Table IV. The 3-year PFS and OS rates according to the clinical factors.

	No. of patients	The 3-year PFS (%)	P-value	The 3-year OS (%)	P-value
Stage					
Ib2/IIb	16	68.7		86.5	
IIIb/IVa	24	47.9	0.380	60.4	0.160
Tumor size (cm)					
≤6	19	52.3		69.4	
>6	21	64.3	0.450	76.9	0.630
Pelvic lymph nodes					
Swelling (-)	23	74.4		89.3	
Swelling (+)	17	39.2	0.010	41.1	0.016

PFS, progression-free survival and OS, overall survival.

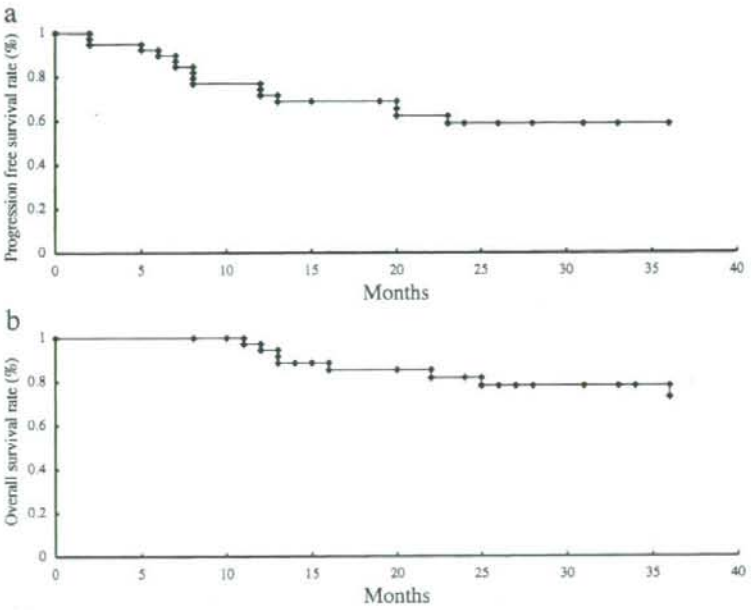

Figure 1. The 3-year progression-free survival at a median follow-up of 29 months (range, 8-52) (a) and the 3-year overall survival at a median follow-up of 29 months (range, 8-52) (b).

diarrhea and nausea/vomiting were observed in 2 (4.4%) and 1 (2.2%), respectively (Table V). The chemotherapy was delayed for a week due to adverse reactions in 5 out of the 40 patients who completed the treatment. There were no patients in whom the chemotherapy was delayed for 2 weeks or longer. The radiation therapy was suspended for 4-5 days at the same time in 4 out of the 5 patients who delayed the chemotherapy. One patient suffered from radiation proctitis as a delayed adverse reaction and received surgical treatment (Table V). She survived without any evidence of disease.

Discussion

In this phase II trial, we achieved a 90% complete response rate, and all the patients had a successful response. The 3-year PFS and OS rates were 58.7 and 78.0%, respectively (Fig. 1a and b). In addition, ~90% of the enrolled patients completed the trial with a few grade 4 hematological toxicities (6.7%), indicating that weekly nedaplatin of 30 mg/m^2 with concurrent radiotherapy is an effective and well-tolerated regimen for advanced uterine cervical carcinoma.

In the phase II studies of cisplatin and concurrent radiotherapy for advanced uterine cervical carcinoma, Malfetano *et al* reported that 94% of the patients completely responded and 75% survived without evidence of disease with a mean follow-up of 47.5 months (11). However, their scheduled treatment was characterized by extended-field radiation therapy including the para-aortic lymph nodes. In contrast, Fields *et al*, reported that 87% of the patients with this disease were complete responders and the 5-year survival was 67%

Table V. Toxicity profile (45 patients).

Toxicity	Grade 3 (%)	Grade 4 (%)
Hematological		
Leukopenia	17 (37.8)	3 (6.7)
Neutropenia	14 (31.1)	3 (6.7)
Anemia	3 (6.7)	0
Thrombocytopenia	2 (4.4)	0
Non-hematological		
Diarrhea	2 (4.4)	0
Proctitis	1 (2.2)[a]	0
Nausea and vomiting	1 (2.2)	0

[a]According to the radiation therapy oncology group late-radiation morbidity-scoring scheme.

for stage III and 25% for stage IV with a median follow-up time of 65 months (12). The response rate of the present trial with nedaplatin and concurrent radiotherapy is comparable to that of the two previous trials with cisplatin and concurrent radio-therapy. However, while 60.0% of the patients in this trial were FIGO stages IIIb or IVa, only 34.3 and 50.9% were those stages in the two previous trials, respectively.

Five randomized phase III trials have an OS advantage for cisplatin-based chemotherapy with concurrent radiotherapy. Although these trials vary in terms of the stage of disease and schedule of cisplatin and radiation, all of them showed a significant survival benefit for the combined treatment, decreasing the risk of death by 30-50% (1-5). However, the local recurrence rate, which is between 19 and 24%, is still high. Similarly, the local recurrence rate in this trial was 25%.

As shown in Table IV, the pelvic lymph node status significantly influenced the 3-year PFS and OS rates. Of the 4 patients who had distant recurrence, 3 relapsed in the para-aortic lymph node (PAN) region (Table III). Of the 3 patients with PAN metastasis, 2 also had a pelvic lymphadenopathy. Regarding the independent factor influencing the OS rate for the patients who had a high-risk uterine cervical carcinoma and were treated with intra-arterial cisplatin/nedaplatin, intravenous 5-fluorouracil and concurrent radiotherapy, Kawase *et al* reported that the pelvic lymph node status was the only risk factor and recommended that patients without a pelvic lymphadenopathy should be selected as candidates for CCRT (13). It is suggested that the drug concentration in the pelvic lymph nodes was low in patients with a pelvic lymphadenopathy and these patients were reported to respond poorly to CCRT (13).

In this study, the para-aortic recurrence was 7.5% and was compatible with the results reported by Eifel *et al* who showed that the rate of para-aortic recurrence in advanced uterine carcinoma patients treated with pelvic radiotherapy, concurrently using fluorouracil and cisplatin, was 7% at 5 years (14). In addition, Eifel *et al* showed that pelvic radiation with concurrent chemotherapy significantly prolonged the OS of advanced uterine cervical carcinoma patients without PAN involvement, compared to extended-field radiation including para-aortic radiation, suggesting that prophylactic para-aortic radiation does not appear to be appropriate for the treatment of locally advanced cervical carcinoma (14). However, Malfetano *et al* suggested the effectiveness of para-aortic radiation in combination with chemotherapy. They showed that although 7 (10.7%) out of the 67 locally advanced cervical carcinoma patients treated with extended-field radiation, including prophylactic para-aortic radiation and weekly cisplatin had a distant failure, no patient had PAN failure (11). Thus, it is still uncertain whether the addition of prophylactic para-aortic radiation to CCRT may improve the therapeutic effect on nodal involvement and prevent nodal failure, which warrants further investigation for the improvement of survival of patients with a pelvic lymphadenopathy.

In this phase II trial, grade 3 and 4 leukopenia was found in 37.8 and 6.7% of the enrolled patients, respectively but no grade 4 non-hematological toxicity (Table V). Of the 45 enrolled patients, 5 (11.1%) voluntarily withdrew from the trial due to bone marrow suppression and anorexia, although the levels of the adverse reactions were medically mild. In this trial, nedaplatin was administered at a total dosage of 180 mg/m^2 to each patient. The completion rate was ~90% and the delayed duration was a maximum of 1 week, suggesting that the present regimen of using weekly nedaplatin and radiotherapy was clinically effective and well-tolerated.

The results of the GOG protocols 120 and 123 after using radiation and concurrent cisplatin demonstrated that the incidence of grade 3-4 leukopenia was 13.1 and 21.3%, respectively (2,3). In these studies, the dose of cisplatin administered to each subject was 192 and 143 mg/m^2 or more at the GOG protocols 120 and 123, respectively (2,3). However, Ohno *et al*, who employed a dose of cisplatin at either 100 or 151 mg/m^2 with concurrent radiation, reported that the incidence of grade 3-4 leukopenia was 50 and 58%, respectively (15). Moreover, Mitsuhashi *et al* reported that the incidence of grade 3-4 leukopenia treated with cisplatin and concurrent radiation reached 60% at the dosage of 168 mg/m^2 of cisplatin per patient (16). These differences in the incidence of adverse reactions suggest that the tolerance for cisplatin in Japanese women may be lower than that in American women. It is suggested that cisplatin is a radiation sensitizer with the ability to inhibit the repair of sublethal radiation damage. Fu *et al* and Dewit showed an enhancement of cell kill in various tumors by the concomitant administration of cisplatin and radiation (17,18). Nedaplatin is also reported to have radiation-sensitizing properties but its exact mechanism has yet to be understood. Nakamura *et al* showed that although the antitumor effect of nedaplatin on xenografted human brain tumors was comparable to that after exposure to the radiation, the peak incidence of apoptosis in the tumor after treatment with nedaplatin was much lower than that after exposure to the radiation and suggested that a different mechanism rather than the p53-dependent apoptosis be postulated for the antineoplastic activity caused by nedaplatin (19). More recently, Tanaka *et al* reported that the anti-proliferative effect of nedaplatin on uterine cervical carcinoma cells could be enhanced several hours before or after radiation, suggesting that nedaplatin may be the most appropriate anticancer drug for CCRT (20).

