The progression of radiation-induced damage is the result of an early activation of an inflammatory reaction leading to the expression and maintenance of an elevated cytokine cascade [12]. Kong *et al.* [13] concluded that blood biomarkers such as transforming growth factor (TGF)-beta1, interleukin (IL)-6, krebs von den Lungen-6 (KL-6), surfactant proteins (SP), and IL-1ra could accurately predict radiation-induced lung damage. Serum KL-6 and SP-D were also evaluated as predictive biomarlers for radiation pneumonitis (RP) in this study.

For normal tissues, the use of a single dose rather than a conventional fractionated dose can increase the risk of complications. However, few cases with severe toxicity have been reported [14-16]. In the current study, cases of severe RP (grades 4-5) that received SBRT for lung tumors in our institution were evaluated. In our previous report [17], the overall incidence rate of grades 2-5 RP was 29% (7/25 cases) and three patients (12%) died from RP from May 2004 to April 2006 at the median follow-up time of 18 months after completing SBRT. A significant decrease of the incidence rate of severe RP was observed for the period entering into 2006. The purpose of this study was to determine the risk factors of severe RP after SBRT for primary or secondary lung tumors.

Methods and materials

Subjects

From January 2003 to March 2009, SBRT was performed on 117 patients with lung tumors in our institution. SBRT was performed for primary lung cancers in 74 cases (63%) and for metastatic or recurrent lung tumors in 43 cases (37%) (Table 1). These consecutive 117 patients were evaluated retrospectively. There were 98 males and 19 females, and the median age was 72 years (range; 28-84 years). Thirteen patients (11%) had a shadow of interstitial pneumonitis (IP) in the CT before SBRT, 23 patients (20%) had high serum KL-6 value, and 19 patients (16%) had high SP-D value. The upper limit of serum KL-6 and SP-D was defined as 500.0 U/mL and 110.0 ng/mL, respectively.

Table 1: Characteristics of the tumor

Subject	N	(%)
Biopsy proved primary lung cancer	60	51
cT1N0M0	39	33
cT2N0M0	19	16
the others	2	2
Unconfirmed histology (suspected of primary lung cancer)	14	12
Metastatic or recurrent lung cancer	43	37
Total	117	100

All patients enrolled in this study satisfied the following eligibility criteria: a) solitary or double lung tumors; b) tumor diameter < 40 mm; c) no evidence of regional lymph node metastasis; d) Karnofsky performance status scale > or = 80%; and e) tumor not located adjacent to major bronchus, esophagus, spinal cord, or great vessels. Patients with an active malignant lesion other than lung were excluded. Therefore, no chemotherapy was combined with SBRT. There were 32 patients (27%) who were treated before 2005. After 2006, patients with a high risk for RP who had an obvious IP shadow on CT with a 3-mm slice before SBRT together with a high value of serum KL-6 & SP-D were excluded from receiving SBRT.

In the high resolution chest CT, IP shadow was defined as a mandatory observation beneath the pleura and a honeycomb lung. IP shadows were graded by their radiographically estimated total lung volume as follows: slight, less than 10%; moderate, 10-50%; and severe, >50%.

Planning procedure and treatment

The treatment methods which included the definition of the internal target volume (ITV) were performed according to JCOG 0403 phase II protocol [2,3]. The following gives a brief description of the treatment methods, which were described in detail in our previous report [17]. SBRT was performed daily with a central dose of 48 Gy in four fractions over 4-8 days. Each CT slice was scanned with an acquisition time of four seconds to include the whole phase of one respiratory cycle. The axial CT images were transferred to a 3-dimension RT treatment-planning machine (Pinnacle3, New Version 7.4i, Philips). Spicula formation and pleural indentation were included within the ITV. The mediastinal lymph nodes were not included from the irradiation field. The setup margin (SM) between ITV and the planning target volume (PTV) was 5 mm in all directions. There was an additional 5 mm leaf margin to PTV, according to JCOG0403 protocol, in order to make the dose distribution within the PTV more homogeneous. No pairs of parallel opposing fields were used. The target reference point dose was defined at the isocenter of the beam. The iso-dose distribution of an SBRT treatment was shown in Figures 123.

The dose limitation for pulmonary parenchyma was mean lung dose (MLD) < 18.0 Gy, percentage of total lung volume receiving greater than or equal to 20 Gy (V20) < 20%, and V15 < 25% according to JCOG0403 protocol.

Radiation method

SBRT was given in at least 8 ports by linear accelerator (Elekta Synergy System, Elekta Ltd, Crawley, UK) after the Synergy system was available in our institution from February 2007. At least eight beams (I-rotation angle was 0 degree only in two beams) were used. CT verification of

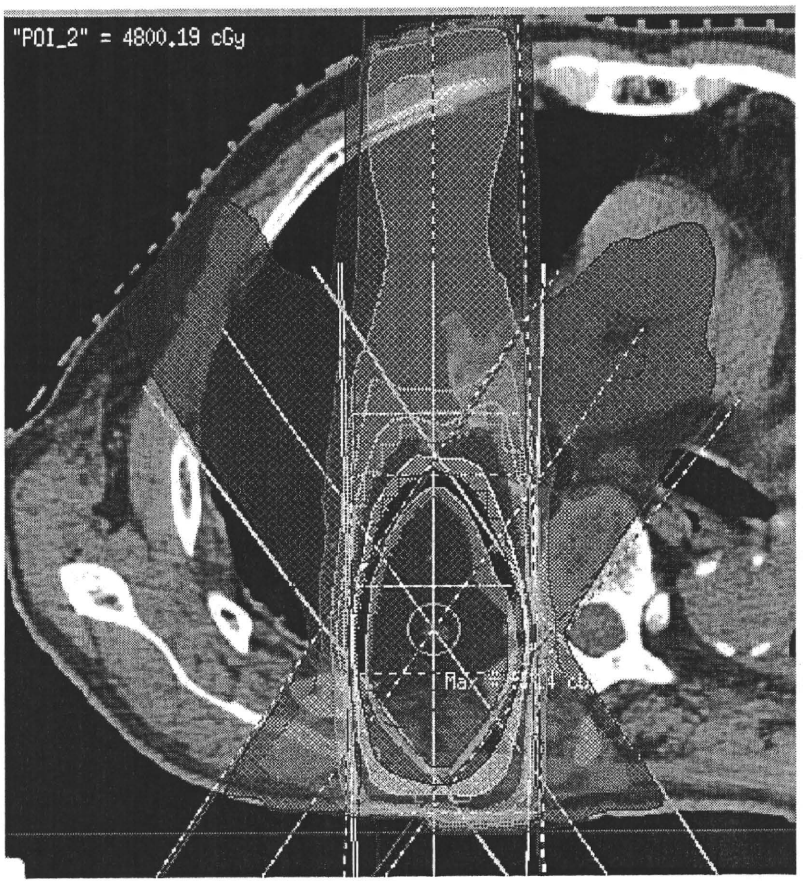

Figure 1 An example of dose distribution of SBRT (Pt. No. 5).

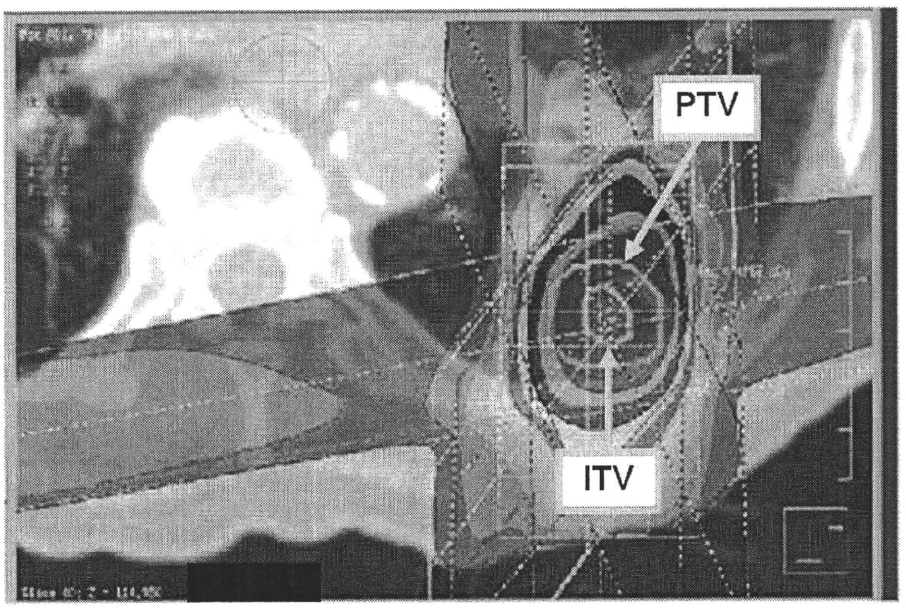

Figure 2 An example of dose distribution of SBRT (Pt. No. 7).

