used. Total treatment time was 6 to 7 weeks. We performed EBRT in the morning and brachytherapy in the afternoon on the day of brachytherapy.

Intra-arterial infusion chemotherapy

Concurrent intra-arterial infusion chemotherapy was performed using CDDP or carboplatin (CBDCA). In the case of poor renal function due to aging, hydronephrosis, or for any other reason, we used CBDCA instead of CDDP. We performed catheterization according to Seldinger's technique. As a general rule, at first infusion the drug was administered through the bilateral uterine arteries to be distributed to the primary tumor. For the second infusion, the bilateral internal iliac artery was used, to perfuse pelvic lymph nodes (Fig. 1). The dose of CDDP was 100–120 mg/body (mg/patient), and in the case of CBDCA the dose was 300 mg/body (mg/patient). At first, the proportion of CDDP dose to the bilateral arteries was determined according to the proportion of tumor stain on the angiographic findings. Since 2001 we have used angio-CT (interventional procedures with CT) and obtained CTPA (CT during pelvic arteriography) to confirm the distribution of the enhanced area for the tumor. We determined the proportion of CDDP dose to the bilateral arteries on the basis of the findings of the pelvic examination, CT/MRI, and CTPA; homogeneous distribution for the tumor was obtained (Fig. 2). The theoretical bases and technical details of our IAIC have been described previously (36).

Regarding the timing of IAIC and RT, the RT theoretically should be done immediately after administration of CDDP (CBDCA) if the effect of CDDP (CBDCA) for radiation sensitization is expected. However, because clinically the patient has to maintain bed rest after IAIC overnight for hemostasis, it is impossible to administer RT immediately after IAIC. Until April 2000 we stopped RT for 1 day at the time of IAIC. In our institution, brachytherapy or IAIC was only performed in the afternoon. Therefore, CDDP (CDBCA) administration and brachytherapy were not performed on the same day. However, after May 2000, to avoid prolongation of treatment time, EBRT was performed in the morning and IAIC in the afternoon.

The number of patients treated with CDDP was 22 and with CBDCA was 7. The length of injection time was 5–10 min. To perform IAIC concomitantly during 6 to 7 weeks of RT, we performed the first IAIC at the start of RT, and 3 or 4 weeks later a second IAIC was performed. Two or three cycles of IAIC were performed every 3 to 4 weeks. Most patients (27 [93%]) received two cycles of IAIC; 1 patient refused the second IAIC; and another patient had a very large tumor (diameter approximately 8 cm), and response was insufficient (partial response) after two cycles of IAIC, so a third cycle of IAIC was carried out. We use 31 cycles of injections for internal iliac arteries, 20 for uterine arteries, 6 for the two together, and 1 for ovarian artery.

Follow-up

After completion of RT, patients were followed monthly for the first year, every 2 months during the second year, every 3 or 4 months in the third to fifth year, and twice yearly thereafter. At the time of each consultation the patient was evaluated by pelvic examination. To evaluate disease status and recurrence, patients underwent a CT scan of the chest, abdomen, and pelvis every 6 months. Suspected persistent or recurrent disease was confirmed by biopsy wherever possible. Treatment failures were classified as pelvic recurrences or distant metastasis. Late radiation complications were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (40). The median duration of follow-up was 60 months (range, 11–156 months). Information concerning disease status, late complications, and cause of death was available for 97% (follow-up rate) of the patients either from institutional records, through telephone contact directly with the patient or her relatives, or through communication with the referring physicians. One patient could not be observed 1 year after treatment. The patient developed vaginal recurrence 5 months after treatment and received brachytherapy using a vaginal cylinder.