This is the first report to evaluate the effectiveness and safety of nedaplatin and concurrent radiation in advanced uterine cervical carcinoma. Although the statistical power of this study is limited due to the small number of subjects, the results in this trial are sufficient to warrant further investigation. A randomized phase III trial with this or similar regimens should be conducted to validate whether nedaplatin is equal to or superior to cisplatin in the survival of patients with this disease.

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Clinical Studies

Adjuvant hysterectomy for treatment of residual disease in patients with cervical cancer treated with radiation therapy

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The objective of this retrospective study was to determine the efficacy of adjuvant hysterectomy for treatment of residual disease in cervical carcinoma treated with radiation therapy. Between 1971 and 1996, 1590 patients with carcinoma of the uterine cervix (stages I–IIIb) were treated with radiation therapy. Three months after completion of radiation therapy, the status of local control was investigated, and total abdominal hysterectomy was performed in cases in which central residual disease existed in the cervix. Of the 1590 patients, residual disease was identified in 162 patients. Among these patients, 35 showed an absence of distant metastasis or lateral parametrial invasion and underwent hysterectomy. The overall 5- and 10-year survival rates for these patients were 68.6 and 65.7%, respectively. There was no significant difference in survival between patients with squamous cell carcinoma and those with non-squamous cell carcinoma or between patients with stage I/II carcinoma and those with stage III carcinoma. With respect to treatment-related morbidity, five (14.3%) patients suffered grade III or IV complications after hysterectomy. Adjuvant hysterectomy is an effective addition to radiation therapy in the treatment of cervical cancer, even in patients with stage III disease and in those with non-squamous cell carcinoma.

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Keywords: cervical carcinoma; radiation; residual disease; hysterectomy

Cervical cancer is one of the most common cancers in women worldwide. Annually, it is estimated that 493 000 women worldwide will be diagnosed with cervical carcinoma and that 273 000 will die from the disease (Parkin *et al*, 2005). Traditionally, radical hysterectomy or radiation therapy alone has been accepted as standard treatment for early-stage invasive cervical cancer, and locally advanced cancer has been treated by radiation therapy alone, consisting of a combination of high-dose-rate intracavitary brachytherapy (ICBT) and external beam radiation therapy (EBRT) (Coia *et al*, 1990; Komaki *et al*, 1995; Barillot *et al*, 1997). In the last few years, substantial advances in the management of locally advanced cervical cancer have been reported. Five randomised trials have shown improved survival and local control when cisplatin-based chemotherapy is performed concurrently with radiation therapy in patients with locally advanced cervical cancer (Keys *et al*, 1999; Morris *et al*, 1999; Rose *et al*, 1999; Whitney *et al*, 1999; Peters *et al*, 2000). This combined modality approach produced an absolute increase in 5-year survival of 12% compared with radiation therapy alone and has resulted in a dramatic change in the standard of care for this disease.

Although the general prognosis of patients with cervical cancer treated with radiation therapy has improved, how to best treat patients with residual disease after radiation therapy remains controversial. These patients have been considered to have an extremely poor prognosis (Moore *et al*, 2004; Long *et al*, 2005). The value of surgical treatment for such patients has been investigated, but in most of these studies, extended surgery, such as radical hysterectomy or pelvic exenteration, was performed, resulting in a high rate of severe treatment-related morbidity and decreased quality of life. For more than 30 years, we have performed simple abdominal hysterectomy in patients with residual disease identified 3 months after the completion of radiation therapy if the residual disease is central, without distant metastasis. The present study evaluated the treatment results of 35 cases who underwent so-called 'adjuvant hysterectomy' after radiation therapy.

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METHODS

During the period 1971 through 1996, a total of 1590 new patients with primary invasive cervical carcinoma were treated by radiation therapy alone at the Cancer Institute Hospital, Tokyo, Japan. Disease stages were as follows: Ib, 197 patients; IIa, 29 patients; IIb, 620 patients; IIIa, 18 patients; and IIIb, 726 patients. Staging was performed according to the International Federation of Gynecology and Obstetrics criteria. A combination of EBRT and ICBT was used in all patients. The regimen for radiation therapy is described elsewhere (Ota *et al*, 2007). In brief, EBRT of a total dose of 50 Gy was delivered at 2 Gy per day, 5 days a week for 5 weeks. High-dose-rate remote after loading ICBT was also performed. A dose of 4 Gy was administered 2 or 3 times per week for a total of 40 Gy.

Three months after the completion of radiation therapy, the status of local control was investigated. Simple hysterectomy (class I hysterectomy) (Piver *et al*, 1974) was performed predominantly in incidence of patients with central residual disease within 2 months of discovery. The local control in response to radiation therapy and the number of patients who underwent subsequent hysterectomy are shown in Figure 1. Of the 1590 patients, 1428

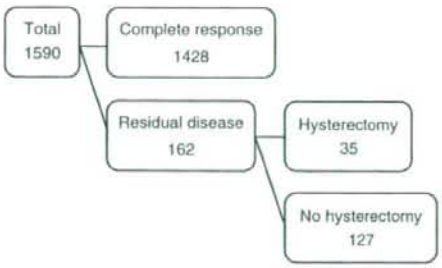

Figure 1 Incidence of local control in response to radiation therapy (complete response) and number of patients who underwent subsequent hysterectomy because of residual disease.

experienced a complete response, as shown by cytologic and histologic assessment. Of 162 patients with persistent local disease, 35 underwent hysterectomy. The other 127 patients did not undergo surgery because of the presence of concomitant distant metastasis ($n=26$) or because of advanced age, poor medical condition, or refusal of surgery ($n=101$).

Follow-up examinations were performed every 3 months during the first 5 years after treatment and then at 6-month intervals for the next 5 years. All follow-up examinations included pelvic examination with cytologic assessment of the uterine cervix and tumour marker SCC antigen, and identification late complications. Every 6 months, we obtained CT scan of the abdomen and chest X-ray were performed. All patients were followed up for more than 10 years after radiation therapy. Our hospital is one of the few institutions permitted access to the family registry database. We consulted the district legal affairs bureau for survival information or the cause of death for each patient; none of the patients was lost to follow-up. Of the 1590 patients, 1323 (83.2%) were followed-up directly at the hospital, and 267 (16.8%) were followed-up through the district legal affairs bureau.

The survival data for each patient was calculated from the date therapy was started to the date of the latest follow-up examination. Survival curves were drawn according to the Kaplan–Meier method. The log-rank test was used for univariate analysis. P values less than 0.05 were considered statistically significant. With respect to radiation-related morbidity, late rectal and bladder complications and non-rectal gastrointestinal sequelae (small-bowel complications) were graded according to the *RTOG/EORTC* scoring system (Cox *et al*, 1995).

RESULTS

Study population

The numbers of patients who underwent hysterectomy, listed by initial stage and cell type, are shown in Table 1. The mean age was 55.7 years (range, 36–74 years). Of the 35 patients, the number of patients with squamous cell carcinoma stage Ib, IIb, or IIIb were 3, 12, and 13, respectively, and the numbers with non-squamous cell carcinoma stage Ib, IIb, or IIIb disease were 1, 4, and 2.

Hysterectomy

Details of the hysterectomy procedures are listed in Table 2. Type I hysterectomy was performed in 32 patients, and type III radical hysterectomy was performed in three patients; none of the patient underwent pelvic or para-aortic lymphadenectomy (Piver *et al*, 1974). The duration of surgery type for type I and type III hysterectomy was 95.6 ± 34.1 and 158.0 ± 32.9 min, respectively. Blood loss was 457.6 ± 362.3 and 590.0 ± 101.5 ml, respectively.