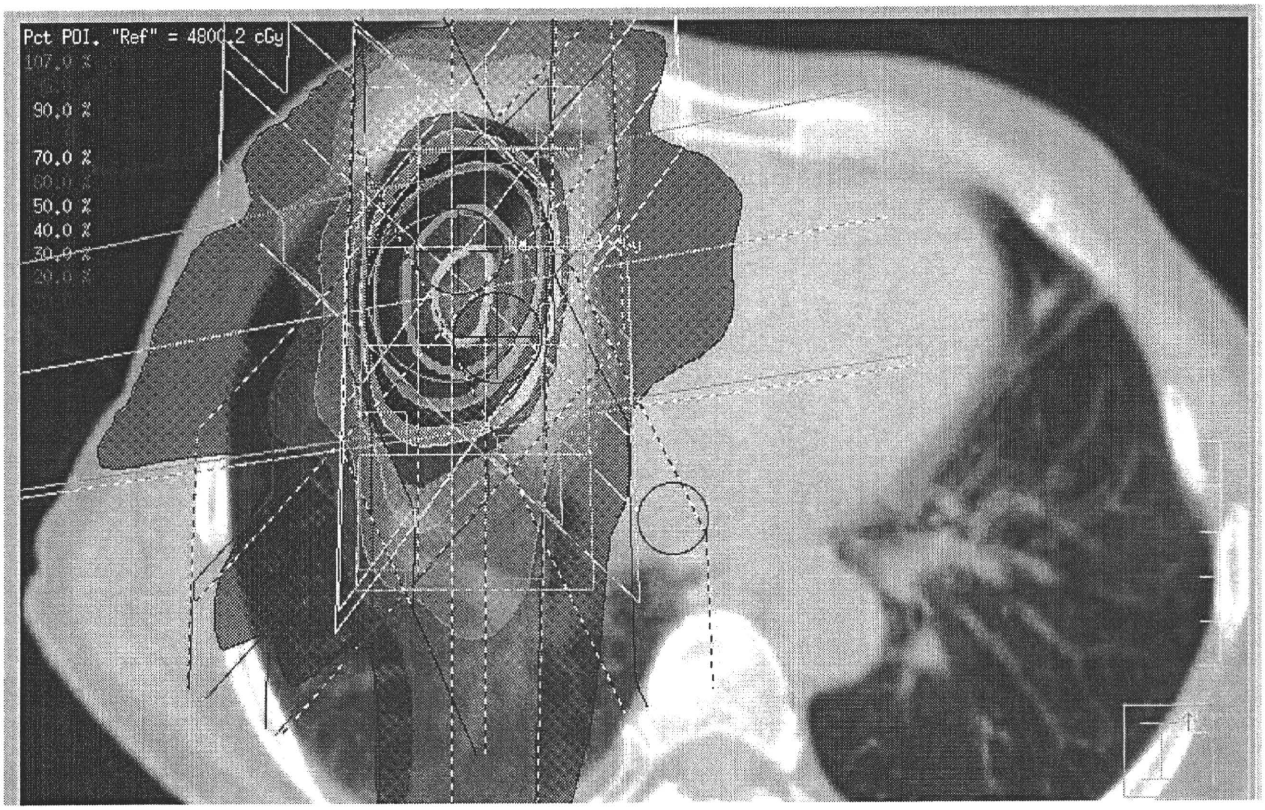

Figure 3 An example of dose distribution of SBRT (Pt. No. 8).

the target isocenter was performed before each treatment session using a kilovoltage-based cone-beam CT (CBCT) unit in the same room and in a treatment position. The Linac machine was Elekta Synergy with the cone-beam CT. The details of the radiation method before 2007 were described in our previous report [17]. The collapsed cone (CC) convolution method in Pinnacle^3 was used as the heterogeneous correction method for lung. The breathing suppression was done with a body frame and an abdominal pressure board (Figure 4).

Definition of RP grading

The toxicity data were collected retrospectively from the patient files. Basically, the RP grading system used followed the Common Terminology Criteria for Adverse Events (CTCAE) v3.0, and the grades were as follows: Grade 1, asymptomatic (radiographic findings only); Grade 2, radiographic findings plus symptomatic and not interfering with activities of daily living (ADL); Grade 3, radiographic findings plus symptomatic and interfering with ADL or O2 indicated; Grade 4, radiographic findings plus life-threatening (ventilatory support indicated), and Grade 5, radiographic findings plus death. Patients with mild pulmonary CT changes after SBRT were categorized as Grade 1. The radiographic findings common to the 5 grades were (a) shadow distribution just beneath pleura, (b) honeycomb lung, (c) traction bronchitis/dilation of small bronchus, (d) ground-glass opacity (GGO), or (e) infiltrative shadow (consolidation), which was not recognized in the CT before SBRT.

Follow-up

CT exams with 3-mm slices were performed at 2, 4, 6, 9, 12, 15, 18, and 24 months after SBRT for asymptomatic

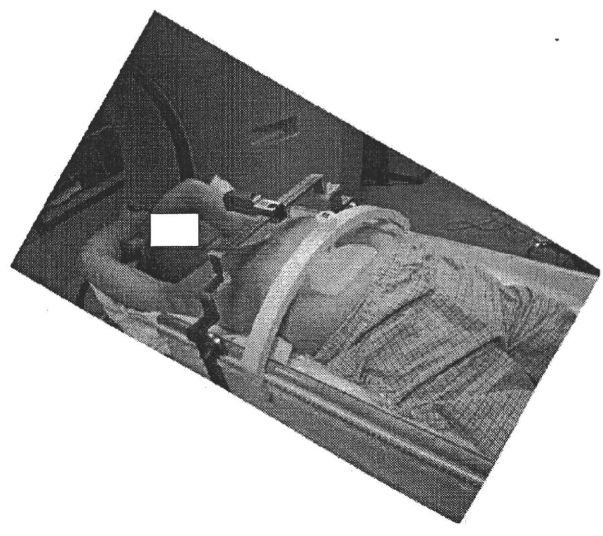

Figure 4 Body frame and abdominal pressure board.

Table 2: Characteristics of nine patients with G4-5 of RP

Case No.	s KL-6	S SP-D	IP shadow	RP grading	Onset time	State	V20 (%)	V40 (%)	MLD (cGy)	Stage	PTV (cc)	D95 (Gy)	Location	
1	950	286	moderate	5	3.0 Mo	Postoperative	6.7	2.7	938	IV	26.4	46.29	Lt	hilum
2	582	95	slight	5	2.0 Mo	Fresh	7.6	1.9	568	IA	47.5	45.57	Lt	hilum
3	852	136	severe	5	6.0 Mo	Postoperative	11.2	4.6	791	IV	120.9	45.00	Rt	S6
4	1590	NA	slight	5	6.0 Mo	Fresh	5.6	1.9	426	IA	29.4	44.05	Rt	S10
5	NA	NA	(-)	4	0.4 Mo	Fresh	5.0	1.5	291	IA	42.5	47.80	Lt	S8
6	289	101	slight	5	5.9 Mo	Fresh	7.0	2.0	440	IA	56.5	48.90	Rt	S10
7	497	321	(-)	4	4.0 Mo	Postoperative	2.6	0.9	269	IV	7.7	45.48	Lt	S10
8	833	135	slight	5	2.1 Mo	Fresh	6.3	2.3	492	IA	20.9	47.62	Rt	S5
9	883	235	slight	5	1.0 Mo	Fresh	3.7	0.7	288	IB	23.9	44.80	Rt	S2
	(0-500)	(0-110)												

Abbreviation; NA = not available

patients. Additionally, on the same day as CT, serum KL-6, SP-D, white blood cell (WBC), lactate dehydrogenase (LDH), C-reactive protein (CRP), and tumor markers were measured in the blood plus an oxygen saturation was measured from a fingertip.

Statistical Analysis

The relationship between G4-5 RP and pre-SBRT factors was compared with the X^2 test. The cumulative probability of RP was calculated and drawn applying the 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 version 5.0 StatView software (SAS Institute, Cary, NC).

Results

The median follow up time for all 117 patients was 14.7 months (range; 0.3-76.2 months). The control rate within the radiation field was 86.3% (101/117 cases).

RP of grade 4 or higher was observed in nine patients (7.7%) and the median time of showing symptoms was 4.0 months (range; 0.4-6.0 months) (Table 2). All of these nine RPs were due to acute exacerbation of IP (Figures 5678910) and steroid pulse therapy combined with an oral anti-pneumocystis carinii drug was administered to these patients. Grade 4 RP with intubation was seen in two cases and the other seven cases were grade 5. Grade 3 RP was seen in two patients during this time period. Grade 4 or higher RP was noted in six out of 32 patients (18.8%) before 2005 and in only three out of 85 patients (3.5%) after 2006 (Figure 11). This difference had a statistical significance (log-rank $p = 0.042$ and X^2 $p = 0.018$).

