Table 6. Intra-arterial infusion chemotherapy with radiotherapy for uterine cervical cancer: data from the literature

First author (reference)	Stage	*n*	Timing	Regimen	Method	Courses	RR*	5-y survival	Side effects
Patton (21)	IIB–IVA	46	NAC	B, C, M (IA); V (IV)	CI	1–3	76%	30	H G3, G4: 39%
Takashima (24)	III	11	CC	C, P	OS	2	—	47% (3 y)	H G3, G4: 45%
Tuji (27)	I–IV	39	NAC	C, A, P	OS	1	—	57% (III: 52%)	R G3: 11% Bl G3: 0
Morris (25)	IIB–IIIB	16	CC	FUDR, C	CI	4 wk	88%	—	Pelvic fibrosis G1: 6%
Toita (29)	IIB–IVA	51	NAC	C	OS	1–2	48%	47%	S G3: 2% RV: 4%
Kokubo (32)	IIIA–IVA	24	CC	C, TA	OS	2	—	67% (3 y)	H G3: 70%
Kaneyasu (31)	II-IVA, rec.	52	CC	I. F, M ± A II. C, M ± F	CI	3-5	I: 63% II: 82%	CR: 30% PR: 13%	H G3: 48% Bowel >G3: 21%
Onishi (35)	IIIA–IVA	18	CC	1. C/3 wk 2. CBDA/wk 3. C/day	OS	2 5-6 d 1–21	100% 100% 100%	44%	Bowel G3, G4: acute 33%, late 44% H G3, G4 : 33%
Chaney (33)	IIIB–IVA	27	CC	F/day	CI	d 1–15		IIIB: 41%	Skin G3, G4: 67% Bl G5: 4% R G5: 4%
Nagai (36)	II–IV	32	CC	C/4 wk	OS	2	—	52%	H G3: 28%
Kawase (37)	IB2–IVA	45	CC	C or Ne (IA)/3 wk F (IV)/3 wk	OS CI	d 1 d 1–4	98%	81%	R G4: 2%
Present study	III	29	CC	C/4 wk	OS	2	—	62%	H G3: 24% Bl ≥G3: 3% R ≥G3: 3% S ≥G3: 10%

Abbreviations: RR = response rate; B = bleomycin; C = cisplatin; M = mitomycin-C; IA = intra-arterial chemotherapy; V = vincristine; IV = intravenous chemotherapy; CI = continuous infusion; H = hematologic; G = Grade; CC = concurrent chemotherapy; P = peplomycin; OS = one shot; NAC = neoadjuvant chemotherapy; A = Adriamycin; R = rectum; Bl = bladder; FUDR = 2-deoxy-5-fluorouridine; S = small bowel; RV = rectovaginal fistula; TA = pirarubicin; CBDCA = carboplatin; Ne = nedaplatin rec. = recurrence; CR = complete response; PR = partial response; F: 5-fluorouracil.

* Response rate of NAC group is just after chemotherapy.

and this medical complication would easily increase rectal bleeding. When the adjustment of chemotherapy with RT is decided, it should be carefully examined in consideration of the patient's underlying disease. In this study, Grade 3 late complications of the small intestine were 10%. Rates of Grade 3 in our study are somewhat high compared with those other studies except for one report (35).

Generally speaking, rare technical and catheter-related complications of IAIC are subcutaneous hematoma of the puncture area and peripheral thrombus. Other complications occurring due to high-density medicine being distributed over the buttocks and the lower limbs are neuropathy and skin ulcer. In this study only 1 patient (3%) had numbness of the bilateral lower limbs due to sensorimotor neuropathy caused by distribution of high concentrations of CDDP. It is believed that the higher concentration of CDDP perfusing the sacral plexus is the etiologic factor precipitating the neuropathy (18, 20). Kavanagh *et al.* (18), LaPolla *et al.* (20), and Roberts *et al.* (26) in a previous study of continuous intra-arterial infusion CDDP with or without the fluorouracil derivative 2-deoxy-5-fluorouridine, noted that 11–37% of patients developed neuropathy of the lower extremity. Because the optimal platinum drug dosage, time interval, and sequence of intra-arterial cisplatin in conjunction with radiation are unknown, neurotoxicity should be carefully documented in the future.

To improve treatment results, the dose of intracavitary brachytherapy in our radiation schedule was chosen to be higher (6 Gy twice weekly) than in the general rules of Japan (39) and general reports (41–47). It is not clear whether the cause of good local control and/or a somewhat high rate of late complications was RT or IAIC. However, both can become the cause. As a result, after April 2008 we decreased the dose of intracavitary brachytherapy to once weekly from 6 Gy twice weekly, to reduce late complications.

Onishi *et al.* (35) evaluated concurrent intra-arterial infusion of platinum drugs with radiation therapy (IAPRT) for patients with Stage III or IV uterine cervical cancer. Patients were randomized to IAPRT or RT alone. The IAPRT group had a better local response than the RT group but had a poorer survival rate. The reason the rate of local recurrence was high despite a good initial local response might be the larger tumor volume in the IAPRT group than in the RT group. In the IAPRT group Grade 3 or 4 late bowel complications were seen in 44% of patients and Grade 3 or 4 myelosuppression in 33%, significantly more than in the RT group. Kokubo *et al.* (32) reported no significant difference between radiotherapy and transcatheter arterial infusion chemotherapy (RT-TAI) and RT-alone groups. However, in the subgroup with well or moderately differentiated squamous cell carcinoma without pelvic lymph node swelling, the cause-specific survival rate in the RT-TAI group was significantly better than in the RT-alone group. In our study there were no significant differences between the subtypes of squamous cell carcinoma. Kawase *et al.* (37) evaluated intra-arterial cisplatin/nedaplatin and intravenous 5-fluorouracil with concurrent radiotherapy for patients with high-risk uterine cervical cancer and found a survival benefit compared with the RT-alone group, despite this being a nonrandomized study. They mentioned that intra-arterial chemotherapy is expected to improve local control whereas intravenous chemotherapy is

expected to reduce the potential systemic disease in patients with high-risk cervical cancer.

Our study showed good local control but a lot of extrapelvic distant metastases, especially PAN metastases. Therefore, to decrease distant metastases it is thought that some whole-body chemotherapies are necessary. We confirmed excellent drug distribution directly by using angio-CT. To improve the survival rate for advanced cervical cancer, it is advocated that IAIC be considered to improve local control and that systemic chemotherapy be considered to reduce potential systemic disease. To improve the prognosis of these patients, we should furthermore consider a combination of IAIC and systemic chemotherapy.

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RADIATION THERAPY FOR ESOPHAGEAL CANCER IN JAPAN: RESULTS OF THE PATTERNS OF CARE STUDY 1999–2001

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Purpose: To describe patient characteristics and the process of radiotherapy (RT) for patients with esophageal cancer treated between 1999 and 2001 in Japan.

Methods and Materials: The Japanese Patterns of Care Study (PCS) Working Group conducted a third nationwide survey of 76 institutions. Detailed information was accumulated on 621 patients with thoracic esophageal cancer who received RT.

Results: The median age of patients was 68 years. Eighty-eight percent were male, and 12% were female. Ninety-nine percent had squamous cell carcinoma histology. Fifty-five percent had the main lesion in the middle thoracic esophagus. Fourteen percent had clinical Stage 0–I disease, 32% had Stage IIA–IIB, 43% had Stage III, and 10% had Stage IV disease. Chemotherapy was given to 63% of patients; 39% received definitive chemoradiotherapy (CRT) without surgery and 24% pre- or postoperative CRT. Sixty-two percent of the patients aged ≥75 years were treated with RT only. Median total dose of external RT was 60 Gy for definitive CRT patients, 60 Gy for RT alone, and 40 Gy for preoperative CRT.

Conclusions: This PCS describes general aspects of RT for esophageal cancer in Japan. Squamous cell carcinoma accounted for the majority of patients. The standard total external RT dose for esophageal cancer was higher in Japan than in the United States. Chemoradiotherapy had become common for esophageal cancer treatment, but patients aged ≥75 years were more likely to be treated by RT only. © 2009 Elsevier Inc.

Patterns of Care Study, Esophageal cancer, Radiotherapy, Chemoradiation, Japan.

INTRODUCTION

The Patterns of Care Study (PCS) was established and developed in the radiation oncology field in the United States. The PCS retrospectively investigates the nationwide structure and practice of care in specific malignancies and provides useful data for improving cancer management. Patient backgrounds and standard clinical practices can be described by PCS. Penetration of clinical evidence and the compliance status of clinical guidelines can be evaluated through PCS results. The PCS also reveals the time-dependent transition of cancer treatments and provides data for international comparison. The U.S. PCS for esophageal cancer demonstrated that a majority of patients treated by radiotherapy (RT) received chemotherapy concurrently and that chemoradiotherapy (CRT) followed by surgery had become important in treatment strategies (1–4).