Table 1 Case of cervical carcinoma treated with hysterectomy after radiation therapy

Clinical stage	Number of patients
Squamous cell carcinoma	
Stage Ib	3
Stage IIb	12
Stage IIIb	13
Non-squamous cell carcinoma	
Stage Ib	1
Stage IIb	4
Stage IIIb	2
Total	35

Table 2 Hysterectomy

Type I hysterectomy ($n=32$)	
Duration of surgery	95.6 ± 34.1 min
Blood loss	457.6 ± 362.3 ml
Residual disease	4 patients
Type III radical hysterectomy ($n=3$)	
Duration of surgery	158.0 ± 32.9 min
Blood loss	590.0 ± 101.5 ml
Residual disease	0 patients

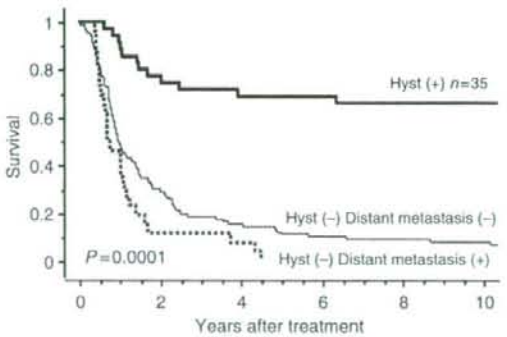

Figure 2 Disease-specific survival according to treatment methods and the presence or absence of distant metastasis for patients with cervical carcinoma. Hyst = Hysterectomy.

Four patients showed residual disease after type I hysterectomy, and none of the patients showed residual disease after type III radical hysterectomy. Two of the four patients with residual disease, two underwent chemotherapy, and the other two underwent palliative treatment after hysterectomy. Thus, there were 31 patients with no residual disease after hysterectomy. However, recurrence developed in eight: local recurrence in four and distant recurrence in four.

Survival

Disease-specific survival for the 35 patients who underwent hysterectomy is shown in Figure 2. The 5- and 10-year survival rates in this group were 68.6 and 65.7%, respectively. Clinical outcomes of patients who did not undergo hysterectomy, with or without distant metastasis, are also shown in Figure 2. Disease-specific 5-year survival rates for patients who did not undergo hysterectomy despite the absence of distant metastasis and those

with concomitant distant metastasis were 14.5 and 0%, respectively. Significant differences were noted between the three groups ($P = 0.0001$). Disease-specific survival curves are shown according to cancer stage in Figure 3. The cumulative 5-year survival rates for initial stages Ib, IIb, and IIIb disease were 100, 73.3, and 56.3%, respectively, and 10-year survival rates for initial stages Ib, IIb, and IIIb disease were 100, 66.7, and 56.3%, respectively. Disease-specific survival curves are shown according to histologic type in Figure 4. The 5- and 10-year survival rates for patients with squamous cell carcinoma were 74.1 and 70.4%, respectively, and those for patients with non-squamous cell carcinoma were both 57.1%. No difference was observed in survival between patients with squamous cell carcinoma and those with non-squamous cell carcinoma ($P = 0.6862$). Disease-specific survival curves are shown according to tumour size in Figure 5. The size of the persistent tumour at the time of hysterectomy was important with respect to survival. The 5- and 10-year survival rates for patients with lesions less than 2 cm in diameter were both 75.0% and those for patients with larger lesions were 54.4 and 45.5%, respectively. There was a trend for better survival of smaller tumours compared with larger tumours, but this difference was not statistically significant ($P = 0.053$).

Postoperative complications

One patient who suffered postoperative small-bowel obstruction was treated conservatively, and was discharged 40 days after surgery. Six patients (17.1%) experienced pelvic or urinary tract infection, but none required surgical intervention. No treatment-related deaths occurred.

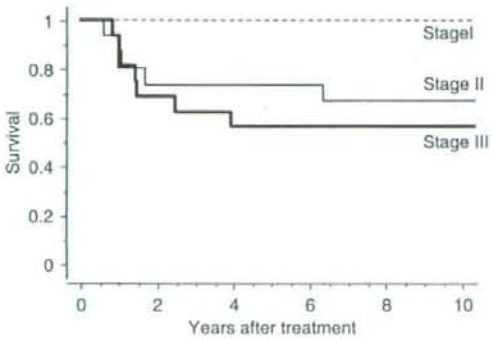

Figure 3 Disease-specific survival according to clinical stage for patients with cervical carcinoma.

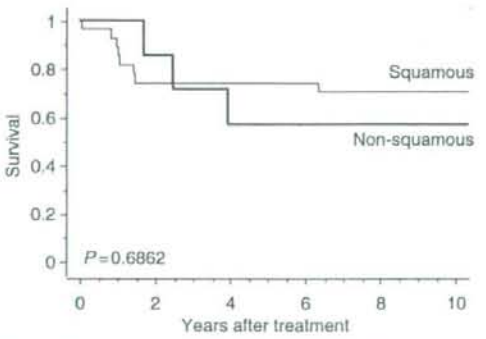

Figure 4 Disease-specific survival according to histologic type for patients with cervical carcinoma.

Late complications

Late complications are listed in Table 3. According to the *RTOG/EORTC* scoring system, grade III or IV late complications involving the rectum, small-bowel, or urinary tract were observed in five (14.3%) cases, three were stage II and two were stage III. The incidences of grade III and grade IV rectal complications were 0 and 2.9% (one patient), respectively. None of the patients experienced grade III or grade IV small-bowel complications. The incidences of grade III and grade IV urinary tract complications were 2.9% (one patient) and 5.7% (two patients), respectively. One patient (stage III disease) required reconstruction of both the urinary tract and lower gastrointestinal tract.

DISCUSSION

There is no standard treatment for residual cervical carcinoma in cases in which radiation therapy is insufficient. Patients with residual disease often undergo chemotherapy, with only minor palliation and without any significant improvement in survival (Moore *et al*, 2004; Long *et al*, 2005). Other treatments include re-irradiation or interstitial irradiation offering local control rates of 64–92% along with a 5-year survival rate of 4–44% for recurrent cervical cancer. However, a high rate of severe complications has been reported in both the urinary and lower gastrointestinal tracts (Russell *et al*, 1987; Sommers *et al*, 1989; Xiang-E *et al*, 1998).

With respect to surgical treatment for residual disease after radiation therapy, the most effective method is probably pelvic exenteration (Stanhope *et al*, 1990). Total pelvic exenteration offers a 5-year survival rate of 23–50%, but it requires alterations of both the urinary and lower gastrointestinal tracts, and a high rate of

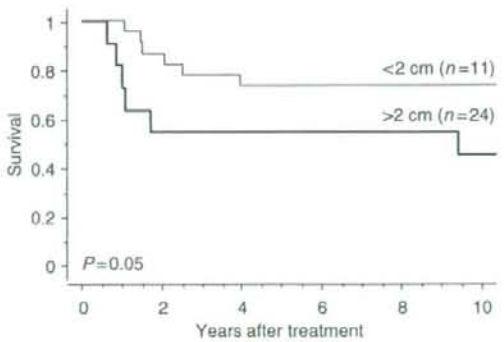

Figure 5 Disease-specific survival according to tumour size for patients with cervical carcinoma.

Table 3 Grades of late complications according to site

	Grade III (%)	Grade IV (%)	Grade V (fatal)
Rectum	—	1 (2.9)	—
Small bowel	—	—	—
Bladder	1 (2.9)	2 (5.7)	—
Combined	—	1 (2.9)	—
Total	1 (2.9)	4 (11.4)	—

Total: Five cases (14.3%).

severe postoperative complications, such as infection, injury of the urinary and lower gastrointestinal tracts, and small-bowel obstruction, occur, in addition to a 4–14% surgery-related mortality rate (Rutledge *et al*, 1977; Morley *et al*, 1989; Shingleton *et al*, 1989; Matthews *et al*, 1992; Moutardier *et al*, 2004).

The utility of radical hysterectomy, a more conservative procedure, has been reported, but it also has a high rate of complications. Coleman *et al* (1994) evaluated the utility of radical hysterectomy (chiefly type III hysterectomy) including pelvic lymphadenectomy in 50 patients with persistent or recurrent cervical cancer after primary radiation therapy. The 5- and 10-year survival rates for all cases was 72 and 60%, but severe postoperative complications (grade III or higher) occurred in 42% of the patients, along with one postoperative death because of sepsis. The most common site of injury was the urinary tract, with 14 patients (28%) developing vesicovaginal fistula, 11 (22%) developing ureteral injuries, and 10 (20%) developing severe long-term bladder dysfunction. Maneo *et al* (1999) evaluated the utility of type III radical hysterectomy including pelvic lymphadenectomy in 34 patients with persistent or recurrent cervical cancer after primary radiation therapy. The 5-year survival rate for all cases was 49%. No treatment-related deaths or early postoperative complications occurred, but 18 major complications occurred in 15 (44%) of the patients. Rutledge *et al* (1994) studied 47 patients with persistent or recurrent cervical cancer after primary radiation therapy and reported that radical hysterectomy resulted in major complications in 20 (42.4%) of the patients, including two treatment-related deaths. These results suggest that radical hysterectomy including pelvic lymphadenectomy can be an alternative to exenteration, but the high incidence of treatment-related morbidity remains a major issue.