Serum KL-6 was determined in 8 of the 9 patients with grades 4-5 RP and in 95 of the 108 patients with grades 0-3 RP. Of the 8 patients with grades 4-5 RP, serum KL-6 (U/mL) was elevated in 6 patients (75%) (Table 2). Serum SP-D was determined in 7 patients with grades 4-5 RP and in 93 patients with grades 0-3 RP. Of the 7 patients with grades 4-5 RP, serum SP-D (ng/mL) was evaluated in 5 patients (71%) (Table 2). Additionally, the IP shadow was seen in seven cases (78%) in the CT before SBRT within or outside of radiation field. The radiation dose prescribed was within the protocol in all 117 patients. The appearance of grades 4-5 RP and serum KL-6 value (1-year cumulative incidence; 32% vs. 3% and log-rank $p < 0.0001$ & X2 $p = 0.0002$), SP-D value (1-year; 29% vs. 3% and log-rank $p = 0.0001$ & X2 $p = 0.0002$), or IP shadow in CT before SBRT (1-year; 57% vs. 2% and log-rank p <

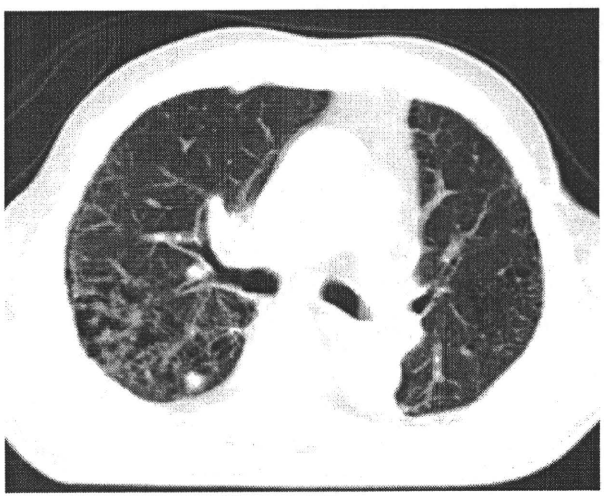

Figure 5 CT images before SBRT (Pt. No. 5).

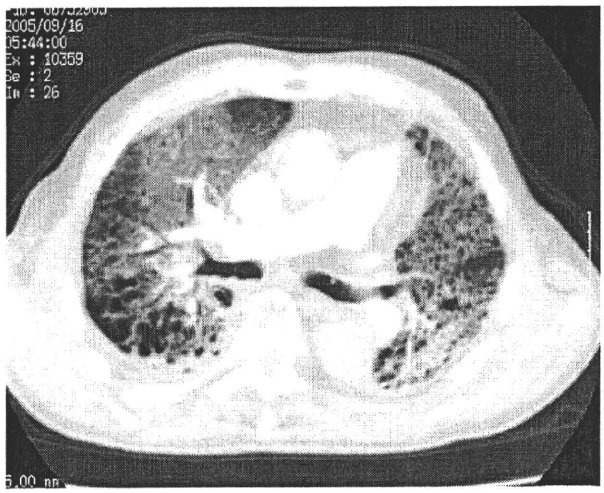

Figure 6 CT images of radiation pneumonitis after SBRT (Pt. No. 5). The finding was acute exacerbation of IP.

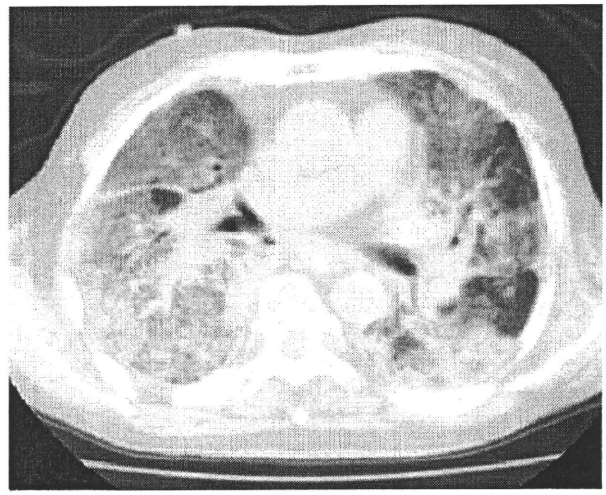

Figure 8 CT images of radiation pneumonitis (acute exacerbation of IP) after SBRT (Pt. No. 7).

0.0001 & X2 p < 0.0001) showed positive correlations (Table 3).

The risk factors of RP other than serum KL-6, SP-D, and IP shadow in CT are shown in Table 4. The mean PTV for nine patients with severe RP was 29.4 cc (range: 7.7-120.9 cc) and was 42.5 cc (range: 7.5-239.4 cc) of for the other low-grade RP patients. None of these risk factors were different for those patients with and without grades 4-5 RP.

Discussion

This was a retrospective study to evaluate the incidence rate and risk factors of severe RP after SBRT for primary (74 patients), metastatic and recurrent (43 patients) lung tumors. Grades 4-5 RP were noted in 9 patients (7.7%); IP shadow in the CT, and high serum KL-6 & SP-D values before SBRT showed positive correlations with grades 4-5 RP. Seven of the 117cases (6.0%) were of grade 5 in our institution. After 2006, severe grades 4-5 RP were significantly reduced.

According to Borst *et al.* [15], the crude incidence rate of grade 2 RP was 10.9% for the SBRT on 128 patients with malignant pulmonary lesions who were treated with 6-12 Gy per fraction with a median MLD of 6.4 Gy (range: 1.5-26.5 Gy). According to Rusthoven *et al.* [16], grades 2-3 RP was rare, occurring in only one out of 38 patients (2.6%) with one to three lung metastases after SBRT of 48-60 Gy in 3 fractions. They used the dose con-

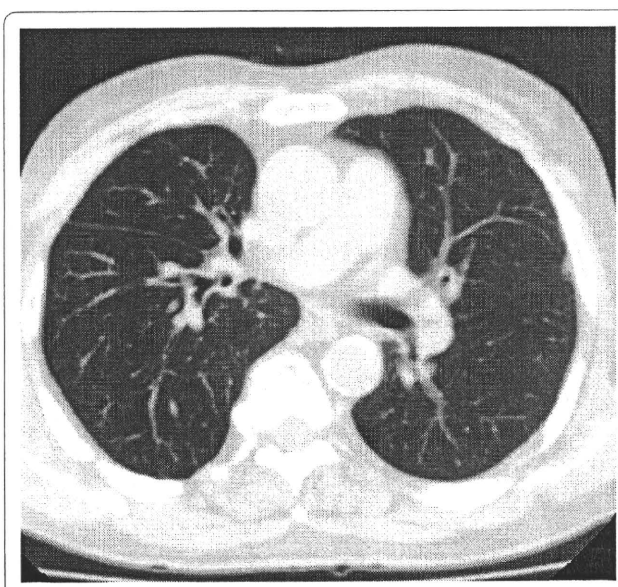

Figure 7 CT images before SBRT (Pt. No. 7).

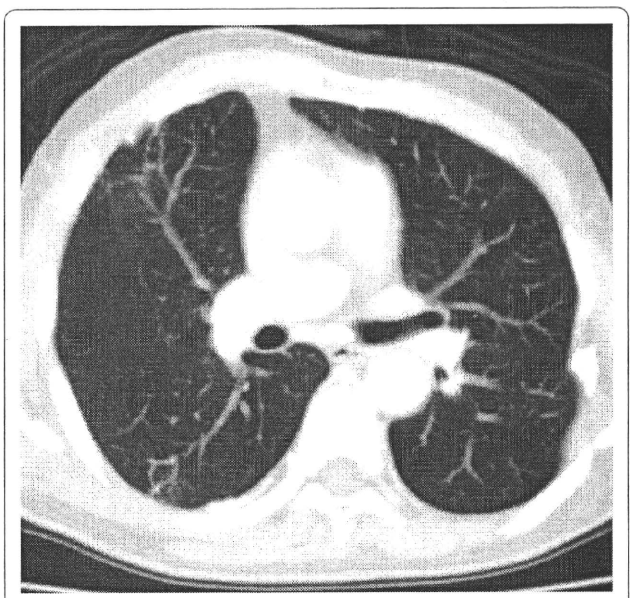

Figure 9 CT images before SBRT (Pt. No. 8).