Statistical analysis

Survival was measured from the date of initiation of therapy to the date of death or the most recent follow-up using the Kaplan-Meier

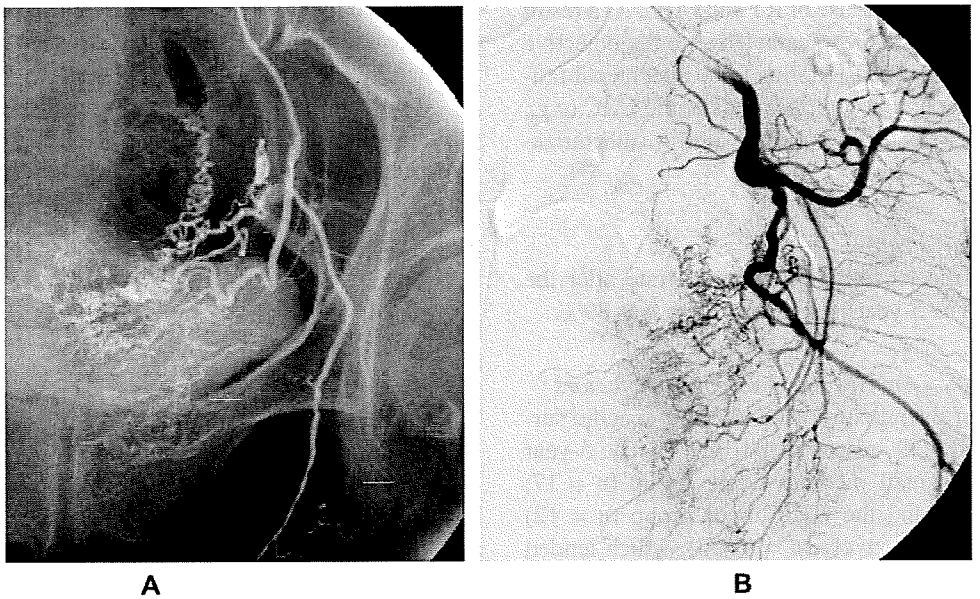

Fig. 1. Intra-arterial infusion chemotherapy (IAIC). (A) A super-selective left uterine arteriography before the first IAIC. At first infusion, cisplatin was administered through bilateral uterine arteries to be distributed to the primary tumor. (B) A selective left internal iliac arteriography before the second IAIC. At second infusion, bilateral internal iliac artery was used to perfuse pelvic lymph nodes and the primary tumor.

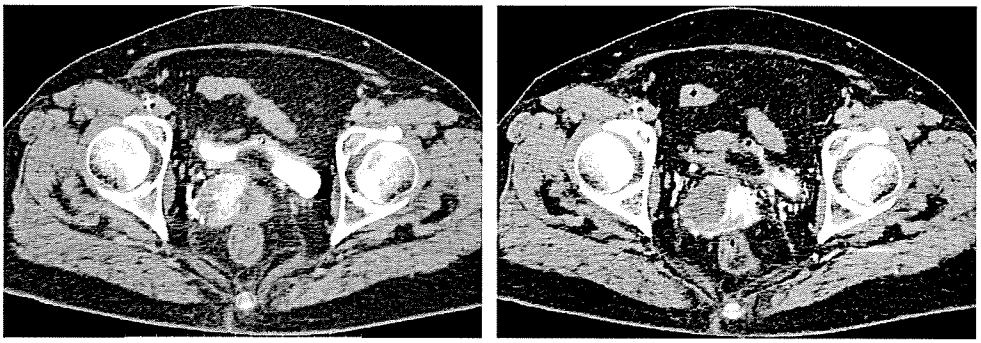

Fig. 2. Computed tomography during pelvic arteriography. Bilateral uterine arteriography before the first infusion. (A) Infusion from right uterine artery. (B) Infusion from left uterine artery. In the case in which the tumor is enhanced by the area, the proportion of cisplatin dose would be 4 to 1 for right to left. The dose of cisplatin was determined according to findings of pelvic examination CT/MRI, and CTPA. The enhanced area on the right is larger than on the left.

method, with significance compared by the Wilcoxon test. Overall survival was used to assess the death rate due to cervical cancer. The time to disease recurrence in the pelvis was measured from the date of initiation of therapy to the date of first disease recurrence or progression in the primary cervical tumor or vagina. Because of the long follow-up period, some deaths were not related to cervical carcinoma. Therefore, we also estimated cause-specific survival on the basis of available information on the cause of death. For calculation of cause-specific survival, deaths owing to cervical cancer, deaths resulting directly from treatment-related complications, and death occurring from unknown causes less than 5 years after treatment were scored as events.