The necessity of lymphadenectomy in recurrent or persistent disease should be addressed. Coleman *et al* (1994) reported that all five patients with positive nodes died of cancer, whereas 14 of 34 patients (41.2%) with negative nodes died of cancer ($P=0.02$). Maneo *et al*, (1999) identified six node-positive patients in their series, and five experienced recurrence, whereas half of 28 node-negative patients experienced recurrence. Thus, it is likely that pelvic lymphadenectomy resulted in little, if any, improvement of survival in residual disease after radiation therapy. Results of the present study, along with these previous studies, suggest that abdominal simple hysterectomy without pelvic lymphadenectomy (class II hysterectomy) may be sufficient in eliminating residual disease after radiation therapy.

The value of adjuvant hysterectomy in the treatment of cervical cancer after radiation therapy has been investigated; most of these studies suggest a decreased incidence of local relapse but no benefit in progression-free survival (Perez *et al*, 1987; Keys *et al*, 2003). Keys *et al* (2003) reported in a Gynecologic Oncology Group trial that performing adjuvant hysterectomy in every case of cervical cancer after radiation therapy is of little value in improving survival, although no significant increase in treatment-related morbidity is observed. In addition, Whitney *et al* (1999) reported that 7 of 30 (23.3%) stage IB patients with residual disease showed recurrence, whereas only 1 of 50 patients (2%) showed recurrence in the absence of evidence of persistent residual disease. Gallion *et al* (1985) reported similar results, with 5 of 14 (35.7%) residual disease showing recurrence compared to 2 of 29 (6.9%) with no residual disease. Thus, our belief is that adjuvant hysterectomy should be performed only in cases of residual disease of the cervix and that surgical treatment is unnecessary in cases with no residual disease.

It is noteworthy that adjuvant hysterectomy for residual disease after radiation therapy can be applied for patients with non-squamous cell carcinoma or stage III disease. Previous reports suggest that adenocarcinoma of the cervix has a poor prognosis (Eifel *et al*, 1990). Nakano *et al* (1995) report resulted of 58 patients with adenocarcinoma of the cervix treated with radiation. The local control rates in stage III and stage IV cases were 56 and 27%, respectively, and 5-year survival rates were 32.3 and 9.1%. These findings suggest that patients with adenocarcinoma who have residual disease as a failure of radiation therapy often have a poor prognosis in the absence of appropriate treatment for the residual disease. Gerdin *et al* (1994) performed radiation therapy and adjuvant hysterectomy in all of their cases, and reported successful results in the treatment of non-squamous cervical cancer and that the histologic tumour type is not a significant prognostic factor. In the present study, we also found no significant difference in the survival between patients with squamous cell carcinoma and those with non-squamous cell carcinoma.

Residual stage III disease is seldom treated surgically. The present study showed 5- and 10-year survival rates for patients with stage III disease of 56.3%, with acceptable treatment-related morbidity, suggesting that adjuvant hysterectomy may be of value in the treatment of advanced cervical cancer.

Previous studies have reported a correlation between tumour size at surgery and survival rate. Coleman *et al* (1994) reported that tumour size at surgery is significantly associated with survival. The 5-year survival rate for the 12 of 44 patients (27.3%) with lesion diameter less than 2 cm was 90% compared with 64% in patients with larger lesions ($P<0.01$). Maneo *et al* (1999) also reported that smaller tumour size (<4 cm) in recurrent disease is predictive of survival. In the present study, there was a trend for better survival smaller-sized tumours (<2 cm) compared with those with larger-sized tumours.

In conclusion, adjuvant hysterectomy is a viable option when applied to patients in whom an incomplete response to radiation leaves residual cervical carcinoma. This treatment is also effective in patients with stage III disease and in those with non-squamous cell carcinoma.

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Patterns of Pretreatment Diagnostic Assessment and Staging for Patients with Cervical Cancer (1999–2001): Patterns of Care Study in Japan*

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Objective: To evaluate the patterns of pretreatment diagnostic assessment in uterine cervical cancer patients treated with definitive radiotherapy in Japan.
Methods: The Japanese Patterns of Care Study working group conducted a second extramural audit survey of 68 institutions and collected specific information on 631 patients with cervical cancer. All patients were treated with radiotherapy in 1999–2001. Of these, 324 patients treated without surgery were the subjects of this study.
Results: International Federation of Gynecology and Obstetrics-prescribed diagnostic procedures were performed at moderate rates in our study cohort. The performance rates of chest X-ray, intravenous urography, cystoscopy, and proctoscopy were 74, 54, 53, and 33%, respectively. Cross sectional imaging studies were frequently performed. Pelvic CT, abdominal CT, and pelvic MRI were performed in 88, 80, and 76%, respectively. Lymphangiography (1%) and surgical evaluation (1%) were rarely done. Only one patient underwent PET scans in this survey period.
Conclusions: This study demonstrated the patterns of pretreatment diagnostic assessment in cervical cancer patients treated with definitive radiotherapy in Japan.

Key words: cervix neoplasm – radiotherapy – patterns of care – FIGO

INTRODUCTION

The pretreatment assessment of cancer extension is extremely important for prognosis estimation and treatment planning. Additionally, a well-defined initial assessment enables the comparison of cancer treatment results among institutions or different treatment methods. The International Federation of Gynecology and Obstetrics (FIGO) provides a global staging system for gynecologic cancers (1). Most clinicians use this staging system in the treatment of uterine cervical cancer. The system describes the rules for stage classification in detail, and the permitted diagnostic procedures are clearly stated. However, some of the procedures included, such as intravenous urography, and skeletal X-rays, could be considered outdated. Although tumor diameter and pelvic nodal status are not accounted for in the FIGO staging system, they are estimated to be the important prognostic factors for cervical cancer (2). In several studies, tumor diameter as assessed by MRI was a significant prognostic indicator for patients with cervical cancer (3–5). Evaluation of pelvic or para-aortic lymph node status with optional imaging studies, such as CT, MRI, and lymphangiograpy, may also be useful for predicting prognosis (6).

Several studies describe the patterns of pretreatment work-up of cervical cancer in the USA (7–9); however, there are few studies from Japan. The objective of this study

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was to review the patterns of pretreatment diagnostic assessment of cervical cancer in Japan.

MATERIALS AND METHODS

Between July 2002 and June 2004, the Japanese Patterns of Care Study group (JPCS) conducted a national survey of patients with cervical cancer treated with radiotherapy. Sixty-eight out of 640 institutions were selected for the survey with a stratified 2-staged cluster sampling method (10). Prior to random sampling, all institutions were classified into one of four groups. The criteria for stratification have been detailed elsewhere (10). In brief, the JPCS stratified Japanese institutions as follows: A1, academic institutions treating $\geq$430 patients annually; A2, <430 patients; B1, non-academic institutions treating $\geq$130 patients annually; B2, <130 patients. Academic institutions included cancer center hospitals and university hospitals. Non-academic institutions consisted of other facilities, such as national, prefectural, municipal, and private hospitals.

The JPCS surveyors performed on-site chart reviews at each participating facility using an originally developed format for cervical cancer. Data collection included patient characteristics (e.g. patient history, age, performance status, laboratory data, pathology, and stage), details of pretreatment work-up, therapeutic information (e.g. radiotherapy, chemotherapy, and surgery), and treatment outcome. Patient eligibility criteria of the survey were as follows: (i) carcinoma, (ii) treatment between January 1999 and December 2001, (iii) no distant metastases, (iv) no prior or concurrent malignancy, (v) no gross para-aortic lymph node metastases, and (vi) no previous pelvic radiotherapy. The JPCS collected clinical data on 631 patients with uterine cervical cancer who were treated with radiotherapy from 68 institutions. In this study, 324 patients treated by radiotherapy without planned surgery (definitive radiotherapy) were analysed. These included 115 patients from A1 institutions, 70 patients from A2 institutions, 104 patients from B1 institutions, and 35 patients from B2 institutions.

Statistical significance was tested using the chi-square test. Cases with 'unknown' and 'missing' values were combined in the tables because their meanings were the same in most cases: no valid data were found in the given resources (11).