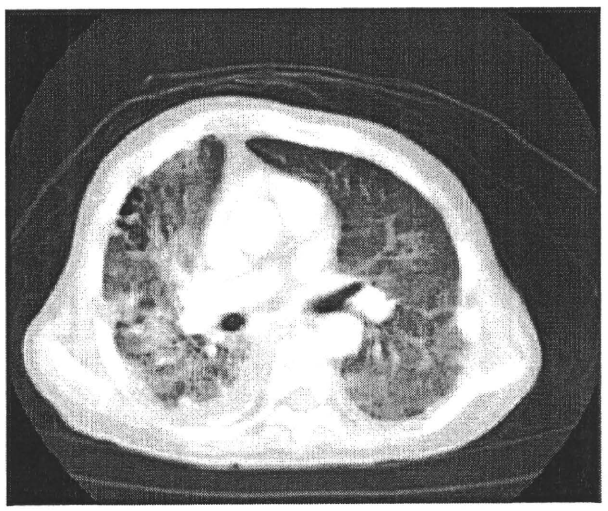

Figure 10 CT images of radiation pneumonitis (acute exacerbation of IP) after SBRT (Pt. No. 8).

straint of V15 < 35%. According to Nagata *et al.* [1], no severe symptomatic pulmonary complications (NCICTC Grade 3 or larger) were encountered. Timmerman *et al.* [14] reported in 2006 that a SBRT treatment dose of 60-66 Gy total in three fractions was administered during 1 to 2 weeks for 70 patients with clinically staged T1-2N0M0 (tumor size < or = 7 cm) biopsy-confirmed non-small cell lung cancer (NSCLC). This resulted in toxicity of grades 3 to 5 in a total of 14 patients (20%) and grade 5 was seen in four patients (5.7%). Le QT *et al.* [18] reported in 2006 that after single-fraction SBRT (15-30 Gy) was performed for 32 patients (21 NSCLC and 11 metastatic tumors), two patients (6%) suffered from RP of grade 5.

Moreover, according to Rusthoven *et al.* [16], patients were required to have adequate lung function, which was defined as stable arterial hemoglobin saturation above 90% with minimal exertion, forced expiratory volume (FEV) of 1.0% higher than the predicted value of 40% or more than 1 L and carbon monoxide diffusing capacity (DLCO) higher than the predicted 40% value. In our institution, the exclusion criteria of SBRT consisted of an FEV of 1.0% at less than 750 mL, and an obvious IP shadow on the roentgen examination according to JCOG 0403 protocol.

RP of grades 4-5 occurred in six out of 32 patients (18.8%) before 2005 and in only three out of 85 patients (3.5%) after 2006 (Figure 11). The significant reduction of severe grades 4-5 RP after 2006 in our institution is believed to be due to the selection of appropriate patients. After 2006, patients were excluded from SBRT if they had an obvious IP shadow on the CT-scan (slice thickness 3.0 mm), and if serum KL-6 and SP-D levels were high. All of the severe RP cases in our institution consisted of acute exacerbation of IP outspreading over the radiation field. Admittedly, these nine patients with severe RP represent a small sample. Whether our results are a coincidence that biomarkers and CT shadows are indeed significantly different in patients with grades 4-5 toxicity compared to patients without RP awaits confirmation in further studies.

KL-6 is the indicator that specificity is high for IP and is clinically evaluated for the purpose of diagnosing IP. In addition, KL-6 is important as an index of the activity of IP because it becomes significantly high for IP with activ-

Table 3: Relationship between G4-5 RP and pre-SBRT factors

Pre-SBRT factors	G4-5 RP	G0-3 RP	Total	X2 test	1-year cumulative incidence of G4-5 RP	log-rank
Serum KL-6						
high value	6	17	23	$p = 0.0002$	32%	$p < 0.0001$
within normal level	2	78	80		3%	
not available	1	13	14			
Serum SP-D						
high value	5	14	19	$p = 0.0002$	29%	$p = 0.0001$
within normal level	2	79	81		3%	
not available	2	15	17			
IP shadow in CT						
(+)	7	6	13	$p < 0.0001$	57%	$p < 0.0001$
(-)	2	102	104		2%	

Table 4: Risk factors of severe RP

	Patients with G4-5 RP	Patients without G4-5 RP	*p* value
Total	9 (8%)	108 (92%)	
Patient specific factors			
Pulmonary function			
VC (L)			
mean +/- SD	3.27 +/- 0.65	2.75 +/- 0.85	*N.S.*
range	2.76-4.01	1.54-4.07	
FEV 1.0 (L)			
mean +/- SD	2.11 +/- 0.68	1.87 +/- 0.82	*N.S.*
range	1.59-3.24	0.59-3.24	
K-PS (%)			
90	5 (56%)	52 (48%)	*N.S.*
80	4 (44%)	56 (52%)	
Age (y)			
mean +/- SD	73.3 +/- 6.8	70.1 +/- 14.1	*N.S.*
range	68-80	24-93	
COPD			
With	2 (22%)	22 (20%)	*N.S.*
Without	8 (78%)	86 (80%)	
Treatment specific factors			
Size of the PTV (cc)			
mean +/- SD	29.4 +/- 33.2	42.5 +/- 13.7	*N.S.*
range	7.7-120.9	7.5-239.4	
Mean lung dose (Gy)			
mean +/- SD	5.0 +/- 2.3	4.2 +/- 1.4	*N.S.*
range	2.7-9.4	1.7-7.9	
Lung V20 (%)			
mean +/- SD	5.9 +/- 2.7	5.8 +/- 2.6	*N.S.*
range	2.6-11.2	1.0-11.0	
Target location			
Central	2 (22%)	17 (16%)	*N.S.*
Peripheral	7 (78%)	91 (84%)	

Abbreviation:
COPD = chronic obstructive pulmonary diseases
RP = radiation pneumonitis
G4-5 = grades 4-5
PTV = planning target vlume
FEV = Forced expiratory volume
K-PS = Karnofsky Performance status
N.S. = not significant

ity. In the human body, KL-6 does not develop in a type I alveolus epithelial cell. However, KL-6 develops in a type II alveolus epithelial cell, in a bronchial epithelial cell, and in a bronchus gland cell. The expression of KL-6 increases in the hyperplasia of the type II of alveolus epithelial cell in IP. A small quantity of KL-6 is present in the liquid coating the alveolus in normal lungs, and its density increases during hyperplasia of the type II alveolus epithelial cell for IP. In addition, because inflammation occurs, blood vessel permeability rises, and KL-6 in the

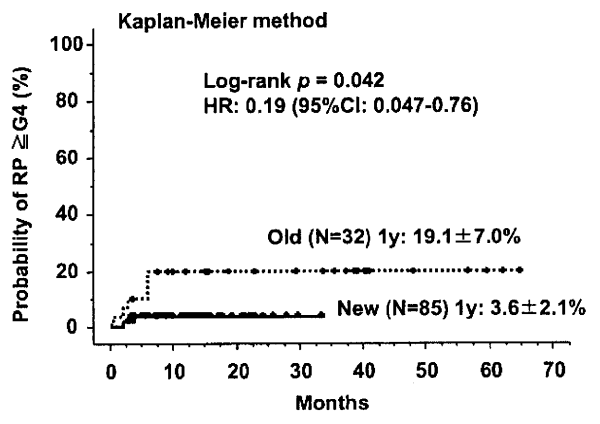

Figure 11 Cumulative probability curves of severe radiation pneumonitis of grades 4-5 divided by pre-2005 (old group) and post-2006 (new group).

alveolus coating liquid shifts easily into the blood. As a result, KL-6 in the blood rises in the IP. When an injury to the lung stroma is evaluated, KL-6, SP-A, SP-D, and MCP-1 are examined. Of these, there is a report that KL-6 was highest in both sensitivity (93.9%) and specificity (96.3%) [19]. Furthermore, SP-D levels at 50 to 60 Gy (midway during radiation therapy) showed greater sensitivity and positive predictive values for RP detection (74% and 68%, respectively) than SP-A (26% and 21%, respectively) [20].

Conclusion

The frequency of severe RP in our institution has recently shown a decrease, by prescreening patients for serum KL-6 and SP-D as biomarkers of severe RP. When SBRT was performed on patients presenting with an IP shadow in CT and a high value of serum KL-6 before treatment, severe radiation pneumonitis occurred at a high rate. Therefore, pre-screening of patients before SBRT appears to be a useful strategy in treating lung tumors.

Authors' contributions

HY collected and analyzed data and performed statistical analysis. HY and SK-S drafted the manuscript. AT, KO, AH, and RW reviewed the data and revised the manuscript. KO and KN designed the study and revised the final version. All authors have read and approved the final version of the manuscript.

Competing interests

The authors declare that they have no competing interests.

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Advanced age is a significant determinant of poor prognosis in patients treated with surgery plus postoperative radiotherapy for endometrial cancer

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Abstract

Aim: A review was conducted in which the effect of age on survival was assessed in a population of endometrial cancer patients treated with surgery and adjuvant radiation therapy in our institution.