RESULTS

Technical successful rate

The technical successful rate of this study was 100%. All of the catheterizations to the objective blood vessels were successful. However, at the time of the second IAIC, arteries had sometimes narrowed because of RT and IAIC. As a result it was occasionally impossible to catheterize to the objective blood vessel. We did not consider this to be a technical failure. There were no technical complications of the IAIC (*e.g.*, hematoma, catheter-related thrombosis) during catheterization in this study.

Local–regional control rate

Figure 3 shows the local–regional control rate after the start of treatment. The 5-year local control rate was 89%.

Overall survival, cause-specific survival, and risk factors

Five-year rates of overall survival and cause-specific survival were 62% and 70%, respectively (Fig. 4). The 5-year survival rate for the small–medium tumor group (n = 17; small 1, medium 16) and the large tumor group (n = 12) was 74% and 46%, respectively (p = 0.083), which tended to be better in the small–medium tumor group (Fig. 5). The 5-year survival rate was 65% in the negative lymph node metastasis group and 51% in the positive lymph node metastasis group, which tended to be better in the negative lymph node metastasis group, but the difference was not significant (p = 0.4856). There were no apparent differences for the results regarding number of IAIC cycles.

Cause of death and patterns of recurrence

Status at the time of last follow-up for all patients is as follows. Of the 12 patients who died before July 2008, 8 died of cervical cancer, 1 of radiation complications, 1 of second primary cancer (lung cancer), 1 of intercurrent disease (mediastinal inflammation), and 1 of an unknown cause. Sixteen patients are alive, and 1 patient has been lost to follow-up.

Patterns of recurrence are listed in Table 3. The methods of diagnosing recurrence were pelvic examination, biopsy, and imaging. Two local recurrences, including one local uncontrolled case, were diagnosed by biopsy of the cervix and vagina. The other patient, who had both local and distant metastasis, was diagnosed by CT imaging for local recurrence; however, metastasis of the pancreatic head was diagnosed by biopsy using endoscopic retrograde cholangiopancreatography. Diagnosis of the distant metastasis was obtained by CT.

Rates of initial local recurrence, distant metastasis, and both were 7% (2 of 29), 38% (11 of 29), and 3% (1 of 29), respectively. One patient did not show local control. The

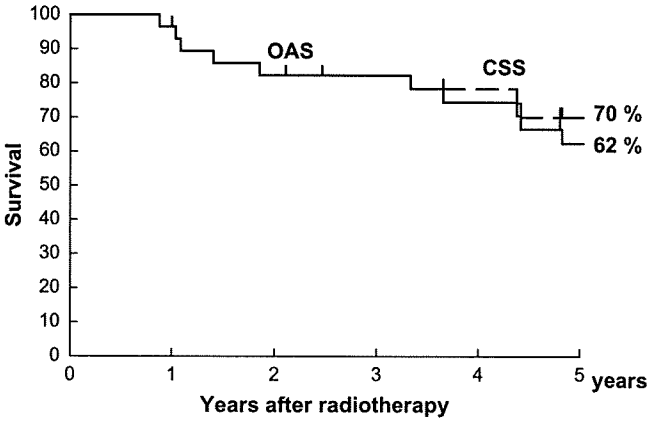

Fig. 3. Overall survival (solid line) and cause-specific survival (dashed line).

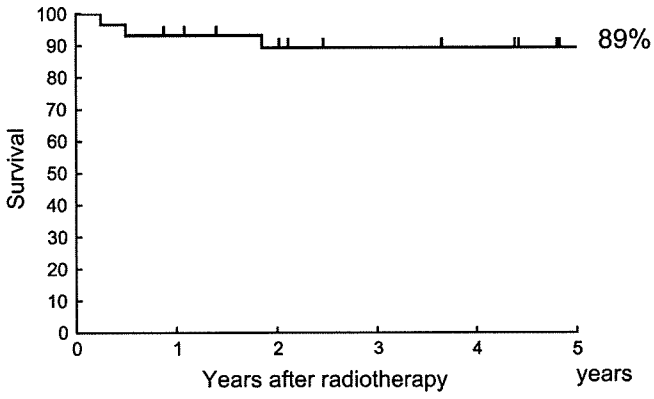

Fig. 4. Local relapse-free survival.