RESULTS

Table 1 describes the patient characteristics in the JPCS 1999–2001 survey of cervical cancer patients treated with definitive radiotherapy. Table 2 shows the performance rates of the diagnostic procedures. Of the diagnostic procedures prescribed by FIGO, three quarters of the patients underwent a chest X-ray. Other examinations, such as intravenous urography, cystoscopy, and proctoscopy, were performed in approximately 30–50% of the patients. Table 3 shows the performance of the examinations according to stage. A substantial number of early stage (I, II) patients underwent these diagnostic tests prescribed by the FIGO system. Majority of the patients underwent both pelvic and abdominal CT. Pelvic MRI was also frequently performed. CT and MRI were performed mostly irrespective of stage. Lymphangiography (LAG) and surgical staging were rarely performed. Only one patient underwent PET examination in the survey period.

Tumor diameter was recorded in 75% (242/324). The tumor diameter evaluation rates by FIGO stage were 67% (29/43) for stage I, 83% (85/102) for stage II, 77% (94/122) for stage III, and 80% (28/35) for stage IVA ($P = 0.01$). MRI was the most common modality for evaluating tumor size (47%) followed by CT (16%). Only a small percentage of patients had a tumor size evaluation consisting of only a pelvic examination (6%). Tumor size increased significantly with increasing stage. Median tumor size was 26 mm (range: 0–45 mm) for stage I, 40 mm (range: 15–90 mm) for stage II, 46 mm (range: 15–100 mm) for stage III, and 55 mm (range: 30–100 mm) for stage IVA ($P < 0.0001$). Pelvic nodal status was recorded in 82% (266/324) of the patients surveyed. The pelvic nodal assessment rate by stage was 88% (38/43) for stage I, 86% (88/102) for stage II, 83%

Table 1. Patient and tumor characteristics of 324 patients with uterine cervical cancer treated with radiotherapy

Characteristics	No. of patients	(%)
Total no.	324	
Age (years)		
Range	26–100	
Median	71	
KPS		
$\leq$ 70	64	20
80	103	32
90	114	35
100	21	6
Unknown/missing	22	7
Histology		
Squamou cell carcinoma	300	93
Adenocarcinoma	14	4
Adenosquamous cell carcinoma	4	1
Other	2	1
Unknown/missing	4	1
FIGO stage		
I	43	13
II	102	31
III	122	38
IVA	35	11
Unknown/missing	22	7

KPS, Karnofsky performance status; FIGO, International Federation of Gynecology and Obstetrics.

Table 2. Pretreatment diagnostic procedures performed

Procedure	No. of patients	(%)
Chest X-ray		
Yes	241	74
No	7	2
Unknown/missing	76	24
Intravenous urography		
Yes	176	54
No	68	21
Unknown/missing	80	25
Cystoscopy		
Yes	171	53
No	60	19
Unknown/missing	93	28
Proctoscopy		
Yes	108	33
No	114	35
Unknown/missing	102	32
Pelvic CT		
Yes	286	88
No	8	3
Unknown/missing	30	9
Abdominal CT		
Yes	258	80
No	14	4
Unknown/missing	52	16
Pelvic MRI		
Yes	246	76
No	39	12
Unknown/missing	39	12
Lymphangiography		
Yes	3	1
No	241	74
Unknown/missing	80	25
PET		
Yes	1	-
No	254	79
Unknown/missing	69	21
Surgical staging		
Yes	3	1
No	257	79
Unknown/missing	64	20

PET, positron emission tomography.

(101/122) for stage III, and 94% (33/35) for stage IVA ($P = 0.12$). CT was most frequently used for the assessment of nodal status (72%). PET and surgical examination were never utilized for this purpose. Positive nodal status significantly correlated with FIGO stage: 2% for stage I, 6% for stage II, 16% for stage III, and 49% for stage IVA ($P = 0.0001$).

DISCUSSION

This study demonstrated the patterns of pretreatment diagnostic assessment for cervical cancer patients who underwent definitive radiation therapy between 1999 and 2001 in Japan. Several of the cases reviewed in this survey had unknown or missing data; and this was a theoretical weaknesses of our audit. Inclusion of cases with incomplete information in the ratio calculations, however, reduced the potential for overestimation of performance rates of the tests.

FIGO permitted procedures were performed more frequently than expected in the patients surveyed. The use of FIGO permitted examinations (e.g. intravenous urography, cystoscopy, and proctoscopy) is gradually decreasing in the USA (7–9). In a 2000–02 US study on the pretreatment evaluation of patients with stage IIB or less disease, the rates for performing intravenous urography, cystoscopy, and proctoscopy were 1, 16, and 17%, respectively (9). In contrast, the present study demonstrated that these exams were performed frequently even for early stage cases in Japan. Schmitz et al. (12) proposed that since the likelihood of upstaging using these examinations was very low in clinical stage IB patients, these exams could be omitted in those with stage IB disease. Now, the National Comprehensive Cancer Network (NCCN) guideline states that cystoscopy and proctoscopy are optional exams for the pretreatment assessment of cervical cancer patients with a disease stage of IB2 or higher (http://www.nccn.org/professionals/physician_gls/PDF/cervical.pdf).

This study demonstrated that CT and MRI were routinely utilized during the surveyed period in Japan. Tumor size and pelvic nodal status are considered to be extremely important prognostic factors for cervical cancer (2). Several studies showed the accuracy of MRI for measuring tumor diameter for uterine cervical cancer (13,14). In the 1990s, several researchers reported that tumor diameter, as assessed by MRI, significantly affected the outcome of cervical cancer patients treated with definitive radiotherapy (3–5). The radiological evaluation of lymph node metastases is also valuable in cervical cancer patients, with both CT and MRI having high predictive values (6). MR imaging had an accuracy of 93%, with 62.2% sensitivity and 97.9% specificity when a minimum axial diameter of 1.0 cm was adopted as a size criterion for detection of pelvic nodal metastases (15). The results of our study reflect the penetration of these findings into the clinical practice in Japan. Unfortunately, we were unable to precisely measure the performance rates of the assessments of tumor diameter and lymph node status due to a flaw in the survey format. Namely, we were unable to distinguish whether the assessments were performed by

Table 3. Pretreatment diagnostic procedures performed according to the FIGO stage

Procedure	Stage				Missing/unknown
	I	II	III	IVA	
Intravenous urography	17/43 (40%)	53/102 (52%)	74/122 (61%)	26/35 (70%)	6/22
Cystoscopy	18/43 (42%)	58/102 (57%)	64/122 (52%)	25/35 (71%)	6/22
Proctoscopy	12/43 (28%)	32/102 (31%)	43/122 (35%)	17/35 (49%)	4/22
Pelvic CT	40/43 (93%)	89/102 (87%)	112/122 (92%)	34/35 (97%)	11/22
Abdominal CT	35/43 (81%)	83/102 (81%)	103/122 (84%)	29/35 (83%)	8/22
Pelvic MRI	31/43 (72%)	84/102 (82%)	88/122 (72%)	27/35 (77%)	16/22

the treating physicians or were performed anew by the visiting surveyors at the time of the analysis. Despite this limitation, we were able to roughly approximate the tumor diameter and the lymph node status in each stage. In the next JPCS presently being conducted, the format has been revised to clarify the aforementioned points. Our data will aid in comparing outcome between Japan and other countries. Abdominal CT has diagnostic value in detecting extrapelvic metastases (i.e. liver and para-aortic node) and the presence of hydronephrosis or a non-functioning kidney. Despite the potential usefulness of CT and MRI, these cross-sectional imaging studies are listed as optional examinations in the FIGO system (1). FIGO also acknowledges the usefulness of these exams. However, FIGO does not accept them for staging purposes, primarily because these instruments are not generally available in developing countries. The FIGO system clearly states that findings from these exams should not be the basis for staging (1). Improper application of these exams could lead to staging migration (2). However, we believe that these cross-sectional imaging studies should be applied universally not to determine FIGO stage but to assess important prognostic factors, namely tumor diameter and nodal status.

Several randomized clinical trials (RCTs) performed in the USA demonstrated the therapeutic value of concurrent chemoradiotherapy (http://www.cancer.gov/newscenter/cervicalcancer). Most of these trials required extensive evaluation of para-aortic lymph nodes by surgical exploration or LAG. This limits the translatability of the recommendations from these trials to the Japanese clinical practice. LAG and surgical staging were rarely performed for patients in our survey. Although Eifel reported that lymph nodal status was assessed by LAG in 13.6%, and surgical evaluation in 12.2% in the US PCS (1996–99), other studies revealed that, the performance of LAG has been decreasing recently (7–9). A similar problem exists in the evaluation of tumor diameter. In the US RCTs, tumor diameter was determined by physical examination. However, tumor size assessment by physical examination is highly subjective. Thus an objective method such as CT or MRI is preferable particularly when patients are being stratified in a clinical trial. This would facilitate the translation of evidence to clinical practice.

PET was rarely performed during the study period in Japan despite being shown to be useful in the late 1990s (16). Its application is expected to increase in the future, because the Japanese health insurance plan has covered it since 2004.