The PCS was introduced to Japan in the early 1990s. The Japanese PCS Group started a national survey for the major diseases in radiation oncology and has been continuously working. We previously reported PCS results for esophageal cancer for the periods 1992–1994 and 1995–1997 (5, 6).

The objectives of this study were (*1*) to summarize the structure and process of RT for patients with esophageal cancer treated between 1999 and 2001 and show comparable data from the U.S. PCS study; and (2) to compare patient characteristics and treatment strategies with regard to patient age.

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Table 1. Investigated institutions and patients with esophageal cancer in the Japanese Patterns of Care Study (1999–2001)

Institutions	No. of Institutions	Patients	Age group		
			<65 y	65–74 y	≥75 y
Total institutions	76	621	244	213	164
Academic (A)	38	358 (57.6)	164 (67.2)	126 (59.2)	68 (41.5)
Treat ≥430/y (A1)	20	196 (31.6)	89 (36.5)	69 (32.4)	38 (23.2)
Treat <430/y (A2)	18	162 (26.1)	75 (30.7)	57 (26.8)	30 (18.3)
Nonacademic (B)	38	263 (42.4)	80 (32.8)	87 (40.8)	96 (58.5)
Treat ≥130/y (B1)	20	186 (30.0)	52 (21.3)	62 (29.1)	72 (43.9)
Treat <130/y (B2)	18	77 (12.4)	28 (11.5)	25 (11.7)	24 (14.6)

Values in parentheses are percentages.

METHODS AND MATERIALS

Between July 2002 and June 2004, the Japanese PCS Group conducted a third national survey for esophageal cancer. Eligibility criteria were as follows: (*1*) thoracic esophageal cancer, (*2*) squamous cell carcinoma (SCC), adenocarcinoma, or adenosquamous cell carcinoma, (*3*) no distant metastasis, (*4*) no prior or concurrent malignancies within 5 years, (*5*) Karnofsky performance score (KPS) >50, and (6) RT started between January 1999 and December 2001. Seventy-six of approximately 700 institutions were selected for the survey by use of a stratified two-stage cluster sampling method. Before the random sampling, all RT institutions were classified into four groups according to type and number of patients who received RT. The criteria for stratification have been detailed elsewhere (7). In brief, Japanese RT institutions were stratified as follows: A1, academic institutions including university hospitals and cancer centers treating ≥430 newly diagnosed patients by RT per year; A2, <430 patients; B1 nonacademic institutions including national, prefectural, municipal, or private hospitals treating ≥130 patients per year; B2, <130 patients.

The Japanese PCS surveyors, who were active radiation oncologists, performed on-site review at each participating facility. They used an originally developed database format for esophageal cancer and investigated patient charts, radiotherapy records, and image films. Data collection included patient characteristics (*e.g.*, history, age, KPS, clinical examination results, laboratory data, diagnostic procedures, histology, and stage), details of therapeutic information (*e.g.*, RT, chemotherapy, surgery, and combinations thereof), and treatment outcomes. The Japanese PCS collected detailed clinical data on 621 patients who met the eligibility criteria for this study. Table 1 lists the number of the investigated institutions and the patients in this study. Three hundred fifty-five patients (57.6%) were from 38 academic institutions, and 263 (42.4%) were from 38 nonacademic institutions. Two hundred forty-four patients (39.3%) were aged <65 years (younger age group), 213 patients (34.3%) were aged 65–74 years (middle age group), and 164 patients (26.4%) were aged ≥75 years (older age group).

Statistical significance was tested using the χ^2 test. Ratios were calculated including unknown data but excluding missing data.

RESULTS

Median age of the patients was 68 years. Median height and body weight were 162 cm and 52.5 kg, respectively. Regarding comorbid diseases, hypertension was seen in 25% of patients, ischemic heart disease in 7%, cerebrovascular disease in 16%, chronic hepatitis in 13%, diabetes in 13%, and chronic nephritis or renal failure in 4%. Fifteen percent of esophageal cancers were detected by mass screening or medical checkup for other disease. Swallowing function at diagnosis was evaluable in 588 patients: 20% had no symptoms related to swallowing function, 33% could eat a normal diet with some symptoms, 32% could eat soft food only, 12% could drink liquids but could not eat solid food, and 3% could take nothing by mouth. Patient and tumor characteristics are shown in Table 2. Eighty-seven percent were male, and 13% were female. The female ratio in the older age group was 21% and was higher than in the other age groups ($p = 0.001$). Median KPS score was 80; 76% of patients had a score of ≥80. Patients with a good KPS score of 90–100 were fewer in the older age group than in the other groups (25% vs. 39%; $p = 0.001$). Six-hundred six (99%) of the evaluable 612 patients had SCC histology. Adenocarcinoma and adenosquamous cell carcinoma accounted for <1%. Fifty-five percent had the main lesion in the middle thoracic esophagus, 27% in the lower esophagus, and 19% in the upper esophagus. The ratio of tumor histology and main tumor location were not different among age groups. Fourteen percent had clinical Stage 0 or I disease, 32% had Stage IIA or IIB, 43% had Stage III, and 10% had Stage IV disease. The ratio clinical of Stage 0 to IIb was different among age groups (41% in the younger age group, 40% in the middle age group, and 59% in older age group).

Major treatment combinations are shown in Table 3. All patients except 8 who were treated by brachytherapy alone received external-beam RT. Chemotherapy was given to 63% of the patients; 39% received definitive CRT without surgery, and 24% received surgery in combination with RT or CRT. Fifty patients (8%) who were treated by RT and surgery did not receive chemotherapy. Twenty-seven percent of the all patients were treated by RT alone without chemotherapy or surgery. In the older age group, 62% were treated by RT alone, 35% by chemotherapy, and only 4% received surgery. Utilization ratios of chemotherapy and surgery in the older age group were significantly lower than in the younger and middle age groups ($p < 0.01$). Combinations of surgery and CRT were more frequently used in academic institutions than in nonacademic institutions (31% vs. 14%; $p < 0.01$); RT alone was applied to 33% of patients in nonacademic institutions.

Regarding drugs used for chemotherapy, 5-fluorouracil was used by 98% of patients who received CRT, cisplatin

Table 2. Characteristics of esophageal cancer patients according to age groups

Characteristic	Age group			Total (n = 621)	p
	<65 y (n = 244)	65–74 y (n = 213)	≥75 y (n = 164)		
Gender					0.014
Male	219 (90)	191 (90)	129 (79)	539 (87)	
Female	25 (10)	22 (10)	35 (21)	82 (13)	
KPS					0.001
60–70	42 (20)	33 (18)	49 (36)	124 (24)	
80	85 (41)	79 (43)	54 (39)	218 (41)	
90–100	81 (39)	70 (39)	34 (25)	185 (35)	
Missing	36	31	27	94	
Histology					0.547
SCC	238 (99)	209 (99)	159 (100)	606 (99)	
Adeno.	1 (0)	2 (1)	0	3 (0)	
Adenosq.	2 (1)	1 (1)	0	3 (0)	
Missing	3	1	5	9	
Site of lesion					0.8422
Upper	42 (18)	43 (20)	31 (18)	116 (19)	
Middle	132 (55)	114 (54)	89 (62)	335 (55)	
Lower	65 (27)	56 (26)	42 (20)	163 (27)	
Missing	5	—	2	7	
Longitudinal tumor size by endoscopy (cm)					0.595
≤5.0	75 (52)	63 (49)	67 (59)	205 (53)	
5.1–10.0	56 (39)	54 (42)	40 (35)	150 (39)	
10.1–15.0	12 (8)	10 (8)	6 (5)	28 (7)	
≥15.1	2 (1)	3 (2)	0	5 (1)	
Missing	99	83	51	233	
Median (cm)	5	6	5	5	
Clinical stage*					0.001
0, I	21 (10)	28 (15)	26 (18)	75 (14)	
IIa, IIb	68 (31)	48 (25)	59 (41)	175 (32)	
IIII	96 (44)	94 (49)	47 (33)	237 (43)	
V	30 (14)	30 (10)	7 (5)	57 (10)	
Unknown	4 (2)	3 (2)	5 (4)	12 (2)	
Missing	25	20	20	65	

Abbreviations: KPS = Karnofsky performance status; SCC = squamous cell carcinoma; Adeno. = adenocarcinoma; Adenosq. = adenosquamous cell carcinoma.

Values are number (percentage) except where noted.

* Staging system by the International Union Against Cancer, 1997.

by 85%, and nedaplatin by 98%. Only 1 patient used a taxane.

Thirty-eight patients (6%) received brachytherapy. High-dose-rate iridium or cobalt therapy was used for 28 patients, and low-dose-rate therapy was given to 10 patients. Five hundred fifty-six patients (90%) were admitted to hospitals during RT. Fifteen patients (3%) were treated on investigational approved protocols.