Methods: From 1988 to 2008, 111 endometrial cancer patients underwent total abdominal hysterectomy and adjuvant whole pelvic radiation therapy (RT). After surgery, for patients with low or intermediate risk without lymph node metastasis, no postoperative adjuvant therapy was performed. For patients with high risk or positive cytology from the abdominal cavity, postoperative radiation therapy was performed. A total dose of 50–50.4 Gy of RT was delivered sequentially. Forty-four patients (44%) were given chemotherapy consisting of epirubicin/cisplatin/carboplatin or paclitaxel/carboplatin. Univariate and multivariate analyses were performed to identify significant prognostic clinicopathological factors.

Results: With a median follow-up time of 59.2 months, the 5-year overall survival was 74% for those 60 years or older versus 90% for those younger than 60 years ($P = 0.044$). For disease-free survival, it was 65% for those 60 years or older, versus 85% for those younger than 60 years ($P = 0.013$). On multivariate analysis, poor disease-free survival was associated with age $\geq$ 60 years ($P = 0.035$).

Conclusions: Older patients (age $\geq$ 60 years) with endometrial cancer had significantly lower overall survival and disease-free survival following postoperative RT independent of other prognostic factors and/or treatment technique.

Key words: age, endometrial carcinoma, prognostic factors, radiation therapy, treatment.

Introduction

The preponderance of data in the literature indicates that advanced age is a predictor of poor outcome in patients with endometrial carcinoma.[1–4] Whether the poor outcome among elderly patients can be accounted for entirely by a more advanced stage at the time of diagnosis, staging, treatment or that endometrial carcinoma among the elderly is intrinsically more aggressive than in younger patients remains to be determined.[5,6] In general, older patients with endometrial carcinoma tend to have deep myometrial invasion, poorly differentiated histology, or extra-uterine spread.[7,8] Consequently, the perception of a negative influence of advanced age on outcome was prevalent even in patients who underwent full surgical staging or those with well- to moderately differentiated tumors.[2,9]

Poor outcome in some of the published reports may be attributed to the less aggressive adjuvant therapy (i.e. radiation therapy), offered to elderly patients.[6] This

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is conceivably a valid argument, especially when dealing with elderly patients who are less likely than younger patients to consent to and tolerate recommended adjuvant therapy in general.[10,11] According to Alekitar *et al.*,[12] even when treated in a similar fashion, endometrial carcinoma patients aged ≥ 70 years appeared to fare worse than younger patients independent of other prognostic factors, thus mandating further improvement in their treatment strategies. Therefore, to determine whether advanced age is an intrinsically poor prognostic factor or whether it is due to less aggressive adjuvant therapy, a comparison was made of the outcomes according to age in a group of patients who all received adjuvant radiation therapy.

Methods

Patients

A total of 111 consecutive endometrial cancer patients were treated with postoperative radiation therapy in our institution between October 1988 and January 2008. All patients were followed in detail and evaluated. This was a retrospective study in a single institution.

In this study, several categories of risk were defined as follows:

1 Intermediate–low risk ($n = 2$, 2%): Stage IA + histological International Federation of Gynecology and Obstetrics (FIGO) grade 3, Stage IB + grade 2, and Stage IIA + grade 1–2 + <50% myometrial invasion (MI)
2 Intermediate–high risk ($n = 30$, 28%): Stage IB + grade 3, Stage IIA + grade 3 + <50% MI, Stage IC + grade 1–2, Stage IIA + grade 1–2 + ≥50% MI, or lymph vascular space invasion or 1/3 above + age ≥70, 2/3 above + age <50–69, or 3/3 above + age <50
3 High risk ($n = 76$, 70%): Stage IC + grade 3, Stage IIA + grade 3 + ≤50% MI, Stage IIB + any grade, or uterine papillary serous carcinoma or clear cell carcinoma, or Stage III–IV.

Basically, simple total abdominal hysterectomy (TAH), bilateral salpingo-oophorectomy (BSO), pelvic lymphadenectomy (PLA), para-aortic lymphadenectomy (PALA), and peritoneal washing cytology (PWC) were applied for the endometrial cancer patients with stage I or II where the disease was confined to the uterine body. Abdominal radical hysterectomy (ARH) or modified radical hysterectomy (mRH) was carried out in place of TAH for the patients with clinically obvious interstitial infiltration. TAH was performed in 12 cases (11%) and RH in the other cases (89%) including mRH for eight cases (7%). PLA was performed in 98 cases (88%), PALA in 92 cases (83%), and bilateral and ipsilateral SO in 60 (54%) and six cases (5%) in this study.

After surgery, for patients with low or intermediate risk without lymph node metastasis, no postoperative adjuvant therapy was performed. For patients with high risk or positive cytology from the abdominal cavity, postoperative radiation therapy (PORT) was performed.

Postoperative chemotherapy

For patients with lymph node metastasis, those with only one lymph node metastasis were given PORT alone and those with two or more lymph node metastases were given chemotherapy followed by external beam radiation therapy. From 2003, the cyclophosphamide, doxorubicin, and cisplatin (CAP) regimen was administered to patients with histological FIGO grade 1 and without vascular invasion and the paclitaxel and carboplatin (TC) regimen was administered for patients with histological FIGO grade 2 or 3 and/or with vascular invasion. Before 2003, only the CAP regimen had been used for postoperative chemotherapy. The CAP regimen consisted of three cycles of 70 mg/m^2 of cisplatin, 500 mg/m^2 of cyclophosphamide, and 50 mg/m^2 of doxorubicin. The TC regimen consisted of three cycles of paclitaxel at 175 mg/m^2 and carboplatin with an area under the curve (AUC) of 6, tri-weekly or monthly.

PORT

The whole pelvis was irradiated in all cases. For para-aortic lymph node metastasis, the para-aortic area and the whole pelvis were irradiated. Two parallel ports, the anterior–posterior and posterior–anterior, were used for whole pelvis irradiation until the year 2000. Thereafter, four ports (box field) were used. The upper edge included the bifurcation of the common iliac artery (around L4–5). The lower edge was between the obturator foramen and the ischial tuberosity, and the lateral edge was 1.5–2 cm outside the small pelvic cavity. The energy was basically 10 MV. The prescribed irradiation dose was 50–50.4 Gy/25–28 fractions. On the irradiation to the para-aortic area, the upper edge was between the 11th and 12th thoracic vertebrae, and the lateral edge included the transverse process.

Evaluation and follow up

Response to radiotherapy was evaluated using pelvic examination, computed tomography, and cytology. Follow up after PORT was usually conducted every

month for the first 2 years and every 3 months thereafter. Follow-up computed tomography was performed every 6 months and cytology every month. Swab samples were obtained from the vaginal stump. For patients suspected of recurrent disease, the follow up was conducted at more frequent intervals in consideration of alternative salvage treatment. Follow-up examination included physical and pelvic examinations and cytology.

In addition, toxicity was scored using the Common Terminology Criteria for Adverse Events (CTCAE) v3.0.

Statistical analysis

Associations between variables were assessed using the χ^2-test, Fisher's exact test, and linear-by-linear exact tests. The Kaplan–Meier product–limit method was used to estimate the probability of overall survival (OS) and disease-free survival (DFS); the log–rank test was used to estimate any differences. Multivariate analyses were performed using the Cox proportional hazards regression model. OS was calculated in months from the date of surgery to the date of death from any cause or to January 2009. Patients who were still alive in June 2008 were treated as censored. *P*-values < 0.05 were regarded as statistically significant. Statistical analyses were carried out using StatView Dataset File version 5.0 J for Windows.

Results

Patients

The patient characteristics are shown in Table 1. Of the 111 patients receiving PORT, the median age was 57 years (range, 28–78). One of these 111 patients was not followed up after PORT, and was therefore excluded from the analysis. Thirty-six patients had positive pelvic lymph nodes, 71 patients were negative, and others

Table 1 Univariate analysis of OS and DFS

Factor	*n*	%	5-y OS	*P*-value	5-y DFS	*P*-value
Age						
<60 y	67	61	90%	0.044	85%	0.013
≥60 y	43	39	74%		65%	
PLN						
(+)	36	34	81%	0.36	71%	0.150
(−)	71	66	87%		81%	
PALN						
(+)	24	22	72%	0.12	52%	0.001
(−)	86	78	88%		85%	
FIGO stage						
I	36	34	93%	0.11	87%	0.040
II–III	69	66	79%		71%	
Histological type						
EA	84	78	83%	0.51	76%	0.32
Not EA	24	22	87%		80%	
FIGO grade						
1	41	48	97%	0.35	81%	0.440
2	25	29	82%		76%	
3	18	23	77%		70%	
Risk group						
High	76	70	82%	0.61	72%	0.180
Intermediate–high	30	28	88%		86%	
Intermediate–low	2	2	100%		100%	
Chemotherapy						
With	46	44	82%	0.75	66%	0.13
Without	58	56	84%		84%	
Depth						
a–b†	18	18	100%	0.19	75%	0.67
c–d‡	80	82	83%		77%	

†<50% myometrial invasion. ‡>50% myometrial invasion. DFS, disease-free survival; EA, endometrioid adenocarcinoma; FIGO, International Federation of Gynecology and Obstetrics; OS, overall survival; PALN, para-aortic lymph node; PLN, pelvic lymph node.