In summary, the JPCS describes the general patterns of pretreatment diagnostic assessment in cervical cancer patients treated with definitive radiotherapy during 1999–2001 in Japan. Patterns of pretreatment work-up should be continuously monitored in order to avoid staging migration, to properly treat individual patients, and to fairly compare treatment methods.

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Conflict of interest statement

None declared.

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CLINICAL INVESTIGATION **Cervix**

PATTERNS OF RADIOTHERAPY PRACTICE FOR PATIENTS WITH CERVICAL CANCER (1999–2001): PATTERNS OF CARE STUDY IN JAPAN

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Purpose: To describe the patterns of definitive radiotherapy practice for patients with uterine cervical cancer from 1999 to 2001 in Japan.

Methods and Materials: The Japanese Patterns of Care Study (JPCS) working group conducted a third extramural audit survey of 68 institutions and collected specific information on 324 cervical cancer patients treated with definitive radiotherapy.

Results: Almost all patients (96%) were treated with whole pelvic radiotherapy using opposing anteroposterior fields (87%). A midline block was used in 70% of the patients. Intracavitary brachytherapy (ICBT) was applied in 82% of cases. Most patients (89%) were treated with high-dose rate (HDR) ICBT. Calculation of doses to organs at risk (ICRU 38) was performed for rectum in 25% of cases and for bladder in 18% of cases. Only 3% of patients were given intravenous conscious sedation during ICBT applicator insertions. The median total biologically effective dose at point A (EBRT+ICBT) was 74 Gy_{10} in cases treated with HDR-ICBT. There was no significant difference in total biologically effective dose between stages. The median overall treatment time was 47 days. Concurrent chemoradiation was applied in 17% of patients.

Conclusions: This study describes the general patterns of radiotherapy practice for uterine cervical cancer in Japan. Although methods of external radiotherapy seemed to be appropriate, there was room for improvement in ICBT practice, such as pretreatment. A substantial difference in total radiotherapy dose between Japan and the United States was observed. © **2008 Elsevier Inc.**

Patterns of care study, Cervix, Radiotherapy.

INTRODUCTION

Several randomized controlled trials (RCTs) conducted in the 1990s have demonstrated that concurrent chemoradiotherapy (CCRT) reduced the mortality risk in uterine cervical cancer patients by 30%–50% compared with radiotherapy alone (1–3). Another RCT demonstrated no difference in the survival rates between definitive radiotherapy and surgery for early-stage cancer patients with Stages IB and IIA (4). Consequently, radiation therapy has become the more appropriate option in the treatment of cervical cancer. In the United States, the American Brachytherapy Society (ABS) issued the radiotherapy guidelines for uterine cervical cancer (5, 6), and in Japan, the General Rules for Clinical and Pathological Study of Uterine Cervical Cancer provide treatment guidelines, including the standard treatment schedule of radiotherapy (7). Currently, organizations such as the Gynecologic Cancer Intergroup (GCIG) are trying to set up international clinical trials of radiotherapy for uterine cervical cancer (8). Although international standardization of radiotherapy is an important issue, some between-country differences in the clinical practice of radiotherapy can be expected.

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The Patterns of Care Study (PCS) initially surveyed radiotherapy practice in the United States. The subjects of the survey were selected by the two-staged cluster sampling method (medical institutions and patients) from institutions providing radiotherapy throughout the United States. The national averages for radiotherapy practice can be demonstrated using this method (9). In the United States, PCSs have been conducted for more than 30 years, and the structure, process, and outcome of radiotherapy, as well as various problems in clinical practice, have been identified for uterine cervical cancer (10–13). In Japan, the Japanese Patterns of Care Study (JPCS) began in 1996 and used the same methods (14). We previously reported the PCS results for radiotherapy practice in uterine cervical cancer patients treated in 1992–1994 and 1995–1997 (15, 16). We report here the corresponding results for 1999–2001. We compared the data from this study with those of the preceding JPCS (1995–1997) and the U.S. PCS. The changes over the years in radiotherapy practice were examined for cervical cancer in Japan, and the differences between Japan and the United States were also examined.

METHODS AND MATERIALS

Between July 2002 and June 2004, the JPCS conducted a third national survey of patients with uterine cervical cancer treated with radiotherapy. Eligibility criteria for the survey were as follows: (*1*) carcinoma, (2) treated between January 1999 and December 2001, (*3*) no distant metastases, (*4*) no prior or concurrent malignancy, (*5*) no gross para-aortic lymph node metastases, and (*6*) no previous pelvic radiotherapy. Sixty-eight of 640 institutions were selected for the survey using a stratified two-staged cluster sampling method. Before the random sampling, all institutions were classified into four groups. Institutions were classified by type and number of patient treated with radiotherapy. The criteria for stratification have been detailed elsewhere (14). In brief, the JPCS stratified Japanese institutions as follows: A1, academic institutions treating ≥430 patients annually; A2, <430 patients; B1, nonacademic institutions treating ≥130 patients annually; B2, <130 patients. Academic institutions included cancer center hospitals and university hospitals. Nonacademic institutions consisted of other facilities, such as national, prefectural, municipal, and private hospitals.

The JPCS surveyors performed on-site chart review at each participating facility using an originally developed database format for uterine cervical cancer. Data collection included patient characteristics (e.g., patient's history, age, performance status, laboratory data, pathology, and stage), details of pretreatment workup, therapeutic information (e.g., radiotherapy, chemotherapy, and surgery), and treatment outcome. The JPCS collected clinical data on 631 patients with uterine cervical cancer who were treated with radiotherapy from 68 institutions. In this study, 324 patients treated by radiotherapy without planned surgery were analyzed. These included 115 patients from A1 institutions, 70 patients from A2 institutions, 104 patients from B1 institutions, and 35 patients from B2 institutions.

Statistical significance was tested using the chi-square test. Unknown and missing data were combined in the tables because these were the same in most cases: no valid data were found in the given resources (17). Ratios were calculated using unknown or missing data, but continuous variables did not include these data (17), as seen in a U.S. PCS report (18).

RESULTS

Table 1 shows the characteristics of the 324 patients in our survey. In total, 276 patients (85%) were hospitalized for treatment. Of these, 190 patients (59%) were hospitalized during both external beam radiotherapy (EBRT) and brachytherapy, 78 (24%) were hospitalized only during EBRT, and 8 (2%) only during brachytherapy.

External beam radiotherapy

External beam radiotherapy (EBRT) was performed in 320 patients (99%). Twenty-two patients (7%) received EBRT at another facility. In 142 cases (44%), multileaf collimators (MLC) were used to shape the portals. For 308 patients (96%), the planning target volume (PTV) included the whole pelvic region. The upper border of the pelvic field was at the L4 to L5 interspace in 238 of the 308 patients (77%). Only 10 patients (3%) received extended field radiotherapy including the para-aortic region. Treatment parameters of pelvic EBRT are shown in Table 2. The most frequently used beam energy was 10-14 MV X-rays. Pelvic EBRT was most often given using an opposing anteroposterior (AP-PA) technique. The median isocenter depth of the AP-PA portals was 9 cm (range, 6.5–12.9 cm). A midline block was used in 70% of the patients. A single-daily fraction dose of 1.8 or 2.0 Gy was used for most patients.

Brachytherapy

No patient surveyed received interstitial brachytherapy. Table 3 shows the details of intracavitary brachytherapy (ICBT). ICBT was applied in more than 80% of cases. The ICBT application rate by Fédération Internationale de

Table 1. Patient and tumor characteristics of 324 patients with uterine cervical cancer treated with radiotherapy.

Characteristics	No. of patients	(%)
Total no.	324	
Age (yrs)		
Range	26-100	
Median	71	
KPS		
<=70	64	20
80	103	32
90	114	35
100	21	6
Unknown/missing	22	7
Histology		
Squamous cell carcinoma	300	93
Adenocarcinoma	14	4
Adenosquamous cell carcinoma	4	1
Other	2	1
Unknown/missing	4	1
FIGO stage		
I	43	13
II	102	31
III	122	38
IVA	35	11
Unknown/missing	22	7

Table 2. Treatment parameters of pelvic external beam radiotherapy

Parameters	*n*	%
Beam energy		
Co-60	2	1
3–5 MV	30	10
6–9 MV	45	15
10–14 MV	220	71
15 MV	9	3
other	0	0
Unknown/missing	2	—
Technique		
AP-PA	269	87
Four-field box	21	7
Other	17	6
Unknown/missing	1	—
Midline block		
Yes	215	70
No	72	23
Unknown/missing	21	7
Daily fraction size (Gy)		
<1.8	25	8
1.8	135	44
1.8–2	2	1
2	137	45
>2	6	2
Missing	3	—

Gynécologie Obstétrique (FIGO) stages was 88% for Stage I, 88% for Stage II, 89% for Stage III, and 51% for Stage IVA. Its application was significantly less frequent in stage IVA patients (p <0.0001). Sixty-four patients (25%) received ICBT at another facility. Approximately 90% of the patients were treated with high-dose rate (HDR) ICBT. The most frequent radionuclide for ICBT source was cobalt-60 (Co-60), followed by iridium-192 (Ir-192). A rigid-type applicator was used for about 60% of the patients. In vivo rectal dosimetry was performed in approximately one quarter of the patients, whereas bladder dosimetry was rarely performed. ICRU 38 reference doses at the rectum and bladder were calculated in one quarter or less of the patients. Supportive medication before or during the applicator insertion was almost never given; when it was administered, it seemed to be inadequate. The dose calculation was performed for every HDR-ICBT fraction for more than three quarters of the patients. In most patients, all HDR-ICBT procedures (applicator insertion, radiograph generation and treatment) were performed in the same room.