Details about external RT given to 412 patients who did not receive surgery but were treated by definitive CRT or RT alone are shown in Table 4. The median total dose of external RT was 60 Gy and did not differ among age groups. The median fractionation dose was 2 Gy.

Hyperfractionation was used for 16% of patients. The median initial longitudinal field size was 17 cm. Significant differences in field size among age groups were observed (mean value: 20 cm, 17 cm, and 15 cm in the younger, middle, and older age groups, respectively).

Mediastinal nodal RT for apparent or subclinical lymph node metastases was given to 82% of patients, whereas supraclavicular or upper abdominal area irradiation was given to 33% and 22%, respectively.

Table 5 shows patient backgrounds and RT parameters for definitive CRT, RT alone, and preoperative CRT. Median age of the preoperative CRT patients was 63 years and was younger than for definitive CRT and RT-alone patients. The preoperative CRT group contains 71% of the patients with Stage III–IV disease, and the ratio was higher than in the definitive CRT and RT-alone groups (62% and 58%, respectively). Median total dose was 60 Gy in definitive CRT and RT-alone patients and 40 Gy for preoperative CRT patients. Median initial longitudinal field size was 18 cm for definitive CRT patients and was longer than in RT-alone patients.

DISCUSSION

In the United States two PCSs for esophageal cancer were conducted for the periods 1992–1994 and 1996–1999 (1–4). They established the national and international benchmarks of esophageal cancer treatments and showed the role of RT

Table 3. Treatment combinations according to age groups

Treatment combination	Total	Age group			Institutions	
		<65 y (n = 144)	65–74 y (n = 141)	≥75 y (n = 164)	Academic (n = 358)	Nonacademic (n = 263)
RT with chemotherapy						
Total	393 (63)	180 (74)	155 (73)	58 (34)	240 (67)	153 (58)
Definitively	244 (39)	87 (36)	101 (47)	56 (34)	128 (36)	116 (44)
With surgery	148 (24)	92 (38)	54 (25)	2 (1)	111 (31)	37 (14)
Unknown	1	1	0	0	1	0
RT without chemotherapy						
Total	219 (35)	59 (24)	56 (26)	104 (63)	111 (31)	108 (41)
Definitively	169 (27)	26 (11)	42 (20)	101 (62)	83 (23)	86 (33)
With surgery	50 (8)	33 (14)	14 (7)	3 (2)	28 (8)	22 (8)
Unknown	0	0	0	0	0	0
Unknown about chemotherapy						
Total	9 (1)	5 (2)	2 (1)	2 (1)	7 (2)	2 (1)
Definitively	2	1	1	0	2 (1)	0
With surgery	6 (1)	3 (1)	1	2 (1)	4 (1)	2 (1)
Unknown	1	1	0	0	1	0

Abbreviation: RT = radiotherapy.
Values are number (percentage).

in multidisciplinary management of this disease. The Japanese PCS group conducted two large surveys in the 1990s and reported patient backgrounds and RT practices for esophageal cancer (5, 6). A summary of patient backgrounds and treatments from three Japanese PCSs and two U.S. PCSs is shown in Table 6.

The incidence of adenocarcinoma of the esophagus has rapidly increased in the United States since the 1970s and has accounted for approximately half of esophageal cancers in recent years (8, 9). The U.S. PCS for 1996–1999 reported the ratio of adenocarcinoma and SCC as 48.7% and 49.6%, respectively (3). Some reports from European countries also showed an increasing incidence of adenocarcinoma (10). On the other hand, this trend is not observed in Asian countries. A recent report based on the cancer registry in Japan showed the ratio of SCC to adenocarcinoma to be 26:1 (11). Preliminary results of the Korean PCS reported that 96% of investigated patients had SCC histology (12). Consistent with the previous two Japanese PCSs, 99% of patients in this study had SCC. Although adenocarcinoma mainly arises in the lower esophagus near the esophagogastric junction, the most common location of the main lesion for SCC is the midthoracic esophagus. More than half of patients had the main lesion in the midthoracic esophagus in this study. Differences in tumor histology and main tumor location may have an influence on treatment strategies and results (*i.e.* type of surgery, setting of target volume of RT, and adverse effects of the treatments).

The discrepancy between the United States and Japan was also identified in the pretherapy evaluations. Both endoscopy and esophagram were the standard evaluation methods for esophageal cancer in Japan, but approximately one third of patients did not receive an esophagram in the United States. Barium study is the traditional and relatively easy method for evaluating the gastrointestinal tract and is used for mass screening for gastric cancer in Japan. Because most gastroenterologists are skilled in doing esophagrams in Japan, it was routinely used for evaluation of esophageal cancer. Endoscopic ultrasound is the most accurate method to define both T and N staging of esophageal carcinoma in the current staging system (13). The current International Union Against Cancer staging system adopted depth of tumor invasion for T staging, which increased use of endoscopic ultrasound in each country.

Since the Intergroup study reported by Cooper *et al.* (14) showed the superiority of CRT over RT alone for esophageal cancer, the application of CRT has increased in the United States (3, 4). The ratio of using chemotherapy in combination with RT in Japan has also increased, from 40% in PCS 1995–1997 to 63% in PCS 1999–2001. Most of the CRT patients in Japan used cisplatin and 5-fluorouracil for chemotherapy. One reason is that taxanes had not been approved for esophageal cancer in Japan until 2003. The other reason was that not enough evidence was shown regarding the use of taxanes in CRT for esophageal cancer in the 1990s.

In the U.S. PCS, median total external RT dose was 50.4 Gy (1, 3). However, our data showed the median total external dose in Japan to be 60 Gy, and it was same for RT-only patients and definitive CRT patients. Not many clinical trials have investigated the total dose in CRT for esophageal cancer. The standard dose used in the United States is considered to be based on the results of a Phase III trial (INT 0123) showing no benefit of higher radiation on survival or locoregional control (15). After publication of the results of INT 0123, clinical studies investigating total RT dose in esophageal cancer in the United States seem to have been stopped. On the other hand, some Phase II studies conducted in Japan in the 1990s testing the efficacy of CRT for esophageal cancer used a total dose of 60 Gy, and preliminary results showed excellent outcomes (16, 17). Ohtsu *et al.* (16) studied 44 patients

Table 4. External RT parameters in nonsurgery patients

Characteristic	Age group <65 y (n = 244)	65–74 y (n = 213)	≥75 y (n = 164)	Total (n = 621)	p
Total external RT dose (Gy)					—
<30	4 (4)	7 (5)	6 (4)	17 (4)	
30.1–40	14 (12)	13 (9)	9 (6)	36 (9)	
40.1–50	7 (6)	12 (9)	13 (8)	32 (8)	
50.1–60	40 (35)	40 (28)	47 (30)	127 (31)	
60.1–70	40 (35)	66 (47)	77 (49)	183 (44)	
>70	9 (8)	3 (2)	4 (3)	16 (4)	
Missing	—	—	1	1	
Median (Gy)	60.0	60.0	60.0	60.0	
Hyperfractionation					0.500
Done	14 (12)	25 (18)	25 (16)	64 (16)	
Not done	100 (88)	116 (82)	132 (84)	348 (84)	
Missing	—	—	—	—	
Initial longitudinal field size (cm)					0.001
≤10.0	3 (3)	14 (10)	25 (16)	42 (10)	
10.1–15.0	21 (19)	39 (28)	53 (34)	113 (28)	
15.1–20	35 (31)	48 (34)	47 (30)	130 (32)	
20.1–25	34 (30)	26 (19)	18 (12)	78 (19)	
≥25.1	19 (17)	13 (9)	12 (8)	44 (11)	
Missing	2	1	2	5	
Mean (cm)	20	17	15	17	
Mediastinal nodal area irradiation					0.063
Done	96 (86)	110 (79)	116 (74)	322 (79)	
Not done	16 (14)	29 (21)	41 (26)	86 (21)	
Unknown	—	—	—	—	
Missing	2	2	—	4	
Supraclavicular nodal area irradiation					
Done	41 (37)	31 (22)	27 (17)	99 (24)	0.003
Not done	70 (63)	108 (78)	129 (82)	307 (75)	
Unknown	—	—	1 (1)	1	
Missing	3	2	—	5	
Upper abdominal nodal area irradiation					0.050
Done	32 (29)	33 (24)	25 (16)	90 (22)	
Not done	79 (71)	106 (76)	130 (83)	315 (77)	
Unknown	—	—	2 (1)	2 (1)	
Missing	3	2	—	5	
Field reduction					0.517
Done	87 (78)	104 (74)	111 (71)	302 (74)	
Not done	24 (21)	35 (25)	45 (29)	104 (25)	
Unknown	1 (1)	1 (1)	1 (1)	3 (1)	
Missing	2	1	—	3	

Abbreviation: RT = radiotherapy.
Values are number (percentage).

with T4 and/or M1 by lymph node treated with 60 Gy of external RT and concurrently administered cisplatin and 5-fluorouracil. Three-year overall survival was 23%. This result, published in 1999, may have impacted clinical practice during this study period. Supported by the results of this study, a total dose of 60 Gy in CRT might become standard practice in Japan. Ishikura *et al.* (18) reported substantial late pulmonary and cardiac toxicities by 60 Gy of thoracic CRT with a conventional opposed two-beam technique. Additional investigation regarding the optimal total dose of CRT for esophageal cancer with modern RT techniques is warranted.