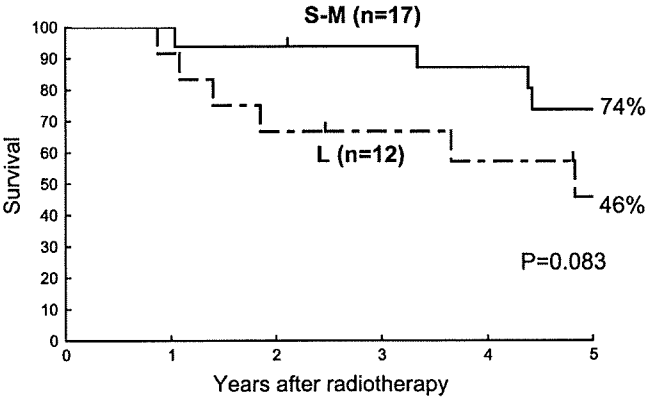

Fig. 5. Overall survival by tumor size. Solid line represents overall survival rates of 17 patients with small- and medium-sized tumor; dashed line represents that of 12 patients with large tumors.

patient had a medium-sized tumor and died of progressive local disease (cervix) without distant metastasis. Of the 28 patients who showed local control, only 2 developed local recurrences: 1 patient had vaginal recurrence, and the other had both local and distant metastasis. Sites (patient number) of distant metastases were PAN (8 patients), multiple lymph nodes (PAN, media stinal and virchow's lymph nodes) and lung (1), multiple liver, lung, and PAN (1), and lung and bone (1). Sites of both local recurrence and distant metastasis were peritoneal carcinoma, including the cervix and pancreatic head. The most frequent site of distant metastasis was PAN (28% [8 of 29]). In these 8 patients, all, apart from 1 patient who refused RT at 32 Gy, received radical RT (50–60 Gy) with or without chemotherapy. Of these 7 patients, 1 had a second relapse in the radiation field, and the remaining 6 patients were controlled. However, of these 6 patients, 3 had another lymph nodes metastasis.

Treatment sequelae

Acute toxicities according to CTCAE version 3.0 are listed in Table 4. These were transient and rendered nonlethal. Rates of Grade 3 hematologic effects were 7% for anemia, 24% for leukocytopenia, and 0 for thrombocytopenia, but no interruption of RT was needed. Rates of severe nonhematologic effects (Grade ≥3) were 3% for nausea and ileus. Only 1 patient who developed ileus during RT had RT interrupted for 1 week.

Another complication that was observed with this combined-modality treatment was CDDP sensorimotor neuropathy of the bilateral lower limbs. The neuropathy was mild sensory and motor deficit, and it slowly self-resolved within several years. No clinically significant renal toxicity was noted.

Late complications are listed in Table 5. Of 29 patients, 5 (17%) developed Grade 3 complications. Grade 3 enteritis was observed in 3 patients: 2 patients had paralytic ileus, and 1 patient had perforation of the small intestine and partial resection of the small intestine. One patient had a Grade 3 late complication of bladder tamponade. A Grade 3 small bowel complication was observed in 1 patient, who suffered from radiation enteritis with perforation of the ileum 3 months after RT and received surgical correction. Grade 5 proctitis was observed in 1 patient (3%). The patient was 68 years old and had chronic hepatitis. She had refractory rectal bleeding and fell into a shock state and died 4 years and 3 months after RT. There was no evidence of recurrence at that time.

DISCUSSION

Because the treatment policy of RT for cervical cancer is different between the West and Japan, we compared treatment results within Japan. In Japan, treatment results of high-dose-rate brachytherapy (mainly RT alone) for Stage III disease were as follows. Five-year overall survival for patients with Stage III disease was reported by many investigators as 47–56%, with mean of 51.2% (41–46). On the other hand, 5-year overall survival rates for low-dose-rate brachytherapy were 45–60%, with mean of 48.6% (41, 42, 45–47). In this study the overall survival rate was 62%. Compared with the above-mentioned results, our results are reasonably good.