Radiation dose and overall treatment time

Table 4 shows radiotherapy dose as a function of the FIGO stage. Total EBRT dose to the central pelvis (point A dose) significantly increased with increasing FIGO stage. Although a significant difference was also observed in total dose to the lateral pelvis (point B dose), median dose was almost the same at all stages. Median ICBT fraction size at point A was 524 cGy for HDR and 1740 cGy for LDR. The most frequent HDR-ICBT dose per fraction at point A was 500–599 Gy (79/215, 37%), followed by 600–699 cGy (48/215, 22%),

Table 3. Details of intracavitary brachytherapy

Parameters	*n*	%
ICBT given		
Yes	265	82
No	58	18
Unknown/missing	1	0
Dose rate		
HDR	215	89
LDR	27	11
HDR+LDR	0	0
Other	0	0
Unknown/missing	23	-
Source		
Co-60	112	46
Ir-192	102	42
Cs-137	21	9
Ra-226	7	3
Unknown/missing	23	-
Method of ICBT		
Tandem + vaginal applicator	202	83
Tandem only	26	11
Vaginal applicator	16	6
Unknown/missing	21	-
Applicator		
Rigid	166	63
Nonrigid	66	25
Unknown/missing	33	12
In vivo dosimetry: bladder		
Yes	8	3
No	207	78
Unknown/missing	50	19
In vivo dosimetry: rectum		
Yes	71	27
No	145	55
Unknown/missing	49	18
ICRU38: bladder		
Yes	48	18
No	146	55
Unknown/missing	71	27
ICRU38: rectum		
Yes	65	25
No	128	48
Unknown/missing	72	27
Preparation		
None	90	54
NSAIDs; orally/rectally	68	41
IV continous sedation	5	3
other	3	2
Unknown/missing	99	-
All procedures in same room*		
Yes	167	78
No	11	5
Unknown/missing	37	17
Each fraction planned*		
Yes	159	74
No	49	23
Unknown/missing	7	3

Abbreviations: HDR = high dose rate; ICBT = intracavitary brachytherapy; ICRU = International Commission on Radiation Units and Measurements; LDR = low dose rate, NSAIDs = nonsteroidal anti-inframmatory drugs.

* 215 patients treated with HDR-ICBT.

Table 4. Radiotherapy dose according to Fédération Internationale de Gynécologie Obstétrique stage

Dose (Gy)	Missing (n)	Stage I	Stage II	Stage III	Stage IVA	Total
EBRT						
Total point A dose						p<0.001
0–20	1	6 (18%)	5 (5%)	0	2 (6%)	13 (5%)
20–30	6	8 (24%)	19 (19%)	10 (8%)	3 (9%)	40 (14%)
30–40	3	10 (30%)	38 (38%)	65 (54%)	8 (24%)	121 (42%)
40–50	7	4 (12%)	19 (19%)	32 (27%)	7 (21%)	62 (22%)
50–60	2	5 (15%)	18 (18%)	12 (10%)	11 (34%)	46 (16%)
>60	0	0	0	1 (1%)	2 (6%)	3 (1%)
Missing	3	10	3	2	2	39
Median		30	30.6	34.9	41.1	32.4
Total point B dose						p=0.0003
0–20	0	2 (5%)	0	0	2 (6%)	4 (2%)
20–30	2	2 (5%)	1 (1%)	3 (3%)	2 (6%)	8 (3%)
30–40	1	3 (8%)	2 (2%)	5 (4%)	3 (9%)	13 (4%)
40–50	11	15 (38%)	35 (35%)	38 (31%)	7 (21%)	95 (32%)
50–60	5	17 (44%)	60 (60%)	72 (59%)	16 (49%)	165 (56%)
>60	0	0	2 (2%)	3 (3%)	3 (9%)	8 (3%)
Missing	3	4	4	1	2	31
Median		46.0	50.0	50.0	50.0	50.0
HDR-ICBT						
Total point A dose						p=0.025
0–10	0	0	2 (3%)	2 (2%)	1 (7%)	5 (2%)
10–20	3	5 (17%)	14 (18%)	34 (40%)	5 (36%)	58 (28%)
20–30	3	18 (62%)	49 (64%)	40 (47%)	6 (43%)	113 (54%)
30–40	0	2 (7%)	5 (6%)	1 (1%)	0	8 (4%)
>40	0	1 (3%)	0	0	0	1
Missing	4	3 (11%)	7 (9%)	8 (10%)	2 (14%)	24 (11%)
Median		23.1	22.0	20.0	20.0	20.3

Abbreviations: EBRT= external beam radiotherapy; HDR-ICBT= high dose rate intracavitary brachytherapy.

0–499 cGy (43/215, 20%), and 700–799 cGy (15/215, 7%). A single dose to point A over 8 Gy was applied only in two patients. The median number of HDR-ICBT insertions was 4 (range, 1–8). The median total dose of ICBT at point A was 20.3 Gy for HDR and 40.1 Gy for LDR. In cases of HDR-ICBT, total dose to point A decreased significantly with increasing stages. Median total dose of HDR-ICBT at point A was 23.1 Gy for Stage I, 22.0 Gy for Stage II, 20.0 Gy for Stage III, and 19.9 Gy for Stage IVA ($p = 0.025$). For calculation of total dose of EBRT and HDR-ICBT, biologically effective doses (BED) for tumor effect were calculated on the basis of $\alpha/\beta = 10$. The median total BED at point A was 74 Gy_{10} in cases treated with HDR-ICBT. There was no significant difference in total BED among the stages. Median total point A BED was 72 Gy_{10} for Stage I, 75 Gy_{10} for Stage II, 72 Gy_{10} for Stage III, and 77 Gy_{10} for Stage IVA ($p = 0.47$).

The median overall treatment time (OTT) was 47 days. OTT exceeded 8 weeks in 88 patients (28%).

Chemotherapy

Chemotherapy was applied in 104 patients (32%). Fifty-six patients (17%) were treated with concurrent chemoradiation (CCRT). Use of CCRT significantly varied according to FIGO stage ($p = 0.0039$). Chemotherapy was administered to 3 patients (7%) in Stage I, 12 patients (12%) in Stage II, 34 patients (28%) in Stage III, and 5 patients (14%) in Stage IVA. Neoadjuvant chemotherapy (NAC) before radiation therapy was given in 52 patients (16%).

DISCUSSION

This study describes the general patterns of radiotherapy practice for uterine cervical cancer from 1999 to 2001 in Japan. We examined the changes within Japan over the years and the differences in practice between Japan and the United States (Table 5).

External beam radiotherapy

For the radiation field (planning target volume [PTV]), almost all patients were treated with whole pelvic radiotherapy. Only a small number of patients received radiotherapy with an extended field including the para-aortic region. These results did not change over the years when comparisons were made with the previous JPCS (16). The U.S. PCS reported that only 11% of patients received extended field radiotherapy (12). Despite the positive results of the Radiation Therapy Oncology Group trial 79-20 (19), the standard PTV for EBRT in clinical practice in both Japan and the United States remained the whole pelvic region without para-aortic irradiation.

Table 5. Comparison of patterns of radiotherapy in cervical cancer patients between Japan and the United States

Parameters	Japan PCS 1995–1997*	Japan PCS 1999–2001	US PCS
Exrternal beam			
PTV			
Extended field	1%	3%	11%†
Beam energy			
Co60–9 MV	30%	26%	17%†
10–14 MV	57%	71%	19%†
15 MV≤	8%	3%	62%†
Technique			
Anteroposterior	95%	87%	19%†
Four-field box	2%	7%	80%†
Midline block			
Yes	69%	70%	6%†
Intracavitary brachytherapy			
Performed			
Yes	77%	82%	93%‡
Dose-rate			
LDR	8%	11%	78%‡
HDR	85%	89%	13%‡
Total dose to central tumor§ (median BED)	—	74 Gy_{10}	103 Gy_{10}‡
Overall treatment time (median)	49 days	47 days	57 days‡

Abbreviations: BED = biologically effective dose; LDR = low dose rate; HDR = high dose rate; PTV = planning target volume.