Patients aged ≥75 years account for 26% of all patients in this study. Some characteristics of patient backgrounds and differences of treatment for elderly patients are apparent from this study. More early-stage patients and more low-KPS patients were included in the elderly group than in the middle or younger age groups. Elderly patients were not frequently treated by multimodality treatments in combination with surgery and chemotherapy but rather by RT alone. Although surgery in combination with CRT or chemotherapy is the standard treatment for operable esophageal cancer, patients with a low performance status or with comorbid disease were medically unfit for surgery. Radiotherapy alone might be frequently chosen as the most noninvasive treatment for elderly esophageal cancer patients. Meanwhile, 34% of elderly patients received

Table 5. Backgrounds and radiotherapy parameters of patients who received definitive CRT, RT alone, or preoperative CRT

Parameter	Definitive CRT (n = 241)	RT alone* (n = 146)	Preoperative CRT (n = 86)
Male/female	89/11	80/20	86/14
Age (y), median	68	78	63
KPS >90	29	34	36
Main tumor lesion, upper	21	18	20
Stage 0–IIb	36	34	29
Stage III–IV	62	58	71
Total external RT dose (Gy)			
≤30	4	5	35
30.1–40	11	4	33
40.1–50	7	10	12
50.1–60	32	31	12
60.1–70	43	45	10
≥70.1	4	4	
Median (Gy)	60	60	40
Initial longitudinal† field size (cm)			
≤10	5	17	3
10.1–15.0	23	36	27
15.1–20.0	36	26	37

Abbreviations: CRT = chemoradiotherapy; RT = radiotherapy.
Values are percentages except where noted.
* RT without chemotherapy.
† Craniocaudal direction.

definitive CRT. There are not enough data available regarding the efficacy of chemoradiation in elderly or low-KPS patients (19), and criteria for reducing RT dose and chemotherapy dose for these patients have not been established. The intensity of chemotherapy used for CRT was not clearly investigated in this study, but regarding RT field, a narrow field excluding the supraclavicular area was generally preferred for elderly patients. Further clinical investigations evaluating the role of CRT and RT in elderly esophageal cancer patients are needed.

In conclusion, this PCS describes patient backgrounds and general patterns of RT practice for esophageal cancer

Table 6. Comparison of patient backgrounds and treatment combinations among three Japanese PCSs and U.S. PCSs

Parameter	PCS 1992–1994 (n = 561)	PCS 1995–1997 (n = 776)	PCS 1999–2001 (n = 621)	U.S. PCS 1992–1994 (n = 400)	U.S. PCS 1996–1999 (n = 414)
Academic/nonacademic	46/54	62/38	58/42	51/49	NA
Median age (y)	66	67	68	66.7	64
Male/female	86/14	85/14	87/13	76.5/23.5	77/23
KPS ≥90	33	27	35	47	56
Esophagram done	NA	92	93	69	64
Endoscopy done	NA	91	96	94	96
Endoscopic ultrasound done	NA	21	27	4	18
Clinical Stage I by AJCC, 1983 version	15	19	20	15	16
Squamous cell carcinoma	99	100	99	61.5	49
Main tumor location, middle thorax	NA	62	55	NA	NA
External RT done	99	99	99	Nearly all	100
External beam energy >6 MV	85	78	92	>76	NA
Median fraction external RT dose (Gy)	2.0	2.0	2.0	1.8	1.8
Median total external RT dose (Gy)	60.0	60.0	60.0	50.4	50.4
Brachytherapy done	10	12	6	8.5	6
Chemotherapy done	35	40	63	75	89
Preoperative RT + CT followed by surgery	16	9	16	14.5	27
Surgery followed by RT + CT	22	19	18	11	6
Definitive CRT	22	25	39 5	4	56
RT alone without surgery or CT	34	44	27	20	10

Abbreviations: PCS = Patterns of Care Study; NA = not applicable; KPS = Karnofsky performance status; AJCC = American Joint Committee on Cancer; RT = radiotherapy; CT = chemotherapy; CRT = chemoradiotherapy.
Values are percentages except where noted.

in Japan. Tumor histology and standard RT dose were different between the United States and Japan. Care should be taken when comparing data from these two countries. This study also revealed the treatment characteristics for elderly esophageal cancer patients. Repeated surveys will demonstrate the trends for esophageal cancer treatment in Japan and will provide useful data for international comparison.

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Radiotherapy of keloids

Dose–response relationship and dose optimization in radiotherapy of postoperative keloids

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ABSTRACT

Background and purpose: The treatment dose and fractionation dose that are considered in postoperative keloids had been reported in the previous studies. We performed retrospective analysis to elucidate the factors influencing the treatment outcome.
Materials and methods: From 1979 to 1994, 194 lesions in 119 patients received postoperative radiotherapy after excision with the total dose ranging from 16 Gy/8 fr to 40 Gy/8 fr (mean: biologically effective dose (BED) 33.5 Gy). Kilo-voltage X-rays (55 or 100 kVp) or electron beams (4 or 6 MeV), including entire keloid scars, and any suture/puncture holes with a margin around the lesion were used. The median follow-up period was 36 months (range 12–164 months).
Results: Symptomatic pain and itching relief were achieved in 96% and 91%, respectively. The relapse rate was 11% at 20 Gy in five fractions or higher dose, while 43% at less than 20 Gy. On the other hand, the incidence of adverse effects was significantly higher for patients receiving more than 20 Gy in five fractions.
Conclusion: There was a significant correlation between the relapse rate and the total dose of irradiation, and between adverse effects and the total dose. To correlate local control and adverse effects, we proposed 20 Gy in five fractions as the optimal dose for the postoperative of keloids. A significant correlation between relapse rate and the interval time between excision and radiotherapy was not found in our current study.
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There is no universally effective treatment method for keloids and hypertrophic scars. The recurrence rates after surgical excision alone vary from 50% to 80%, thus leading to the development of many adjuvant therapeutic modalities [1]. Several therapeutic techniques have been tested, including continuous pressure after surgery, corticosteroid injections [2], carbon dioxide laser [3], NdYaG laser [4], silicone gel [5], retinoic acid [6], and silastic sheet coverage [7]. However, these methods seem unsatisfactory for preventing keloid recurrence; the recurrence rate is reported to be above 50%.

The value of radiation therapy in the treatment of keloids has been known for many years. In a randomized trial, Sclafani et al. [8] observed a higher recurrence of keloids after surgery and steroid injections than after surgery and radiotherapy. After the total excision of keloids and hypertrophic scars, radiation therapy has been demonstrated as one of the most effective treatment methods to prevent recurrence, showing a recurrence rate around 20% [9–12].

In this study, we reviewed keloids treated with postoperative radiotherapy in our hospital, and retrospectively analyzed in regard to long-term control, symptomatic relief and adverse effects to elucidate the factors influencing the treatment outcome.

Materials and methods

Patients

From September 1979 to July 1994, 194 lesions in 119 patients received postoperative radiotherapy at Kyoto University Hospital. The characteristics of the patients and lesions are summarized in Tables 1 and 2. All patients were Asian, 35 men and 84 women, aged 4–75 years with a median age of 25 years. Fifty-seven of the 194 lesions had been treated previously with surgical excision and/or local steroid injection, but none had received radiotherapy previously.

Treatment methods

The treatment parameters are summarized in Table 3. Various dose schedules were used, with the total dose ranging from 16 Gy in 8 fractions to 40 Gy in 8 fractions. The total treatment

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Table 1
Characteristics of 119 patients.

	Number of patients
Sex	
Male	35
Female	84
Age	
<10	3
10–19	32
20–29	44
30–39	10
40–49	10
50–59	10
60–69	5
70≤	5
Median (range) 25 (4–75)	
Keloid lesions	
1	84
2	19
3	5
4	6
5	1
6	2
7	1
12	1
Median (range) 1 (1–12)	
Total	119

Table 2
Characteristics of 194 keloids.