Since 1999 many investigators have started paying attention to CCRT (1–11), since the National Cancer Institute announced its recommendation of CCRT for cervical cancer, based on the treatment results of five randomized trials (12–16). However, there are some differences between the West and Japan in treatment policy: in the West, patient age for CCRT is approximately in the 40s (median), younger than Japanese patients, who are approximately in their 60s. Additionally, patients with early-stage (IB–IIB) cancer receive CCRT in Europe and America, whereas in Japan they receive surgery. The treatment schedule for radical RT in Europe and America is different from that in Japan in terms of overall treatment time, central shield, and dose rate of brachytherapy. Therefore, the regimen of CCRT in Europe and America does not apply to Japanese patients.

In Japan, a comparison of treatment results between RT alone and CCRT has been reported from retrospective research by the Japan Radiation Oncology Study Group (48). There are no significant differences in overall survival between the two groups by stage (Ib–II and III–IV), though there is a bias that age is low, performance score is excellent, tumor diameter is large, and many pelvic lymph node

Table 3. Initial recurrence*

Local	Distant	Local and distant
2 (7)	11 (38)	1 (3)
Cervix: 1	PAN: 8	Cervix + P: 1
Vagina: 1	LN + lung: 1	
	LN + lung + liver: 1	
	Lung + bone: 1	

Abbreviations: PAN = para-aortic lymph nodes; P = peritoneal cancer; LN = lymph nodes.

Values are number (percentage).

* Including 1 local uncontrolled case.

Table 5. Late complications*

	Grade					
Toxicity	0	1	2	3	4	5
Bladder	25 (87)	1 (3)	2 (7)	1 (3)	0	0
Rectum	23 (80)	2 (7)	3 (10)	0	0	1 (3)
Small bowel	24 (83)	2 (7)	0	3 (10)	0	0
Leg edema	26 (90)	0	3 (10)	0	0	0
Bone	28 (97)	1 (3)	0	0	0	0

* According to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

metastases exist in the CCRT group. Thus, in Japan it is still uncertain whether CCRT can improve the survival rate in the present report.

Table 6 shows treatment results of IAIC in other studies and from the present study (21, 24, 25, 27, 29, 31–33, 35-37). Intra-arterial infusion chemotherapy is considered useful for improvement of local control because it makes possible high concentrations of drug distribution for the local region and greater antitumor effects and fewer systemic adverse effects than with systemic chemotherapy in CCRT. Many investigations have shown good response rates after neoadjuvant chemotherapy or concomitant use with RT, ranging from 41% to 100% (17–38). However, some investigators point out that there is no definite survival benefit from using IAIC with RT for advanced cervical cancer compared with RT alone (24, 29, 35). On the other hand, the technique of IAIC requires a lot of skill. The technical successful rates were 100% in this study. We believe the reasons for this are the good catheterization technique of the interventional radiologists and the management of trouble in our institution. Systemic chemotherapy provides lower concentrations of drug distribution for the local region than IAIC, but its method and management are easy and universal. No published study has compared treatment results of intravenous chemotherapy vs. intra-arterial chemotherapy. Therefore, it is uncertain whether either intravenous chemotherapy or intra-arterial chemotherapy is an effective treatment.

Table 4. Acute toxicities*

	Grade				
Toxicity	0	1	2	3	4
Hematologic					
Anemia	6 (21)	9 (31)	12 (41)	2 (7)	0
Leukocytes	3 (10)	10 (35)	9 (31)	7 (24)	0
Thrombocytopenia	26 (90)	2 (7)	1 (3)	0	0
Gastrointestinal					
Nausea	15 (52)	8 (28)	5 (17)	1 (3)	0
Diarrhea	18 (62)	8 (28)	3 (10)	0	0
Ileus	28 (97)	0	0	1 (3)	0
Cystitis	25 (86)	3 (10)	1 (3)	0	0
Fever	19 (65)	6 (21)	4 (14)	0	0
Neurologic	28 (97)	1 (3)	0	0	0

Values are number (percentage).