($n = 3$) could not be clearly determined. For the para-aortic lymph nodes, 24 patients were positive and 86 patients were negative. There were 36 patients (32%) in stage I, 15 patients (14%) in stage II, and 54 patients (50%) in stage III according to the FIGO staging. Five patients (4%) could not be staged because of insufficient FIGO staging information. Endometrioid adenocarcinoma, with 84 patients (76%), was the most frequent histological type encountered. Six other types were detected with considerably fewer frequencies. The histological types for two patients were not described in their medical records.

Among the cases not receiving postoperative chemotherapy, just the whole pelvis was irradiated in 86 cases (78%) and the para-aortic lymph node area plus the whole pelvis were irradiated in 24 cases (22%). As for the cases with postoperative chemotherapy, the CAP regimen was used in 32 cases (29%) and the TC regimen in 14 cases (13%).

To account for the high risk of local recurrence after surgery, a strong primary possibility was deep invasion in over 50% in 80 patients (82%) (Table 1). Secondarily, there were positive lymph node metastases in 36 patients (34%) (Table 1). Other reasons were ovarian invasion in five patients and cervical invasion in one patient. PORT was performed even for four patients with FIGO stage IA or IB with high risk of local recurrence. The reasons were histological FIGO grade 3 in three patients, and adenosquamous carcinoma in one patient. Although the intermediate low-risk group was not a target of PORT, two patients with intermediate low risk were given PORT because the residual lesions were strongly doubted by the surgeon in spite of negative histopathology.

Survival

The median follow-up time for all patients was 59.2 months (range; 6.5–235.2 months). The number of survivors at the end of the observation period was 93 (84%), and the number of disease-free survivors was 81 (73%). The OS rate at 5 years was 84%, and the DFS rate at 5 years was 77% for all patients. Both OS and DFS reached a plateau at approximately 3 years. Patients younger than 60 years had significantly better OS (log–rank $P = 0.044$, odds ratio [OR] = 0.383, and 95% confidence interval [CI] = 0.145–1.008) and DFS (log–rank $P = 0.013$, OR = 0.389, and 95%CI = 0.180–0.840) than patients 60 years or older (Fig. 1). Moreover, when limited to the histological type of endometrioid adenocarcinoma ($n = 84$), there was a significant difference in DFS between patients 60 years or older, and those

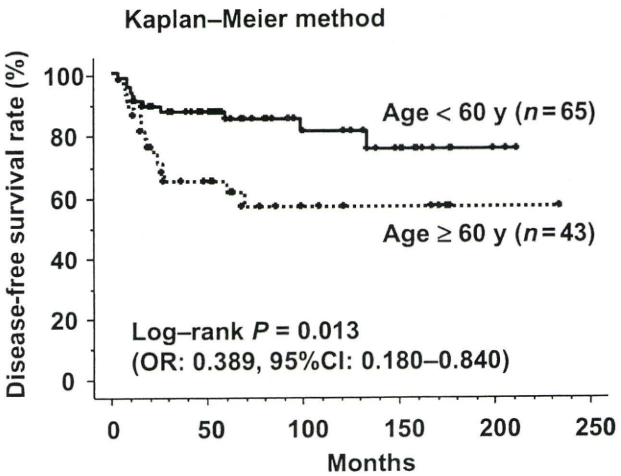

Figure 1 Disease-free survival curves by age (less than 60 years old vs 60 years or older). CI, confidence interval; OR, odds ratio.

under 60 years old (log–rank $P = 0.004$, OR = 0.289, and 95%CI = 0.119–0.703). However, when the age was raised to 65 years, the earlier significant difference in DFS shown for those younger than 60 years vanished ($P = 0.067$). When the age was raised to 70 years, there was a significant difference in DFS ($P = 0.0030$, OR = 0.274, and 95%CI = 0.109–0.685). The numbers of patients aged ≥65 and 70 years old were 25 (23%) and 10 (9%), respectively.

Certain prognostic factors (as determined by univariate analysis, Table 1) for both OS and DFS were examined. Pathological stage, with or without lymph node metastasis, and with or without chemotherapy, and age were studied. The 5-year OS and DFS rates were 93% and 87% in FIGO pathological stage I cases, 85% and 79% in stage II cases, and 83% and 74% in stage III cases, respectively. A significantly higher DFS rate in stage I ($n = 36$) emerged when compared with stages II–III ($n = 69$) (log–rank $P = 0.040$). Significant differences for DFS were not shown for those with and without lymph node metastasis (log–rank $P = 0.15$) and with and without postoperative chemotherapy (log–rank $P = 0.13$). However, for those with and without para-aortic lymph node metastasis the difference was significant (log–rank $P = 0.0006$, OR = 0.285, 95%CI = 0.133–0.612) (Table 1).

On multivariate analysis (Table 2), poor DFS correlated only with age ≥ 60 years ($P = 0.035$).

The distribution of variables according to age (age <60 vs age ≥60) is summarized in Table 3. There were significantly more cases of endometrioid

Table 2 Multivariate analysis of disease-free survival

Factor	*P*-value	OR	95%CI
Age			
<60 y	0.035	0.427	0.193–0.944
≥60 y			
PALN			
(−)	0.067	0.451	0.192–1.058
(+)			
FIGO stage			
I	0.18	0.484	0.167–1.405
II–III			

CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; OR, odds ratio; PALN, para-aortic lymph node.

adenocarcinoma on histological type ($P = 0.019$) and fewer high-risk cases ($P = 0.017$) in patients ≥60 years old than in patients <60 years old.

Complications

According to the CTCAE v3.0, lower limb edema, intestinal obstruction, and diarrhea were adverse events of grade 3 or more. Regarding complications of grade 3 or more, lower limb edema was seen in 16 patients (14%), intestinal obstruction was seen in nine patients (8%), and diarrhea was seen in three patients (3%). In this study, lower limb edema was recorded in 15 patients with grade 1 complications and 13 patients with grade 2 complications. There was no grade 3 or 4 myelosuppression in any of the cases.

Discussion

In this retrospective study of endometrial cancer in our institution, prognostic factors were evaluated in endometrial cancer patients and were focused particularly on the effect of advanced age on the outcome of surgery and PORT. The limitations of our study included the retrospective nature of the study and the heterogeneity of the patient population in the two arms (<60 years vs ≥60 years).

In a prospective randomized trial of postoperative radiation therapy in endometrial carcinoma (PORTEC) for stage I disease, Creutzberg *et al.*[13] reported that patient age ≥60 years was an independent predictor of death from endometrial carcinoma (hazard ratio of 3.1 and 95%CI , 1.2–8; $P = 0.02$). The data in the literature also suggest that there is an incremental increase in the risk of dying from endometrial carcinoma with increasing age. In a review of 819 patients with stage I–II endometrial carcinoma from the Gynecologic Oncology Group database, Zaino *et al.* demonstrated that the relative risk (RR) increased from 1.0 for patients who were aged ≤45 years (reference) at the time of diagnosis to 2.0 for patients aged 55 years, to 3.4 for patients aged 65 years, and to 4.7 for patients aged ≥75 years.[2] According to Alektiar *et al.*,[12] patient age ≥70 years was found to be an independent predictor of poor locoregional control (RR: 3 and 95%CI , 1–10; $P = 0.019$), DFS (RR: 2 and 95%CI , 1–13; $P = 0.03$), and OS (RR: 4 and 95%CI , 2–7; $P = 0.001$). Jolly *et al.*[14] concluded from a retrospective study that older endometrial cancer (age >63 years) patients had a significantly decreased OS, cause-specific survival, and greater risk of recurrence following PORT that were independent of other prognostic factors and/or treatment technique. According to Lee *et al.*,[15] their study ($n = 51\,471$) of a large population of uterine cancer patients demonstrated that those 40 years or younger have an OS advantage compared with women older than 40 years, independent of other clinicopathological prognosticators. Farley *et al.*[16] concluded that age (older than 50) is a specific and significant predictor of outcome in endometrioid adenocarcinoma of the uterus ($n = 328$). The frequent association between older age in endometrial carcinoma patients on the one hand and deep myometrial invasion and aggressive histologies always raises the possibility that the poor outcome in older patients is entirely the result of such an association. Why older patients with early-stage endometrial carcinoma tend to fare worse independent of other factors is not clear. Nevertheless, clinical efforts should be directed toward maximizing the therapeutic ratio in those patients. The notion of limited life expectancy should not hinder that effort because survival to the age of 80 years and beyond has been reported to have increased in many developed countries.[17] The remaining life expectancy of a white US woman aged 75 years is estimated to be 11.7 years.[18]