	Number of keloids
Previous treatment	
(−)	137
(+)	57
Size (cm)	
<2.0	10
2.0–3.9	44
4.0–5.9	34
6.0–7.9	26
8.0–9.9	23
10.0–14.9	26
15.0–19.9	17
20≤	14
Site	
With high stretch tension	149
Sternum	68
Shoulder	40
Chest wall	23
Arm	11
Back	7
Without high stretch tension	45
Neck	15
Upper abdomen	11
Lower abdomen	10
Ear	4
Lower limbs	4
Face	1
Etiology	
Minor stimulations	109
Acne	44
Varicella	16
Vaccination	15
Insect wound	7
Herpes	1
Unknown	26
Major stimulations	85
Surgery	48
Burn	17
Trauma	17
Abscess	5
Total	194

time ranged from 5 days to 47 days, with a median of 9 days. The interval from excision to irradiation ranged from 1 day to 72 days, with a median of 7 days. Four fractions of 4 Gy in 8–10 days were the most common treatment schedule for postoperative radiotherapy.

In most cases, either 55 kVp (10 mA, 1.0 mm Be and 0.78 mm Al filters) or 100 kVp (8 mA, 1.0 mm Be and 1.7 mm Al filters) X-ray at a dose rate of 1–11 Gy/min was used. For only six lesions, 4 or 6 MeV electron beams were used. The choice of radiation source depended on the height, size, and position of the lesion. The 90% isodose target area included the entire postoperative scar and any suture/puncture hole with a margin of 3–5 mm around the lesion. Non-target areas were shielded by an individually cut 1–2 mm lead sheet.

Evaluation of treatment response and adverse effect

The initial response to treatment was evaluated in all 194 lesions at the first follow-up examination (1–6 months after the end of radiation treatment). Symptomatic relief was assessed if the lesion had caused pain and/or itching before treatment. A judgment of recurrence was made when the height of a lesion began to increase even just a little.

The existence of moderate to severe skin hyperpigmentation and/or telangiectasis with depigmentation was regarded as a positive adverse effect. Mild or transitory pigmentation, which disappeared within a year after treatment and did not affect cosmesis, was not regarded as a positive adverse effect.

Our follow-up policy for patients with keloids consists of a 6-month observation for at least 2 years after radiotherapy. We used telephone interviews for some patients who could not visit our hospital. All keloids were enrolled in the present study were followed up for 12 months or longer. The follow-up time ranged from a minimum of 12 months to a maximum of 164 months, with a median follow-up of 36 months.

Statistical analysis

In long-term recurrence rate and the positive adverse effect rate, univariate analysis using the logrank test and multivariate analysis using the Cox proportional hazard model were performed with the following factors: gender, patient age, involved site, etiology, keloid size, previous treatment, affliction time, interval from excision, source of radiation, and total dose. Various dose schedules were used, instead of the total dose, so we calculated biologically effective dose (BED) according to Kal et al. [13]. All calculations were with Stat View J 5.0 software (SAS Institute Inc, Chicago, IL). Differences with a p-value of less than 0.05 were considered statistically significant.

Results

Symptomatic relief is summarized in Table 4. Itching and pain relief was achieved in 91% and 96% of symptomatic keloids, respectively.

We calculated BED according to Kal et al. [13], and plotted the control rates as a function of BED. We showed a dose–response relationship in Fig. 1a. Long-term recurrence rates of postoperative keloids are shown in Fig. 1b. At 36 months, 64 of 194 keloids treated with excision and radiotherapy had relapsed (33%). The univariate and multivariate analyses are shown in Table 5. Univariate

Table 3
Treatment methods of 194 keloids.

	Number of fractions	Number of keloids
Fraction dose (Gy)		
2	8	3
2	10	5
2	13	4
2	20	2
2.5	8	1
2.5	10	1
2.5	14	1
3	6	1
3	10	13
3	12	1
3	13	1
4	4	128
4	5	4
4	6	24
5	4	1
5	5	1
5	6	2
5	8	1
Radiation source		
X-ray		
55 kVp		74
100 kVp		114
Electron		
4 MeV		4
6 MeV		2
Total treatment time (days)		
5–9		106
10–14		47
15–19		11
20–24		9
25–29		12
30–34		2
35–39		5
40≤		2
Median 9 days		
Interval between operations and irradiations (days)		
<2		22
2–5		66
6–9		33
10–14		37
15–19		14
20–24		5
25–29		12
30≤		5
Median 7 days		
Total		194

Table 4
Symptomatic relief.

Symptomatic relief	Pain lesions (%)	Itching lesions (%)
None	116	65
Relief	75/78 (96)	118/129 (91)
No change	3/78 (4)	11/129 (9)
Worse	0	0
Total	194	194

analysis showed that the recurrence rate was significantly higher for doses lower than 20 Gy in five fractions and for women. In multivariate analysis, these factors remained significant.

The positive adverse effect rate was 19% (36/194) in all lesions, and univariate and multivariate analyses of adverse effect rate are shown in Table 6. Univariate analysis showed that the adverse effect rate was significantly higher for elderly patients (≥25 years old), minor etiology, large keloids (longer axis ≥5 cm), previous treatment, use of high voltage X-rays (100 kVp) or electrons, and total dose of 20 Gy in five fractions or higher. In multivariate analysis, the factors of elderly patients, minor etiology, and of previous treatment remained significant.

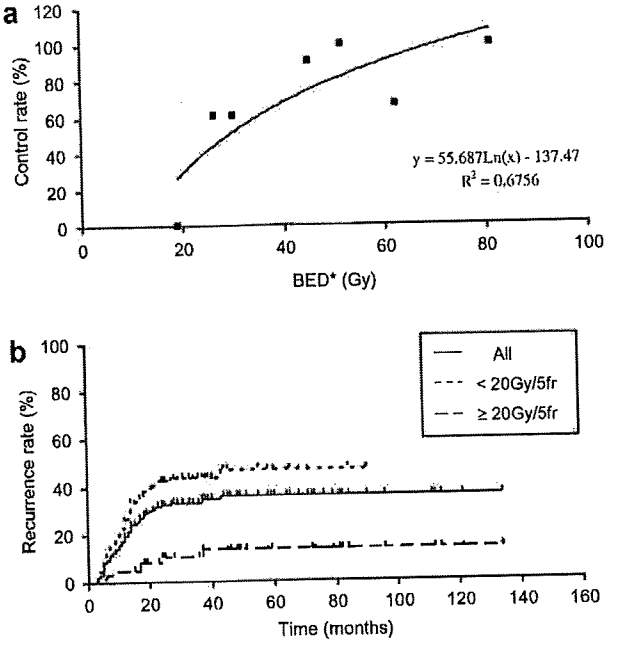

Fig. 1. (a) Control rate of keloids as function of the biologically effective dose (BED). There was a significant correlation between the control rate and biologically effective dose (BED*). *BED calculation according to Kal et al. [13]. (b) Long-term recurrence rate in post-operative radiotherapy according to the total dose. The recurrence rate ≥20 Gy in five fractions was significantly lower than that with <20 Gy in five fractions. **Significant (logrank test).

There were no cases of serious toxicity, defined as World Health Organization grade 3 or higher. There were no cases of malignant tumors being generated at the keloid site.

Discussion

Consistent reliable control of keloids using postoperative irradiation has been reported by many authors [10–12,14–18]. There is a controversy concerning the total dose in these previous reports, as well as whether the treatment was given in one fraction or in several fractions. There was no consensus with respect to the total dose and dose fractionation in the treatment of keloids. A summary of the local control rates of postoperative radiotherapy of keloids is shown in Table 7 [1,10–12,14,19–27].

The mechanism of the radiotherapeutic prevention of keloids is still poorly understood. One of the proposed mechanisms is the control of collagen synthesis by eliminating abnormally activated fibroblasts and promoting the existing normal fibroblasts [28]. In vitro experimental evidence suggests that a fraction dose of about 5 Gy may be effective in inducing radiolysis of fibroblasts [18]. Using in vivo experiments with rat skin, the radiolytic process of fibroblasts starts minimally from 0.5 to 2.5 Gy. Recoiled collagen fibrils return to their normal shape and size 4–6 weeks after radiotherapy [18].

However, a higher dose seems necessary in the clinical situation. Brown and Bromberg identified a minimum isoeffect time–dose line for reliable postoperative keloid control at 9–10 Gy delivered over 1 week or 15 Gy over 2 weeks. With BED above this level, 100% control was achieved [29]. Edsmyer et al. confirmed the threshold dose for reliable control as 12–14 Gy in single fraction by X-ray in the postoperative setting and it is probably best to give the radiotherapy immediately after the excision [24,30]. Van den

Table 5
Long-term control of 194 keloids.

