2: 49.5%) than that of non-academic institutions (B1: 42.3% and B2: 18.1%). However, 3DCRT functions were disseminated widely in both academic and non-academic institutions, with 69% even in B2 institutions. The use of image-guided radiation