The treatment methods were changed for postoperative adjuvant therapy in our institution due to a pathological result after operation. Seeing the treatment outcome, the 5-year DFS rate of each FIGO stage was 82% in stage I, 79% in stage II, and 74% in stage III. These outcomes are comparable to other institutions. In the gynecology tumor committee report of 1993 in Japan,[19] the OS rate for five years was 84.0% in stage I, 73.5% in stage II, and 54.8% in stage III. As for our outcome results, only those cases receiving PORT in our department were evaluated, and it is likely that the results would show further improvement for stage I if the patients in the low-risk group were included. There

Table 3 Distribution of variables according to age

Variables	<60 years	(*n* = 67)	≥60 years	(*n* = 43)	*P*-value (×2)
PLN					
(+)	21	(41%)	15	(27%)	0.96
(−)	30	(59%)	41	(73%)	
PALN					
(+)	15	(23%)	9	(20%)	0.67
(−)	50	(77%)	36	(80%)	
FIGO stage					
I	20	(33%)	16	(36%)	0.65
II–III	41	(67%)	28	(64%)	
Histological type					
EA	43	(69%)	41	(89%)	0.019
not EA	19	(31%)	5	(11%)	
FIGO grade					
1	25	(50%)	16	(47%)	0.81
2	14	(28%)	11	(32%)	
3	11	(22%)	7	(21%)	
Risk group					
High	51	(80%)	25	(57%)	0.017
Intermediate–high	12	(19%)	18	(41%)	
Intermediate–low	1	(1%)	1	(2%)	
Chemotherapy					
With	30	(49%)	16	(37%)	0.21
Without	31	(51%)	27	(63%)	
Depth					
a–b†	10	(19%)	8	(18%)	0.27
c–d‡	44	(81%)	36	(82%)	

†<50% myometrial invasion. ‡>50% myometrial invasion. DFS, disease-free survival; EA, endometrioid adenocarcinoma; FIGO, International Federation of Gynecology and Obstetrics; OS, overall survival; PALN, para-aortic lymph node; PLN, pelvic lymph node.

were only 15 examples for stage II, and the number of cases might not be sufficient to analyze treatment results. On the other hand, there were 55 examples of stage III, which constitutes an excellent OS rate. A phase III randomized trial showed improved survival with the use of chemotherapy for stage III and IV endometrial cancer.[20,21] However, pelvic and abdominal failure rates were alarmingly high, which appears to be persuasive for the integration of radiation and chemotherapy as performed in our institution.

According to our multivariate analysis of DFS, being a senior citizen is in itself an independent risk factor. More intensive treatment may be necessary for senior citizens than for young people. A total dose of approximately 50 Gy in PORT has already been prescribed, and because any further dose increase is difficult, the inclusion of postoperative chemotherapy can be expected. According to a recent Japanese Gynecologic Oncology Group study,[22] adjuvant CAP chemotherapy may be a useful alternative to PORT for intermediate-risk endometrial cancer. Moreover, adjuvant vaginal high-dose-rate brachytherapy alone may be a safe and effective alternative to pelvic external beam PORT for surgical early stage endometrial cancer.[23,24]

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Development of a Personal Digital Assistant (PDA) System To Collect Symptom Information from Home Hospice Patients

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Abstract

Purpose: Previous studies have found that inappropriate assessment of cancer pain can lead to inadequate pain management. To improve assessment, it may be helpful to collect real-time data in a natural environment using computerized ecological momentary assessment (cEMA). Therefore, the aim of the study was to develop a personal digital assistant (PDA) system to collect information on symptoms such as pain and mood states in patients with cancer using cEMA.

Methods: Following a pilot study in inpatients with cancer, the second phase of the study involved patients with terminal cancer receiving home hospice care. These patients were asked to record their symptoms in a PDA (a palm-sized portable device) several times per day for a week when they took rescue medications and when an alarm sounded. At the end of the week, an interview on the usability of the device was conducted and overall response rates were calculated.

Results: Fifteen patients completed the second phase of the study. Their median age was 64 years and the median survival time after the study period was 22 days. The overall response rates were 90.3% to the sound of the alarm and 80.2% after taking rescue medications. The user-friendliness of the device was rated as 8.8 on a scale of 0 (worst) to 10 (best).

Conclusions: The cEMA technique using a PDA might be applicable to patients with cancer in palliative care to evaluate symptoms in a natural setting. This system may also be useful for managing symptoms such as pain and mood states in patients with cancer.

Introduction

CANCER REMAINS A LEADING CAUSE OF DEATH despite advances in treatment. Symptoms such as pain, fatigue, nausea, drowsiness, depression, and anxiety are prevalent in 50%–84% of patients with cancer and may contribute to a diminished quality of life.[1] Most patients with cancer experience moderate or severe pain during the course of their illness, and pain treatment continues to be a major concern in these patients.[2]

In recognition of this problem, in 1986 the World Health Organization (WHO) developed guidelines for pain control in patients with cancer, which are referred to as the WHO three-step analgesic ladder. However, many studies indicate that pain associated with cancer is still not adequately assessed and managed and many patients do not obtain sufficient relief.[3–6] Effective pain assessment is essential for proper pain management,[7] but pain is often assessed through a patient–clinician interview, a method that is time consuming and may be vulnerable to biases.[4,8–10] On the physician side, undertreatment of patients is likely when the physical condition appears to be good.[11] On the patient side, there may be concerns about the side effects of analgesics and a fear of disappointing their physician by reporting pain.[12–14] Consequently, patients may hesitate to discuss pain with their doctors.

Retrospective recall of pain experiences may also bias assessment and contribute to inadequate pain control.[15] To overcome this kind of bias, a sampling method called

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ecological momentary assessment (EMA) has been developed in the behavioral sciences. EMA techniques can capture real-time levels of state variables, such as pain or mood, at multiple points in a natural setting.[16,17] Paper-and-pencil diaries have been used for this purpose,[18] but Stone et al.[19] pointed out major problems with the paper-and-pencil approach because subjects often do not complete the diaries at the specified times. This constitutes faked compliance and jeopardizes the reliability of self-reported symptoms. Consequently, electronic diaries have been developed to collect self-reported information reliably, with this technique referred to as computerized EMA (cEMA).[19]

Previous studies have used cEMA to assess symptoms in patients with cancer,[20,21] but these patients have not had severe general conditions. In addition, recordings were entered at fixed intervals or randomly, rather than when the symptoms escalated or a rescue medication was taken. Therefore, the results may not give an accurate evaluation of acute exacerbation and may underestimate symptom flare-ups.

In recent years, there has been a growing preference to die at home.[22–25] This has resulted in a wide range of home care services being established.[26] As the number of patients with cancer receiving home hospice care increases, more symptom relief after appropriate assessment at home is required.

Therefore, the aim of the study was to develop a personal digital assistant (PDA) system to act as an electronic diary to collect symptoms in patients with cancer in natural settings, using cEMA to record symptoms at the time of acute exacerbation in addition to regularly scheduled assessments. Frequent recordings were also made after taking a rescue medication to determine more accurate symptom transitions.[20]

Methods

The study was carried out in two phases. The first phase was performed in hospitalized patients since in this setting problems with equipment could be dealt with immediately. The patients were also in relatively good physical condition, which allowed them to bear the burden of the trial procedure.

Following this evaluation of the feasibility of the protocol and the usability of the device, the second phase was conducted in patients with terminal cancer receiving in-home palliative care to evaluate the approach in a home hospice setting.

The study was approved by the Ethics Committee of the University of Tokyo. Informed consent was obtained from all subjects.

Participants

The first phase of the study was conducted in patients with cancer receiving palliative care at the University of Tokyo Hospital to evaluate the feasibility of the protocol (several recordings per day for 4–7 days) and to obtain feedback on the usability of the device.

In the second phase, patients with terminal cancer receiving in-home palliative care were recruited at the Kawagoe Clinic. The inclusion criteria for the study participants were presence of cancer-related pain, use of analgesics, age $\geq$20 years old, ability to tolerate the study, and no current or recent history of cognitive impairment or psychiatric disorders.