Factor	Category (n)	Recurrence rate (%)	Univariate analysis	Multivariate analysis
Gender	Male (85)	25	$p = 0.031^{*}$	$p = 0.0069^{**}$
	Female (109)	39		
Age	<25 y.o. (132)	38	$p = 0.083$	$p = 0.42$
	≥25 y.o. (62)	23		
Site	Without high tension (45)	29	$p = 0.48$	$p = 0.50$
	With high tension (149)	34		
Etiology	Minor (109)	37	$p = 0.23$	$p = 0.075$
	Major (85)	28		
Longer axis	<5 cm (74)	36	$p = 0.53$	$p = 0.75$
	≥5 cm (120)	31		
Previous treatment	– (137)	32	$p = 0.62$	$p = 0.97$
	+ (57)	35		
Affliction time	<5 years (73)	38	$p = 0.17$	$p = 0.063$
	≥5 years (121)	30		
Interval from operation	<6 days (88)	34	$p = 0.83$	$p = 0.62$
	≥6 days (106)	32		
Source	55 kvp (74)	37	$p = 0.54$	$p = 0.15$
	100 kvp, electron (120)	31		
Total dose	<20 Gy (132)	43	$p < 0.0001^{*}$	$p = 0.0002^{**}$
	≥20 Gy (62)	11		

* Significant (logrank test).
** Significant (Cox proportional hazard model).

Brenk et al. reported that possible skin necrosis after single-fraction irradiation encouraged fractionated radiotherapy schedules, regardless of the dose [31]. According to Kal et al. [13], biologically effective doses (BEDs) of the various irradiation regimens were calculated using the linear–quadratic concept, and the recurrence rate decreased as a function of BED in the range of BED above 10 Gy. At a BED higher than 30 Gy, the recurrence rate was lower than 10%.

Thus, the dose–response relationship in the treatment of postoperative keloids had been reported in several previous studies. Also, in our study, we found a significant correlation between the recurrence rate and the total dose. The recurrence rate was 11% at a total dose of 20 Gy in five fractions or higher, while 43% under 20 Gy in five fractions. The recurrence rate was 33% for all lesions evaluated in this study, which was comparable to that of the previous studies (Table 7); however, the recurrence rate for lesions treated with the schedule of 20 Gy in five fractions, equivalent to a BED of 30 Gy according to Kal et al. [13], was 18%. It was suggested that this dose fraction was necessary and sufficient for keloid control. On the other hand, the positive adverse effect rate was also dose-dependent; 44% at a total dose of 20 Gy in five fractions or higher, while 7% at under 20 Gy; however, the positive adverse effect rate for the schedule of 20 Gy in five fractions was not very high (18%). Thus, we considered this dose fraction to be acceptable regarding morbidity. Therefore, since 1995, we have

Table 6
Adverse effects of 194 keloids.

Factor	Category (n)	Adverse effect (%)	Univariate analysis	Multivariate analysis
Gender	Male (85)	22	$p = 0.30$	$p = 0.56$
	Female (109)	16		
Age	<25 y.o. (132)	13	$p = 0.0057^{*}$	$p = 0.0018^{**}$
	≥25 y.o. (62)	31		
Site	Without high tension (45)	11	$p = 0.092$	$p = 0.61$
	With high tension (149)	21		
Etiology	Minor (109)	26	$p = 0.0047^{*}$	$p = 0.032^{**}$
	Major (85)	9		
Longer axis	<5 cm (74)	9	$p = 0.041^{*}$	$p = 0.64$
	≥5 cm (120)	24		
Previous treatment	– (137)	24	$p = 0.0071^{*}$	$p = 0.0089^{**}$
	+ (57)	5		
Affliction time	<5 years (73)	12	$p = 0.25$	$p = 0.33$
	≥5 years (121)	22		
Interval from operation	<6 days (88)	24	$p = 0.53$	$p = 0.70$
	≥6 days (106)	15		
Source	55 kvp (74)	5	$p = 0.0037^{*}$	$p = 0.13$
	100 kvp, electron (120)	27		
Total dose	<20 Gy (132)	7	$p < 0.0001^{*}$	$p = 0.039^{**}$
	≥20 Gy (62)	44		

* Significant (logrank test).
** Significant (Cox proportional hazard model).

Table 7
Summary of local control rates of post-operative radiotherapy of keloids.

Author (Year)	Number of cases	Median follow-up time (months)	Treatment dose (Gy)	Number of fraction	Radiation type	Interval between operation and irradiation (days)	Local control rate (%)	BED (Gy)
Cosman (1961)	94	12	7.7*	4	Deep X	14–42	69	10.6*
Craig (1965)	16	12	7.7*	1	100 kVX	<2	87	16.2*
King (1970)	32	Unknown	9.6–28.8*	1–3	1–3 MeV–E	<1	74.1	Mean 29.7*
Mathangi-Ramakrishan (1974)	36	Unknown	15.4*	2–3	Deep X	<1	98	Mean 34.7*
Edsmyr (1975)	103	2	4.8–23*	1–14	45,100 kVX	<8	80	Mean 28.6*
Levy (1976)	35	6	14.4–17.3*	5–6	100 kVX	1–2	88	Mean 23.8*
Ollstein (1981)	68	12	14.4*	3	100 kVX	<1	79	25.1*
Enhamre (1983)	62	6	9.6–14.4*	1–3	20 kVX	1–14	88	Mean 32.7*
Borok (1988)	375	Unknown	3.8–15.4*	Variety (3–4**)	X, E	<2**	97.6	15.9–21.3**
Kovalic (1989)	113	117	3–20	1–5	X 89%; Co, E 11%	1–21	73	Mean 18.8
Doornbos (1990)	263	12	4.5–18	2–4	120 kVX	3–10	85.7***	24.1***
Escarmant (1993)	570	15	8–30	1	LDR	<2	79	Mean 55.8
Norris (1995)	24	24	8–12*	1–3	E 5; 100 kVX 19	1–68	47	Mean 17.8*
Ogawa (2003)	14	24	15	3	4 MeV–E	<2	67	22.5
Current study	194	36	16–40	4–20	55, 100 kVX 188; 4, 6 MeV-E 6	1–72 (mean 9.7)	67	Mean 33.5

LDR, low dose rate; 192Ir; X, X-ray beam; E, electron beam; Co, cobalt beam.
* For BED calculation we applied 1R = 0.96 cGy.
** After 1981, radiation technique was standardized to 1200–1600 rad in three to four fractions.
*** 15 Gy in three fractions.

employed a schedule of 20 Gy in five fractions for almost all newly treated postoperative keloids, in the expectation of preserving low morbidity without compromising the control rate.

In the prognostic analysis of this study, female gender was associated with a higher recurrence rate. Previous studies had scarcely demonstrated a correlation between gender and recurrence. The cure of hypertrophic scars is occasionally protracted in young women, maybe because the propagation of fibroblasts is exceeded during recovery at the wound [32,33]. In addition, elderly patients and previous treatment were associated with a higher positive adverse effect rate. Aging and treatment history may cause potentially enhanced radiosensitivity of normal cutaneous tissue, possibly resulting in greater adverse effects.

The influence of the interval between excision and the commencement of radiotherapy on recurrence remains controversial. Cosman et al. [1,34] and Hintz [35] suggested an advantage of the rapid initiation of postoperative irradiation. In contrast, Enhamre and Hammar [36] found no association with the results and interval time between excision and irradiation. In our study, we did not find a significant correlation between the recurrence rate and the interval between excision and radiotherapy, possibly because its influence may have been masked by the large variation of the dose fractionation. This should be further studied using a uniform dose fractionation schedule.

The total radiation dose correlated significantly both with the recurrence rate and with the positive adverse effect rate. It was suggested that 20 Gy in five fractions was a recommendable dose fractionation schedule in the expectation of preserving low morbidity without compromising the control rate.

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ORIGINAL ARTICLE

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Results of a preliminary study using hypofractionated involved-field radiation therapy and concurrent carboplatin/paclitaxel in the treatment of locally advanced non-small-cell lung cancer

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Abstract

Background. We aimed to evaluate the feasibility and efficacy of hypofractionated involved-field radiation therapy (IFRT) omitting elective nodal irradiation (ENI) with concurrent chemotherapy for locally advanced non-small-cell lung cancer (NSCLC).

Methods. Between July 2004 and July 2006, ten patients with locally advanced NSCLC were included in this study. One had stage IIIA and 9 had stage IIIB disease. The treatment consisted of IFRT in fractions of 2.5 Gy and weekly carboplatin (CBDCA)/paclitaxel (PTX). Hypofractionated IFRT with a median total dose of 65 Gy with median percent total lung volume exceeding 20 Gy (V20) of 20.2%, and a median of five courses of chemotherapy with weekly CBDCA (area under the curve, 1.5–2.0)/PTX (30–35 mg/m^2) were given to all patients.

Results. The median survival time and the 1-, 2-, and 3-year overall survival rates were 29.5 months and 90.0%, 58.3%, and 43.8%, respectively. No elective nodal failure was encountered during the median follow up of 18.2 months. No acute or late toxicities of grade 3 or worse were observed. No in-field recurrence occurred in the group with a total dose of 67.5 Gy or more, but there was such recurrence in 83.3% of those in the group with less than 67.5 Gy.