* Recalculated % including missing values.

§ point A dose (EBRT+HDR-ICBT).

† 1992–1994.

‡ 1996–1999.

As for beam energy, use of 9 MV or less decreased, and use of 10–14 MV increased (16). In the United States, the percentage of patients receiving 15 MV was largest (9, 12). The four-field technique was applied slightly more frequently in the present JPCS than the preceding JPCS (16). However, most patients were treated with the opposing AP-PA technique. In contrast, the four-field technique was applied in 80% of the patients in the United States (12). In the present survey, median isocenter depth of the AP-PA portals was 9 cm, indicating that the body thickness of females in Japan is small. Although there are no data, the body thickness is presumed to be larger in American patients compared with Japanese patients. Therefore, after taking body thickness into account, we thought that the beam energy and method of external beam radiotherapy used in Japan is appropriate. Even in Japanese patients whose body thickness is smaller than that of American patients, multiple field radiotherapy (*e.g.*, four-field) should be selected when a low-energy beam is used.

In this survey, a midline block was used in most patients, and no change in this practice was observed over the years (16). In contrast, the midline block was rarely used in the United States (12). The widespread use of the midline block was considered the result of following schedules specified in Japanese guidelines (7). One reason for less frequent use of the midline block in the United States may be the use of the four-field technique. Mell *et al.* (20) reported use of intensity-modulated radiation therapy (IMRT) in 27% of patients with gynecologic cancer in the United States. Because the use of IMRT could increase in Japan as well, it will be necessary to reexamine the advantages of using the midline block.

Intracavitary brachytherapy

The application rate of ICBT slightly increased compared with the previous PCS (16). However, the application rate was less in Japan than in the United States (12, 13). Intracavitary brachytherapy should be applied more routinely for patients treated by definitive radiotherapy in Japan. One fourth of the patients had received ICBT at another medical institution. In contrast, the percentage of such patients was reported as 8.5% in the United States (21).

HDR was used in approximately 90% of the patients, which was almost the same rate as that of the previous JPCS (16). In the United States, this rate was lower than that of Japan: 24% according to the ABS survey (1995) (22) and 16% according to the U.S. PCS survey (1996–1999) (21). We consider that the difference in the dose rate is one of the major differences between Japan and the United States. In the present study, the ICBT sources Co-60 and Ir-192 were used in roughly the same number of cases. The use of Ir-192 increased compared with the previous JPCS (16). In the early 2000s, the Japanese Society for Therapeutic Radiology and Oncology recommended the discontinuation of Co-60 as a remote afterloading brachytherapy source in Japan. The increase in the use of Ir-192 could be the result of compliance with this recommendation. Further increase in the use of Ir-192 and decrease in the use of Co-60 are expected in the next survey.

The ABS made a number of recommendations regarding HDR-ICBT techniques (5). The present study showed that analysis of the dose to organs at risk was performed in only a small percentage of patients. The doses were more often determined by using a dosimeter than the ICRU 38 reference point calculation. Sakata *et al.* indicated that the measured rectal dose significantly correlated with the incidence of rectal complications (23). In the United States, the practice of using a dosimeter for dosimetry has been called into question. The ABS recommended the use of the ICRU 38 reference point calculation (5). Many studies showed that late rectal complications can be predicted by the calculated doses at the ICRU 38 reference points (24, 25). According to the ABS survey, rectal/bladder doses are evaluated in 80% or more of patients at U.S institutions where HDR is performed (22).

The ABS also recommends conscious sedation for HDR-ICBT applicator insertions (5). However, it was surprising to discover that many patients in both the present and previous JPCS (16) received no pretreatment for HDR-ICBT applicator insertion. Intracavitary brachytherapy plays an important role in the radiotherapy of uterine cervical cancer. Accurate insertion can hardly be achieved if patients

Table 6. Standard radiotherapy schedule for uterine cervical cancer in Japan

FIGO stage	Central pelvic dose of EBRT (Gy)	Point A dose of HDR-ICBT (Gy/fc.)	Total BED at point A (Gy_{10})
I	0	29/5	46
II small	0	29/5	46
II large	20	23/4	60
III (small-medium)	20–30	23/4	60–72
III (large)	30–40	15/3–20/4	71–78
IVA	30–50	15/3–20/4	71–83

Abbreviations: BED = biologically effective dose; EBRT = external beam radiotherapy; FIGO = Fédération Internationale de Gynécologie Obstétrique; HDR-ICBT: high dose rate intracavitary brachytherapy.

experience discomfort. Therefore, we consider that pretreatment, such as conscious sedation, should be used for HDR-ICBT applicator insertion.

The single, total dose of HDR-ICBT was lower in the present study than the previous JPCS (16). The reason is unknown, but it might be related to an increase in the use of concurrent chemoradiotherapy (CCRT), which will is discussed subsequently.

Radiation dose

Table 6 shows the radiotherapy schedules indicated in the aforementioned general rules (7) and their biologically effective doses (BED) by stages. It also shows that the dose for the cervical tumor—namely, the total dose of EBRT and HDR-ICBT (point A dose)—increases with stage progression. In this present study, BED ranged from 72 to 77 Gy_{10} among the stages, indicating that differences among the stages were small. The schedules advocate the use of the midline block starting at 0–20 Gy of EBRT for Stages I and II. However, only 20% of patients followed the rule in this present study. Many other patients received EBRT exceeding these doses without the midline block. As a result, the total dose (EBRT+HDR-ICBT) to the central pelvis in early FIGO stages was higher than estimated. In contrast, treatment of patients in Stage III and IVA followed the schedules indicated in the general rules.

It was reconfirmed that the dose to uterine cervical tumors was lower in Japan than in the United States (25–27). The biologically effective dose (BED) of the schedules recommended by the ABS is approximately 100 Gy_{10} (5). In the United States PCS, the mean value of the linear quadratic equivalent dose was 85.5 Gy for patients treated using HDR-ICBT in 1996–1999 (21). When converted to BED, this value was 103 Gy_{10}. The difference in dose between Japan and the United States may be attributed to the difference in the standard schedules recommended in each country. The issue of dose range will need to be resolved before an international collaborative study can be initiated (8). The validity of each dose needs to be evaluated by outcome analysis.

Overall treatment time

Overall treatment time (OTT) is considered an important factor that affects the outcome of radiotherapy for uterine cervical cancer (28, 29). The ABS proposed that the OTT should be limited to within 8 weeks (5). The median OTT was shorter in this study (47 days) than in the previous JPCS (16). However, the OTT exceeded 8 weeks in almost 30% of patients. More effort to avoid treatment interruption to limit OTT within 8 weeks should be made. In the United States, the median OTT was reported to be 57 days (21). This difference between Japan and the United States may be due to differences in treatment schedules. In Japan, a midline block is inserted and ICBT starts in the middle of the EBRT treatment period.

Chemotherapy

In the present study, 32% of the patients received chemotherapy, indicating an increase from the previous JPCS (16). In particular, the rate of CCRT increased from 5% to 17% (16). The increase could be due to adoption of practices shown effective by RCTs published in 1999 (1–3). In the U.S. PCS (1996–1999), the percentage of patients who received chemotherapy was reported to be 19% in 1996, 28% in 1997, and 26% in 1998. However, it dramatically increased to 63% in 1999 (13). Further increase in the use of CCRT is expected in both Japan and the United States, and the monitoring of such changes should be continued.

Whereas several RCTs revealed negative therapeutic value of neoadjuvant chemotherapy (NAC) before radiotherapy in the mid-1990s, 16% of the patients were still treated with this strategy during this surveyed period. Surprisingly, the application rate was almost the same as that reported in the 1995–1997 JPCS survey (14%) (16). The usage of this strategy should be further monitored closely as well as CCRT.

Conclusions

We describe the status of definitive radiotherapy for uterine cervical cancer in Japan from 1999 to 2001. As in the previous survey (1995–1997), the EBRT conditions, such as the beam energy and technique of EBRT, were different between Japan and the United States. However, conditions of EBRT in Japan were becoming more standardized. For ICBT, aspects of the technique, such as dosimetry of organs at risk and supportive medication (*i.e.*, conscious sedation), can be improved. The total BED (EBRT + HDR-ICBT) delivered to the primary lesion in Japan was approximately 70% of that in the United States. The median OTT in Japan was approximately 80% of that in the United States. Compared with the previous JPCS, our study found that the use of CCRT has increased. This increase is considered to be due to the adoption of practices shown effective by RCT results published in 1999.

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