* According to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

Effective drug distribution for the tumor is important. It has been doubtful whether appropriate drug distribution is obtained for the tumor. Some investigators have evaluated the blood flow distribution using ^{99m}Tc-MAA from the iliac artery to the pelvis, the tumor, and superior and inferior gluteal parts (20, 25, 26, 38). We used angio-CT to determine whether the tumor was enhanced evenly. We confirmed that the drug was adequately distributed in the tumor. We determined the proportion of CDDP dose to bilateral arteries, and homogeneous distribution for the tumor was obtained.

A high local control rate has been reported by some investigators (17, 19, 20, 32, 35). Also in our study, local recurrence was observed in only 3 patients, including 1 uncontrolled case (10%). The 5-year local control rate was 89%, and their overall survival rate was 62%. In our study tumor size was a prognostic factor, but the difference was not significant. Five-year survival rates for small–medium tumors (n = 17; small 1, medium 16) and large tumors (n = 12) were 74% and 46%, respectively ($p = 0.083$). Some investigators (32, 35, 37) have stated that risk factors are tumor size, lymph node metastasis, and pathologic findings. In our study, the 5-year survival rate was 65% in the negative lymph node metastasis group and 51% in the positive lymph node metastasis group, which tended to be better in the negative lymph node metastasis group; however, the differences were not significant.

The most frequent initial site of distant metastasis was the PAN (n = 11). These sites occupied 72% of recurrences (11 of 14). It seems that hematologic recurrence would be reduced rather than lymphatic recurrence by this combined-modality treatment. It might be possible that a small amount of CDDP used in IAIC would circulate the whole body after injection of uterine artery and prevent some hematologic micrometastasis.

Regarding acute toxicities, severe myelosuppression (Grade 3) was seen in 24% of patients but was transient and no interruption was needed. On the other hand, regarding late complications, Grade 5 proctitis was observed in 1 patient (3%). The patient had chronic hepatitis. Several investigators (35, 48) have reported that concomitant use of chemotherapy with RT compared with RT alone causes an increase in acute and late complications. In our case the patient had chronic hepatitis,

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 <65 y (n = 244)	65–74 y (n = 213)	≥75 y (n = 164)	Total (n = 621)	p
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.

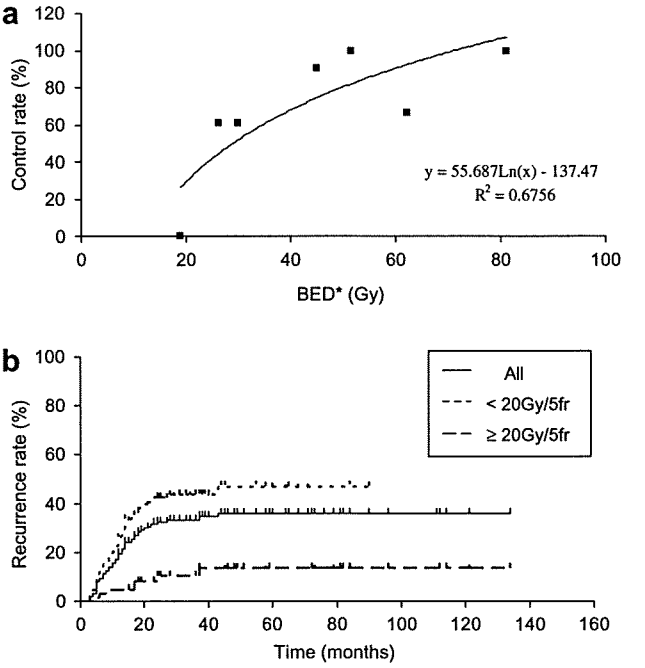

Fig. 1. (a) Control rate of keloids as function of the biologically effective dose (BED). There was a significant correlation between the control rate and biologically effective dose (BED*). *BED calculation according to Kal et al. [13]. (b) Long-term recurrence rate in post-operative radiotherapy according 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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