Conclusion. Hypofractionated IFRT with weekly CBDCA/PTX was a feasible treatment regimen. Hypofractionated IFRT with a total dose of 67.5 Gy or more could be a promising modality to improve the treatment results in patients with locally advanced NSCLC.

Key words Involved-field radiation therapy (IFRT) · Elective nodal irradiation (ENI) · Three-dimensional conformal radiation therapy (3DCRT) · Non-small-cell lung cancer (NSCLC) · Carboplatin (CBDCA) · Paclitaxel (PTX)

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Introduction

At present, the standard evidence-based treatment for advanced non-small-cell lung cancer (NSCLC), based on data in patients with locally advanced disease, is considered to be concurrent chemotherapy (CHT)-radiation therapy (RT) with a platinum-based regimen.[1] This concurrent CHT-RT provides a median survival time (MST) of 16–17 months, a 1-year overall survival (OAS) rate of 60%–70%, and a 2-year OAS rate of 30%–40%,[2–5] but these results should be open to further improvement. In addition, there is a problem regarding the fact that grade 3/4 radiation esophagitis occurs in 20%–30% of these patients.[3–5]

Local recurrence is one reason for the poor survival rate after RT, and it has been reported that an improvement in local control leads to increased survival in locally advanced NSCLC.[6,7] Therefore. intensification of the in-field effect to improve local control has previously been attempted. However, even though an increase in the total dose and a shortening of the overall treatment time are effective for

improving the local control, problems remain due to the increase in severe esophagitis and pneumonitis.

Recently, involved-field radiation therapy (IFRT) omitting elective nodal irradiation (ENI) to achieve improved local control by high total dose irradiation, without increasing toxicity, has been attempted for locally advanced NSCLC, and the results of these attempts suggested that it might be possible to irradiate safely with a high total dose using IFRT.[8,9] After the publication of these results, we introduced IFRT for locally advanced NSCLC within affiliated institutions of Hiroshima University, in 2001. In addition, we started a preliminary study in 2004 to evaluate the feasibility and efficacy of hypofractionated IFRT with concurrent carboplatin CBDCA)/paclitaxel (PTX). The once-daily fraction is 2.5 Gy, in order to improve the in-field control due to the high total dose irradiation with a higher fraction dose and to also to shorten the overall treatment time.

Patients and methods

Between July 2004 and July 2006, a total of ten patients with locally advanced NSCLC were enrolled in this preliminary study and were evaluated. Before inclusion, all patients signed a written study-specific informed consent. In addition to giving them the details of this study, we also explained that the treatment would be cancelled if they rejected the designed treatment of this study during the treatment period. Eligibility criteria included patients with locally advanced stage IIIA-N2 disease or stage IIIB disease (excluding malignant pleural effusion, malignant pericardial effusion, and lymphangitic carcinomatosis), histologically or cytologically confirmed NSCLC, age between 20 and 74 years, Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, no prior therapy for this malignancy, and adequate laboratory and pulmonary functions. Adequate laboratory function included a leukocyte count of 4000/mm^3 or more, platelet count of 100 000/mm^3 or more, hemoglobin 9.5 g/dl or more, total bilirubin level less than or equal to the upper limit of normal, and creatinine clearance of 60 ml/min or more. Adequate pulmonary function was defined as a forced expiratory volume in 1 s of more than 1.0 l and PaO_2 of 70 torr or more. Any patients with previous malignancies or severe complications (such as obvious interstitial pneumonitis, advanced pulmonary emphysema, and poorly controlled diabetes) were excluded. Before therapy, all patients were evaluated clinically with a history, physical examination, laboratory examination, radiographic studies, pulmonary function test, and electrocardiogram (ECG). The laboratory examination included a complete blood cell count, liver function studies, renal function studies, and measurement of electrolytes. The radiographic studies included chest X-ray, thoracic-abdominal computed tomography (CT), head magnetic resonance imaging (MRI), and bone scintigraphy. Whole-body fluorodeoxyglucose-positron emission tomography (FDG-PET) scan was not routinely performed.

The patient and tumor characteristics are shown in Table 1. The patients' median age was 68 years (range, 54–74 years); nine were males, and one was female. Five (50.0%) presented with squamous cell carcinoma, four (40.0%) with adenocarcinoma, and one (10.0%) with large-cell carcinoma. One (10.0%) had stage IIIA disease (T2N2; $n = 1$) and nine (90.0%) had stage IIIB (T1N3, $n = 1$; T2N3, $n = 5$; T4N0, $n = 1$; T4N1, $n = 1$; T4N2, $n = 1$). Regarding the staging, all patients underwent thoracic-abdominal CT, head MRI, and bone scintigraphy. Whole-body FDG-PET/CT was performed in four patients (40.0%).

All patients were treated with three-dimensional conformal radiation therapy (3DCRT) that was planned with a three-dimensional radiation treatment planning system. All patients underwent treatment-planning CT of the chest for identification of the target and normal anatomy. The treatment-planning CT was performed with continuous slices measuring 5 mm in thickness and with a long scan time of 3 s or more per image without breath-holding, throughout the whole lung and tumor. Only lymph nodes with a short-axis diameter of 10 mm or more on CT were included in the gross tumor volume (GTV-LN) without histological confirmation, in addition to the primary tumor (GTV-P). However, when lymph node involvement was suspected on FDG-PET/CT according to diagnosis by a PET specialist, lymph nodes with a short axis of less than 10 mm were included in the GTV-LN. In addition, the clinical target volume (CTV) was defined as the GTV-P plus the GTV-LN. The planning target volume (PTV) was con-

Table 1. Characteristics of patients and tumors

Patient no.	Age (years)	Sex	PS	Histology	T	N	M	Stage	Location of primary tumor
1	57	M	0	SQ	2	3	0	IIIB	Rt. LL
2	60	M	0	AD	1	3	0	IIIB	Rt. UL
3	65	F	0	AD	2	3	0	IIIB	Lt. UL
4	74	M	0	SQ	2	3	0	IIIB	Lt. UL
5	72	M	0	SQ	4	2	0	IIIB	Rt. LL
6	70	M	0	SQ	2	2	0	IIIA	Lt. LL
7	73	M	0	SQ	4	0	0	IIIB	Lt. UL
8	72	M	1	LC	2	3	0	IIIB	Rt. UL
9	58	M	1	AD	4	1	0	IIIB	Lt. UL
10	54	M	0	AD	2	3	0	IIIB	Rt. UL

PS, performance status; SQ, squamous cell carcinoma; AD, adenocarcinoma; LC, large cell carcinoma; Rt., right; Lt., left; LL, lower lobe; UL, upper lobe

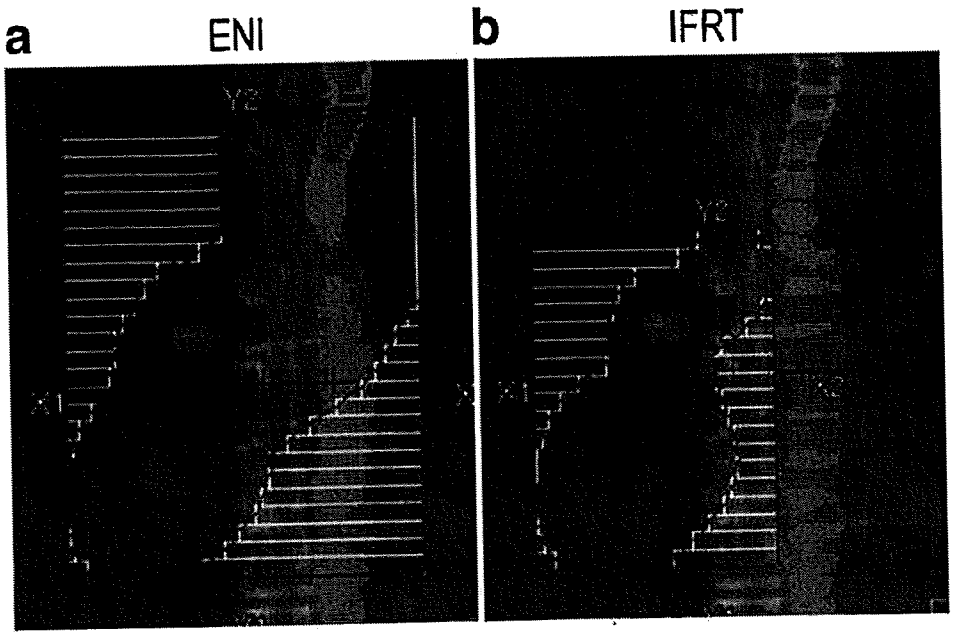

Fig. 1a,b. Digitally reconstructed radiographs (DRRs) demonstrating **a** the typical elective nodal irradiation (ENI) field and **b** the involved-field radiation therapy (IFRT) for a patient with stage IIIA non-small-cell lung cancer (NSCLC). The primary tumor is displayed in *red*; metastatic lymph nodes are displayed in *green*; the esophagus is displayed in *orange*. On DRR of IFRT, the esophagus is outside the radiation field

toured around the CTV with a three-dimensional margin of 10–15 mm (thus making allowances for the location of the primary tumor, the respiratory mobility of the tumor, and the setup margin). In addition, a port margin of 5 mm was set around the PTV. The difference between the ENI and IFRT fields is shown in Fig. 1. The doses were calculated at the isocenter with heterogeneity correction algorithms, using both a superposition method (6 patients) and a convolution method (4 patients). The hypofractionated IFRT was delivered on a linear accelerator, using a 6- to 10-MV photon beam. The hypofractionated IFRT was delivered via a coplanar technique or a noncoplanar technique with multiple fields to deliver a dose of 2.5 Gy once daily in five fractions weekly, and all radiation fields were treated every day. In the course of IFRT, field reductions according to the tumor volume reduction were permitted.