Procedure

Recruitment was conducted from December 2006 until April 2007 for the first phase, and from April 2007 until February 2009 for the second phase. The same procedure was used in both phases. The attending physician used flyers to briefly present the study to potential participants. If a patient indicated a willingness to participate, a researcher visited the patient and explained the content and context of the study. After written consent was obtained, the patient was enrolled in the study. The researcher evaluated the performance status (PS) of the patient using the Eastern Cooperative Oncology Group (ECOG) and Karnofsky Performance Status (KPS) scales. The patients were then instructed by one of the authors (M.H.) on use of the electronic diary, as described in a following section until they became accustomed to its use. Participants were asked to record the intensities of symptoms on the device for 1 week. The next day, the researcher visited or called the participant to ask if any problems had occurred. After 7 days, the researcher visited the patient and collected the device. At this time, the patient was asked to rate the user-friendliness of the device on a numerical rating scale (NRS) from 0 (very awkward to use) to 10 (very easy to use) and the simplicity of the content on an NRS from 0 (very hard to understand) to 10 (very simple to understand).

Materials

The electronic diary was a Sharp Zaurus Model SL-C1000 handheld PDA (Sharp Corporation, Osaka, Japan) of dimensions 124×87×25 mm and weight 278 g. The device was equipped with a liquid crystal screen and a stylus for tapping answers on the screen. However, to enhance usability of the device we designed a program that allowed use of a finger instead of the stylus.

Symptom measurements

Intensities of symptoms (pain, fatigue, nausea, anxiety, depression, and drowsiness) were rated on a visual analogue scale (VAS) from 0 to 100 displayed on the screen of the device. The words "none" and "most intense" were displayed at the respective ends of the VAS. Participants were asked to touch the scale with their fingers to rate each symptom. Data elements recorded in the device were not accessible to the patients. Patients were allowed to voluntarily skip a signal for reasons of inconvenience. Each input required 1–2 minutes. The patients were asked to complete these ratings at the sound of an alarm generated by the device. This signal was produced at a specified time when the patient took their usual analgesics (one to three times per day) and also at randomly scheduled times (once in the morning and once in the afternoon). In addition, each time a patient took rescue medications they were asked to run the device and to record the intensities of symptoms. The device alarm then sounded 30, 45, 60, and 90 minutes later to prompt the participants to record intensities of symptoms at each time point to allow evaluation of the efficacy of the rescue medications.

Analysis

Response rates were calculated in the second phase, since the aim of the study was to develop a PDA system for evaluating symptoms in patients receiving home hospice care.

TABLE 1. DEMOGRAPHIC AND MEDICAL CHARACTERISTICS OF THE SUBJECTS RECEIVING IN-HOME PALLIATIVE CARE

Variables	
Sex	
Women	3 (20.0%)
Men	12 (80.0%)
Age (years)	
Mean ± standard deviation	67.1 ± 9.2
Range	55–91
Medical diagnosis	
Lung cancer	10 (66.7%)
Gastric cancer	1 (6.7%)
Colon cancer	1 (6.7%)
Pancreatic cancer	1 (6.7%)
Renal cancer	1 (6.7%)
Cancer of unknown origin	1 (6.7%)
ECOG PS	
0	3 (20.0%)
1	3 (20.0%)
2	4 (26.7%)
3	5 (33.3%)
4	0 (0%)
Rescue medication	
Used	6 (40.0%)
Never used	9 (60.0%)

ECOG PS, Eastern Cooperative Oncology Group Performance Status.

Overall response rates were calculated by averaging the response rate over all subjects. The number of prompts completed and the number skipped were used to calculate the response rate for each subject. This rate was obtained by dividing the number of prompts completed by the number of prompts scheduled (completed + skipped). When a participant took a rescue medication, 5 was added to the denominator because five entries were required at the time of taking the rescue medication and at 30, 45, 60, and 90 minutes afterwards. A visiting nurse questioned the participant about the use of rescue medications and checked the remaining analgesics to determine use. If a participant did not make any recordings despite taking a rescue medication, the response for the five prompts was regarded as zero.

To assess the relationship of response rates with demographic variables, Pearson correlation coefficients were calculated for response rates with age and KPS scores. The correlation between ECOG PS scores and response rates was evaluated by Spearman rank correlation coefficient analysis.

Results

Patient characteristics

In the first phase, four participants were enrolled in the study and all completed the entire schedule. Among these participants, there was one case each of lung cancer, colon cancer, pancreatic cancer, and acute myeloid leukemia. The median age was 62 years old (range 43–70 years old). The participants reported that the protocol and the device were convenient. Therefore, we did not make any changes in the protocol for the second phase.

Eighteen participants were enrolled in the second phase of the study, but three dropped out due to death, worsening of physical condition, and a PDA malfunction, respectively. Therefore, 15 subjects completed the study and were subjected to analysis. The profiles of these subjects are shown in Table 1. None had previously used a computer or a PDA.

Fourteen out of 15 died after participation in the present study. The range in survival after participation was 6–154 days, and the median was 22 days.

Overall response rates

There were 465 scheduled recordings for all participants and the overall response rate to the sound of the alarm was 90.3 ± 10.5%. Six subjects made 95 recordings of symptoms in conjunction with taking rescue medications, while nine subjects did not take rescue medications. The response rate was 80.2 ± 16.8% for taking rescue medications. The recording profiles are shown in Table 2.

Feasibility of the device

The user-friendliness of the device and the simplicity of the content were both rated as >8 on a scale from 0 (worst) to 10 (best) (Table 2).

Correlations between demographic variables and response rates

Response rates were not significantly correlated with any demographic variables (Table 3).

Discussion

We found a high compliance rate and perceived user-friendliness for a PDA system with a palm-size portable device using cEMA for recording of symptoms in patients with terminal cancer receiving at-home hospice care. Our compliance rate of 90.3% is similar to the rates of 87% and 86% reported by Hacker and Ferrans[20] in a cEMA examination of

TABLE 2. RECORDING PROFILES AND THE FEASIBILITY FOR USE OF THE ELECTRONIC DIARY

Variable	*Scheduled recordings*	*Recordings in rescue medications*
n	465	95
Median no. of data points per participant (range)	33 (21–37)	46 (31–74)
Overall response rate (mean ± SD)	90.3 ± 10.5%	80.2 ± 16.8%
Feasibility (NRS 0–10)		
User-friendliness (mean ± SD)	8.8 ± 1.8	8.0 ± 2.2
Simplicity of the content(mean ± SD)	8.8 ± 1.4	8.5 ± 1.5

SD, standard deviation; NRS, numerical rating scale.

TABLE 3. CORRELATIONS BETWEEN DEMOGRAPHIC VARIABLES AND RESPONSE RATES

	Overall response rate		*Response rate (without rescue medications)*		*Response rate (with rescue medications)*	
Variables[a]	*Correlation*	p	*Correlation*	p	*Correlation*	p
Age	−0.164	0.560	−0.257	0.355	0.545	0.263
KPS	0.211	0.451	0.022	0.937	0.296	0.569
ECOG PS	−0.184	0.512	−0.074	0.794	−0.123	0.816

KPS, Karnofsky Performance Status; ECOG PS, Eastern Cooperative Oncology Group Performance Status.
[a]Data between age or KPS and response rates are Pearson correlation coefficients. Data between ECOG PS and response rates are Spearman rank correlation coefficients.

one item three times a day for 3 days in inpatients before and after hematopoietic stem cell transplantation. Thus, an important aspect of the present study is that it shows the feasibility of using cEMA to collect real-time symptom data in patients with terminal cancer receiving in-home palliative care.

The patients in the study also entered symptom ratings when they took rescue medications, which allowed a post-medication analysis of symptom transition. The compliance rate was 80.2% for entries after taking rescue medications and the patients had relatively good impressions about the availability of the program. Furthermore, the response rates were not significantly correlated with any demographic variables, which indicates that this procedure is feasible for patients with terminal cancer regardless of age or performance status.

The compliance rate for using the PDA system was equivalent to that seen in previous studies.[20,21] This may have been because patients were able to quickly familiarize themselves with operating the PDA, although none had experience in the use of computers. The device was easy to operate, since the input method allowed use of a finger instead of a stylus to tap answers on the screen, and the training procedure was simple. Thus, the participants were able to master operation of the PDA regardless of prior computer experience. In addition, we note that recording of medication intake may also offer benefits in reducing drug noncompliance, since it has previously been shown that patients find that use of an electronic diary helps them to maintain more regular pharmacotherapy.[27]

There are some limitations in the study. First, the sample size was relatively small. Second, the true compliance rate in taking rescue medications was unclear because subjects were required to run the system voluntarily when they took a rescue medication. Third, pain was assessed only based on intensity and should also be assessed in terms of, for example, duration and location.[28]

Within these limitations, we conclude that the cEMA technique might be applicable for patients with cancer for evaluation of severe symptoms such as pain and mood states, which might lead to improved management of patients with cancer at home.

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