The fraction dose setting in this study was selected based on the preliminary results reported by Kimura et al.,[10] which included accelerated hyperfractionated IFRT (66–75 Gy in 1.5-Gy twice-daily fractions) +/– concurrent CHT. Before the induction of IFRT, irradiation by using accelerated hyperfractionation was considered for IFRT to shorten the overall treatment time. However, we thought that twice-daily fractions might not be practical under clinical conditions, and we decided to use once-daily fractions of 2.5 Gy, whose biologically effective doses (BED) Gy 10 and BED Gy 3 in a day were almost equivalent to that of twice-daily fractions of 1.5 Gy. It was prescribed that the dose variation within the PTV be limited to between 90% and 107% of the prescribed dose. The maximum dose to the spinal cord was kept at less than 40 Gy. The percent total lung volume (the volumes of both lungs minus the CTV) exceeding 20 Gy (V20) was kept to less than 30% in principle, as a higher volume was a predictive factor for the risk of radiation pneumonitis.[11,12] The limitation of the V20 value was considered based on the findings of the Radiation Therapy Oncology Group (RTOG) 9311 phase I study performed by Bradley et al.,[13] in which the estimated rate of grade 3 or more lung toxicity was 0% after IFRT of 70.9 Gy was given in 2.15-Gy once-daily fractions to patients with V20 values of 25% to less than 37%.

The minimal planned total dose was prescribed to be 60 Gy/24 fractions (BED Gy10 is equivalent to that of 62 Gy/31 fractions). The maximum planned total dose was prescribed according to the V20 value as follows: (1) V20 less than 15%, 70 Gy/28 fractions (BED Gy10 is almost equivalent to that of 74 Gy/37 fractions), (2) 15% ≤ V20 < 25%, 67.5 Gy/26 fractions (BED Gy10 is almost equivalent to that of 70 Gy/35 fractions), (3) 25% ≤ V20 < 30%, 65 Gy/26 fractions (BED Gy10 is almost equivalent to that of 68 Gy/34 fractions). The decision regarding the final total dose was made by the radiation oncologist under these dose settings. The details of IFRT given are shown in Table 2.

As the concurrent CHT, weekly intravenous CBDCA (area under the curve [AUC], 1.5–2.0) and PTX (30–35 mg/m^2) during IFRT was set up in principle. This regimen and the dose setting were considered based on the findings of a phase I study performed by Ohashi et al.,[14] which defined the dose level of CBDCA (AUC, 2.0) and PTX (35 mg/m^2) in combination with hyperfractionated RT (69.6 Gy in 1.2-Gy twice-daily fractions) with ENI as the maximum tolerated dose. Details of the CHT given are shown in Table 2.

The tumor response rate was analyzed according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines as follows: complete response (CR), the disappearance of all target lesions; partial response (PR), at least a 30% decrease in the sum of the longest diameters of target lesions, taking as a reference the baseline longest diameter sum; progressive disease (PD), at least a 20% increase in the sum of the longest diameters of target lesions, taking as

Table 2. Details of treatment for each patient

Patient no.	Location of primary tumor	Involved-field radiation therapy				Concurrent chemotherapy		
		CTV (cc)	V20 (%)	OTT (days)	TD (Gy)	CBDCA (AUC)	PTX (mg/m^2)	Total no. of courses
1	Rt. LL	47.4	28.0	37	65	2	35	6
2	Rt. UL	65.5	21.4	37	67.5	1.5	30	6
3	Lt. UL	28.3	29.0	36	55	2	35	5
4	Lt. UL	37.1	19.0	37	65	2	30	4
5	Rt. LL	77.7	8.0	40	70	2	30	6
6	Lt. LL	86.7	28.0	37	65	2	35	4
7	Lt. UL	33.4	8.4	40	70	2	30	5
8	Rt. UL	64.2	18.8	33	62.5	1.5	30	5
9	Lt. UL	137.3	16.1	37	65	1.5	30	6
10	Rt. UL	52.6	26.7	38	70	1.5	30	5
Median	–	58.4	20.2	37	65	–	–	5

CTV, clinical target volume; V20, percent total lung volume exceeding 20 Gy; TD, total dose; OTT, overall treatment time; CBDCA, carboplatin; AUC, area under the curve; PTX, paclitaxel

a reference the smallest sum of the longest diameters recorded since the treatment started or the appearance of one or more new lesions; stable disease (SD), neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as a reference the smallest sum of the longest diameters since the treatment started.

In-field and out-of-field recurrences were assessed using varying combinations of radiological assessment. In-field recurrence was defined as an increase in radiologic abnormality within the irradiated volume that was not considered to be radiation-induced scarring or radiation pneumonitis. Elective nodal failure (ENF) was defined as recurrence in any lymph node region that was initially uninvolved, in the absence of in-field recurrence.

Acute and late toxicity was evaluated using the Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE v3.0). Acute toxicity was defined as that occurring within 90 days of treatment initiation, while late toxicity was defined as that occurring beyond 90 days after treatment initiation. During CHT-RT, CHT and RT were to be interrupted for either grade 3 or greater leukopenia or neutropenia or thrombopenia, and thereafter be resumed when that toxicity had decreased to grade 2 or less. In addition, RT was to be interrupted for grade 3 or greater esophagitis or pneumonitis, and thereafter be resumed when that toxicity had decreased to grade 2 or less.. In addition, the treatment was to be canceled if grade 4 or greater severe toxicity occurred.

The follow-up evaluations were performed at 2-month intervals for the first year, at 3-month intervals for the second year, and at 6-month intervals thereafter. The follow-up evaluation routinely included physical examination, chest X-ray, toxicity assessment, and blood tests. Thoracic-abdominal CT scans were performed at 1, 3, 6, 9, 12, 18, and 24 months after the treatment and when indicated thereafter. A restaging with head MRI and bone scintigraphy was performed at 6-month intervals after the first half year. The actuarial curves of OAS and the in-field tumor control rates were calculated using the Kaplan-Meier method, with the day of treatment as the starting point.

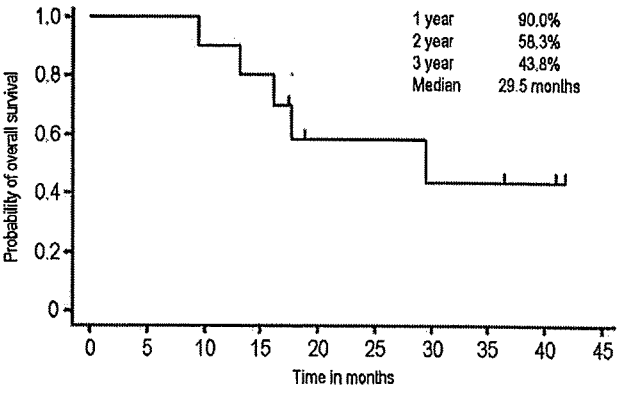

Fig. 2. Overall survival of patients with locally advanced non-small cell lung cancer after hypofractionated involved-field radiation therapy with concurrent carboplatin/paclitaxel (CBDCA/PTX)

Results

Tumor response, overall survival, and in-field tumor control

Of the ten patients, one achieved a CR (10.0%), and nine achieved a PR (90.0%) with a tumor response rate of 100%. The final analysis was performed 17 months after the registration of the last patient. At a median follow up of 18.2 months (range, 9.6–41.9 months), five patients (50.0%) had died at the time of the last follow up. The MST was 29.5 months, and the 1-, 2-, and 3-year OAS rates were 90.0%, 58.3%, and 43.8%, respectively (Fig. 2). A median time to in-field tumor progression of 18.1 months was obtained, and the 1-, 2-, and 3-year in-field tumor control rates were 60.0%, 45.0%, and 45.0%, respectively (Fig. 3).

Toxicity

The acute treatment-related toxicities are shown in Table 3. No hematological toxicities of grade 3 or worse were